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

Sorry for this extremely late release of the first edition of 2017 ESES Reference list. I hope this “record” will not be repeated. The main blame is on me – again. I had been repeatedly on sickleave this year, and after my returns there was a big load of other tasks to be completed. Furthermore, one of the contributors was also pretty late with the submission of references, adding up to this great delay. It looks much better for the second edition of 2017, and I am confident to complete that collection this month.

There are also some good news. This edition only contains 120 references which is a considerable progress compared to the 200 plus references before. Thus, I would like to thank all contributions for being more selective. Please keep up the good work and you can be even more selective, 120 references is still a lot to go through.

As announced already before, this will be the first edition of the ESES Reference List without a Reference Manager file. Support of the program has been stopped and my institution does not support the program any longer. Thus, there will be only the Endnote file and RTF and PDF documents. If you require any other format, please let me know, I see what I can do.

Sorry again for the big delay

Yours

Ulrich Beutner

Journals covered

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

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

Thyroid

Meta-Analyses

Variable relationship of the recurrent laryngeal nerve to the inferior thyroid artery: A meta-analysis and surgical implications.
Head Neck, 39(1):177-86.
B. M. Henry, J. Vikse, M. J. Graves, S. Sanna, B. Sanna, I. M. Tomaszewska, W. C. Hsieh, R. S. Tubbs and K. A. Tomaszewski.
BACKGROUND: The relationship between the recurrent laryngeal nerve (RLN) and inferior thyroid artery (ITA) is highly variable and traceable back to embryological life. METHODS: Comprehensive database searches were conducted, followed by judgment of eligibility, assessment, and extraction of data concerning the RLN/ITA relationship. The data were pooled into a meta-analysis and subjected to sex, side-based, geographic origin of study, and study modality subgroup analyses. RESULTS: Seventy-nine studies (n = 14,269 nerves) reported data on the relationship of the RLN to the ITA. The left versus right-sided comparison revealed stark differences: RLNs were predominantly posterior (62.6% vs 37.0%) and anterior (17.2% vs 37.1%) on the left and right sides, respectively. CONCLUSION: Symmetry of neurovascular relationships should not be assumed. Extra care should be taken during procedures on the right side, because the nerves are significantly more likely to present in patterns (anterior and between) associated with greater risk of iatrogenic injury. (c) 2016 Wiley Periodicals, Inc. Head Neck 39: 177-186, 2017.
PubMed-ID: 27627737
http://dx.doi.org/10.1002/hed.24582

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

Examining the Role of Preoperative Positron Emission Tomography/Computerized Tomography in Combination with Ultrasonography in Discriminating Benign from Malignant Cytologically Indeterminate Thyroid Nodules.
Thyroid, 27(1):95-102.
M. M. Merten, M. R. Castro, J. Zhang, J. Durski and M. Ryder.
BACKGROUND: Cytologically defined indeterminate thyroid nodules are a diagnostic challenge. Surgical lobectomy remains the gold standard for definitive diagnosis. However, 70-85% of nodules are ultimately benign. The primary objective of this study was to evaluate the negative predictive value (NPV) of F18-fluorodeoxyglucose (FDG) positron emission computed tomography (PET/CT) in excluding cancer among cytologically indeterminate thyroid nodules within the authors' institution using surgical pathology as the gold-standard reference. In addition, a systematic review was performed of published prospective studies on the NPV of PET/CT in evaluating indeterminate thyroid nodules. METHODS: A retrospective review was performed of all

patients aged >/=18 years seen at the Mayo Clinic between January 1, 2000, and December 31, 2014, with cytologically defined indeterminate thyroid nodules (suspicious for Hurthle cell neoplasm or follicular neoplasm; N = 858), who had a PET/CT within one year of fine-needle aspiration (n = 80) and underwent definitive diagnostic lobectomy (n = 51). Nodules were considered PET negative if they had a standardized uptake value (SUV) <5. Additionally, a systematic review was performed of published prospective studies on the NPV of PET/CT across multiple sites. RESULTS: Fifty-one patients met the eligibility criteria. The retrospective review combined with a systematic review of eight prospective studies suggests that indeterminate nodules with a negative PET (SUV <5) have a low risk of malignancy (NPV 94%). The cancer prevalence in the institution is 14% and 27% in the combined prospective studies. CONCLUSIONS: PET/CT represents a preoperative, non-invasive tool that when combined with sonographic features can identify indeterminate nodules at low risk for malignancy.
PubMed-ID: 27762671
http://dx.doi.org/10.1089/thy.2016.0379

Systematic review of site distribution of bone metastases in differentiated thyroid cancer.
Head Neck, 39(4):812-8.
M. Osorio, S. P. Moubayed, H. Su and M. L. Urken.
BACKGROUND: Thyroid cancer is the fastest growing cancer in the United States. A small portion of differentiated thyroid cancers (DTCs; 2% to 13%) develop bone metastases, which can decrease a patient's survival rate by more than 60%. METHODS: A systematic literature search of studies, including patients with DTC with bone metastases, was conducted by following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A case series of patients with DTC diagnosed with bone metastases seen at our institution was also included. RESULTS: A total of 616 bone metastases sites in 317 patients were identified in 14 case series. Ten patients were identified in our institutional case series. The most common sites of metastases are spine (34.6%), pelvis (25.5%), sternum and ribs (18.3%), extremities (10.2%), shoulder girdle (5.4%), and craniomaxillofacial (5.4%). CONCLUSION: The axial skeleton is the primary target of bone metastases in DTC. The relative distribution of bone metastases and red marrow content follow a similar rank. (c) 2017 Wiley Periodicals, Inc. Head Neck 39: 812-818, 2017.
PubMed-ID: 28079945
http://dx.doi.org/10.1002/hed.24655

Thyroglossal Duct Cyst Carcinoma: A Systematic Review of Clinical Features and Outcomes.
Otolaryngol Head Neck Surg, 156(5):794-802.
H. M. Rayess, I. Monk, P. F. Svider, A. Gupta, S. N. Raza and H. S. Lin.
Objective Although thyroglossal duct cysts (TGDCs) are relatively common, malignancies within these lesions are infrequent. As a result, there are no large-scale series describing clinical characteristics. Our objectives were to perform a systematic review of the literature evaluating patient demographics, pathology, management, and prognosis of these patients. Data Sources PubMed, Embase, Cochrane reviews, and Google Scholar were searched for relevant articles. Articles meeting inclusion criteria were reviewed for data detailing epidemiology, treatment, and outcomes. Review Methods Inclusion criteria included English-language articles with original reports on human subjects. Two investigators independently reviewed all articles for the data collected, including epidemiology, treatment, and outcomes. Results Ninety-eight articles comprising 164 patients were included in the final analysis. The mean age at presentation was 39.5 years (9-83 years); 68.3% of patients were female. In total, 73.3% of cases were found on final pathologic analysis. The most common pathology was papillary cancer (92.1%). Of the patients, 98.9% underwent a Sistrunk procedure and 61.0% underwent total thyroidectomy. There was a 4.3% recurrence rate with a mean time to recurrence of 42.1 months from initial treatment. One patient died of TGDC carcinoma, while all other patients were disease free at the time of last follow-up (mean follow-up was 46.1 months). Conclusion TGDC carcinoma is typically diagnosed on final pathology. While management encompasses a Sistrunk procedure, further consideration should be given to thyroidectomy among patients >/=45 years of age and individuals with aggressive disease. TGDC carcinoma harbors an exceedingly low rate of mortality.
PubMed-ID: 28322121
http://dx.doi.org/10.1177/0194599817696504

Utility of I-124 PET/CT in identifying radioiodine avid lesions in differentiated thyroid cancer: a systematic review and meta-analysis.
Clin Endocrinol (Oxf), 86(5):645-51.
P. Santhanam, D. Taieb, L. Solnes, W. Marashdeh and P. W. Ladenson.
INTRODUCTION: Diagnostic I-123 scans have been shown to underestimate the disease burden in

differentiated thyroid cancer (DTC) when compared to I-131 post-treatment scans, especially in children and patients who have had prior radioiodine (RAI) therapy and/or distant metastasis. I-124 PET/CT has been shown to be highly effective in imaging DTC-related metastatic disease. METHODS: We performed a systematic review and meta-analysis of studies investigating the sensitivity and specificity of I-124 PET/CT in identifying lesions amenable to RAI therapy as confirmed by I-131 post-treatment scanning. RESULTS: There were 141 patients and 415 lesions of DTC identified altogether. There was significant heterogeneity in the individual studies. The pooled sensitivity of the I-124 PET/CT in detecting lesions of differentiated thyroid cancer amenable to I-131 therapy was 94.2% (91.3-96.4% CI, P < 0.01), and the pooled specificity was 49.0% (34.8-63.4% CI, P < 0.01). The pooled positive likelihood ratio (LR) was 1.43 (1.05-1.94 CI), and the pooled negative LR was 0.28 (0.15-0.53 CI). Overall, the diagnostic odds ratio was 7.90 (3.39-18.48 CI). There were a small but increased number of lesions identified by I-124 PET/CT that was not detected on post-treatment scan. CONCLUSION: I-124 PET/CT is a sensitive tool to diagnose RAI avid DTC lesions, but also detects some new lesions that are not visualized on the post-treatment I-131 scan. Further, carefully designed dosimetric studies may be required to fully establish the role of I-124 PET CT for identifying potential lesions for I-131 therapy. I-124 PET/CT in patients with DTC may have other applications in specific clinical situations.
PubMed-ID: 28160320
http://dx.doi.org/10.1111/cen.13306

Randomized controlled trials

Randomized trial of a short course of preoperative potassium iodide in patients undergoing thyroidectomy for Graves' disease.
Am J Surg, 213(4):805-9.
G. Whalen, M. Sullivan, L. Maranda, R. Quinlan and A. Larkin. 2017.
BACKGROUND: A short course of potassium iodide (SSKI) has been traditionally used to prepare patients with Graves' disease for thyroidectomy. The rationale for this treatment has evolved over time; from control of hyperthyroidism to facilitating surgery by making the gland less friable and bloody. METHODS: Randomized trial of preoperative SSKI vs no SSKI to test whether that is true. RESULTS: Mean estimated blood loss in the SSKI group (62 mL) was less than in the control group (162 mL) as was the median estimated blood loss (50 vs 140 mL). Mean (142 vs 162 minutes) and median (138 vs 150 minutes) operative times were also less in the SSKI arm. Subjective difficulty of operation was similar. Multivariable comparisons of groups with analysis of covariance showed the SSKI group suffered a mean blood loss 35% of the no treatment group (P = .036), the 9.2% decrease in Operating Room (OR) time between the SSKI group and the no treatment group was not statistically different (P = .464). CONCLUSIONS: SSKI given before operation in patients with Graves' disease reduces blood loss during thyroidectomy.
PubMed-ID: 27769543
http://dx.doi.org/10.1016/j.amjsurg.2016.07.015

Consensus Statements/Guidelines

American Thyroid Association Guidelines on the Management of Thyroid Nodules and Differentiated Thyroid Cancer Task Force Review and Recommendation on the Proposed Renaming of Encapsulated Follicular Variant Papillary Thyroid Carcinoma Without Invasion to Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features.
Thyroid, 27(4):481-3.
B. R. Haugen, A. M. Sawka, E. K. Alexander, K. C. Bible, P. Caturegli, G. M. Doherty, S. J. Mandel, J. C. Morris, A. Nassar, F. Pacini, M. Schlumberger, K. Schuff, S. I. Sherman, H. Somerset, J. A. Sosa, D. L. Steward, L. Wartofsky and M. D. Williams. 2017.
American Thyroid Association (ATA) leadership asked the ATA Thyroid Nodules and Differentiated Thyroid Cancer Guidelines Task Force to review, comment on, and make recommendations related to the suggested new classification of encapsulated follicular variant papillary thyroid carcinoma (eFVPTC) without capsular or vascular invasion to noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). The task force consists of members from the 2015 guidelines task force with the recusal of three members who were

authors on the paper under review. Four pathologists and one endocrinologist were added for this specific review. The manuscript proposing the new classification and related literature were assessed. It is recommended that the histopathologic nomenclature for eFVPTC without invasion be reclassified as a NIFTP, given the excellent prognosis of this neoplastic variant. This is a weak recommendation based on moderate-quality evidence. It is also noted that prospective studies are needed to validate the observed patient outcomes (and test performance in predicting thyroid cancer outcomes), as well as implications on patients' psychosocial health and economics.
PubMed-ID: 28114862
http://dx.doi.org/10.1089/thy.2016.0628

Application of the new American Thyroid Association guidelines leads to a substantial rate of completion total thyroidectomy to enable adjuvant radioactive iodine.
Surgery, 161(1):127-33.
W. P. Kluijfhout, J. D. Pasternak, F. T. Drake, T. Beninato, W. T. Shen, J. E. Gosnell, I. Suh, L. C and Q. Y. Duh. 2017.
BACKGROUND: The recently published 2015 American Thyroid Association guidelines recognize lobectomy as a viable alternative for low-risk cancers and advise more conservative use of radioactive iodine. Some factors indicating adjuvant treatment with radioactive iodine (and therefore completion total thyroidectomy), however, only can be found upon pathologic investigation. METHODS: We performed a retrospective analysis including patients with American Thyroid Association low- and low-to-intermediate risk well-differentiated thyroid cancer 1-4 cm. We evaluated how often radioactive iodine would be indicated and compared this with our historic rate. A subanalysis was performed to determine the rate of completion total thyroidectomy necessary, based on the indications for adjuvant radioactive iodine therapy. RESULTS: A total of 394/1,000 (39.4%) patients were included for final analysis. Adjuvant radioactive iodine would have been favored in 101/394 (25.6%) of patients, which is 2.5 times less than was given in our historic cohort. Completion total thyroidectomy to enable adjuvant radioactive iodine would have been recommended in 29/149 (19.5%) patients preoperatively eligible for lobectomy. CONCLUSION: Despite the tightened regulations for radioactive iodine, about 20% of patients with apparently "low-risk" well-differentiated thyroid cancer who are eligible for lobectomy may need completion total thyroidectomy because of pathologic findings for which radioactive iodine use is listed as considered or favored by the current guidelines.
PubMed-ID: 27855968
http://dx.doi.org/10.1016/j.surg.2016.05.056

Thyroid cancer surgery guidelines in an era of de-escalation.
Eur J Surg Oncol,
K. J. Kovatch, C. W. Hoban and A. G. Shuman. 2017.
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

Other Articles

Intratumor heterogeneity and clonal evolution in an aggressive papillary thyroid cancer and matched metastases.
Endocr Relat Cancer, 22(2):205-16.
S. Le Pennec, T. Konopka, D. Gacquer, D. Fimereli, M. Tarabichi, G. Tomas, F. Savagner, M. Decaussin-

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

A comparison of lobectomy and total thyroidectomy in patients with papillary thyroid microcarcinoma: a retrospective individual risk factor-matched cohort study.
Eur J Endocrinol, 176(4):371-8.
H. Kwon, M. J. Jeon, W. G. Kim, S. Park, M. Kim, D. E. Song, T. Y. Sung, J. H. Yoon, S. J. Hong, T. Y. Kim, Y. K. Shong and W. B. Kim. 2017.
OBJECTIVE: Papillary thyroid microcarcinoma (PTMC) accounts for most of the increase in thyroid cancer in recent decades. We compared clinical outcomes and surgical complications of lobectomy and total thyroidectomy (TT) in PTMC patients. DESIGN AND METHODS: In this retrospective individual risk factor-matched cohort study, 2031 patients with PTMC were initially included. Patients who underwent lobectomy or TT were one-to-one matched according to individual risk factors, including age, sex, primary tumor size, extrathyroidal extension, multifocality and cervical lymph node (LN) metastasis. RESULTS: In total, 688 patients were assigned to each group. During the median 8.5 years of follow-up, 26 patients (3.8%) in the lobectomy group and 11 patients (1.6%) in the TT group had recurrences. The relative risk of recurrence was significantly less in the TT than that in the lobectomy group (hazard ratio (HR) 0.41; 95% confidence interval (CI) 0.21-0.81; P = 0.01). Most recurrences (84.6%) in the lobectomy group occurred in the contralateral lobe, and all patients were disease-free after completion of thyroidectomy. There were no significant differences in recurrence-free survival between the two groups after exclusion of contralateral lobe recurrences (HR, 2.75; 95% CI, 0.08-8.79; P = 0.08). There were significantly more patients with transient and permanent hypoparathyroidism in the TT than that in the lobectomy group (P < 0.001). CONCLUSIONS: Lobectomy could be appropriate for most patients with PTMC when there is no evidence of extrathyroidal disease in the preoperative work-up. Preoperative and postoperative imaging studies are important for patients who undergo lobectomy for PTMC, because most recurrences are in the contralateral lobe.
PubMed-ID: 28089996
http://dx.doi.org/10.1530/EJE-16-0845

Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features Accounts for More Than Half of "Carcinomas" Harboring RAS Mutations.
Thyroid, 27(4):506-11.
V. A. Paulson, P. Shivdasani, T. E. Angell, E. S. Cibas, J. F. Krane, N. I. Lindeman, E. K. Alexander and J. A. Barletta. 2017.
BACKGROUND: Molecular testing of thyroid nodules is increasingly being utilized to guide clinical management decisions. RAS mutations are the most frequent mutations detected in the context of an indeterminate fine-needle aspiration (FNA) diagnosis. The term "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP) was recently introduced to promote conservative management of tumors previously classified as noninvasive follicular variant of papillary thyroid carcinoma (FVPTC). This change in terminology was based on the indolent clinical behavior of these tumors and their molecular profile, which includes frequent RAS mutations. The aim of this study was to determine the percentage of RAS-mutant "carcinomas" that would now be classified as NIFTPs. METHODS: A search was performed for cases with known activating RAS mutations in a database of 199 thyroid carcinomas that underwent molecular characterization as part of Profile:Oncopanel

between July 2013 and July 2015. Cases of FVPTC were re-reviewed to identify tumors that now would be categorized as NIFTP. Preceding FNA diagnoses were recorded, and cases with an indeterminate FNA result (defined as a diagnosis of atypia/follicular lesion of undetermined significance, suspicious for follicular neoplasm, or suspicious for malignancy) were identified. RESULTS: A total of 27 RAS-mutant thyroid tumors were identified. Fifteen (56%) cases had an NRAS mutation, nine (33%) had an HRAS mutation, and three (11%) had a KRAS mutation. Twenty-four (89%) cases had a preceding FNA, 19 (79%) of which had an indeterminate FNA diagnosis. The surgical resection specimen demonstrated FVPTC in 20 (74%) cases, classical type PTC in two (7%), solid variant of PTC in one (4%), and follicular thyroid carcinoma in four (15%). Of the 20 FVPTCs, 16 (80%) would now be classified as NIFTP. NIFTPs accounted for 59% of RAS-mutant carcinomas overall and 63% of RAS-mutant carcinomas with a prior indeterminate FNA diagnosis. CONCLUSION: NIFTPs accounted for more than half of RAS-mutant "carcinomas" in this cohort. In cases where clinical and sonographic data support a low-risk phenotype, these results suggest that a lobectomy should be considered as the initial surgical approach for a nodule with an indeterminate FNA diagnosis and a RAS mutation.
PubMed-ID: 28114855
http://dx.doi.org/10.1089/thy.2016.0583

How radiologic/clinicopathologic features relate to compressive symptoms in benign thyroid disease.
Laryngoscope, 127(4):993-7.
B. Siegel, T. J. Ow, S. S. Abraham, P. A. Loftus, A. B. Tassler, R. V. Smith and B. A. Schiff. 2017.
OBJECTIVES/HYPOTHESIS: To identify compressive symptomatology in a patient cohort with benign thyroid disease who underwent thyroidectomy. To determine radiographic/clinicopathologic features related to and predictive of a compressive outcome. STUDY DESIGN: Retrospective cohort study. METHODS: Medical records of 232 patients with benign thyroid disease on fine needle aspiration who underwent thyroidectomy from 2009 to 2012 at an academic medical center were reviewed. Data collection and analyses involved subjects' demographics, compressive symptoms, preoperative airway encroachment, intubation complications, specimen weight, and final pathologic diagnosis. RESULTS: Subjects were ages 14 to 86 years (mean: 52.4 years). Ninety-six subjects (41.4%) reported compressive symptomatology of dysphagia (n =74; 32%), dyspnea (n = 39; 17%), and hoarseness (n = 24; 10%). Ninety-seven (42.2%) had preoperative airway encroachment. Dyspnea was significantly related to tracheal compression, tracheal deviation, and substernal extension. Dysphagia was related to tracheal compression and tracheal deviation. Compressive symptoms and preoperative airway encroachment were not related to intubation complications. Final pathologic diagnosis was not related to compressive symptoms, whereas specimen weight was significantly related to dyspnea and dysphagia. Final pathology revealed 74 subjects (32%) with malignant lesions. Malignant and benign nodular subject groups differed significantly in substernal extension, gland weight, tracheal deviation, and dyspnea. Logit modeling for dyspnea was significant for tracheal compression as a predictor for the likelihood of dyspnea. CONCLUSION: Dyspnea was closely related to preoperative airway encroachment and most indicative of a clinically relevant thyroid in our cohort with benign thyroid disease. Tracheal compression was found to have predictive value for the likelihood of a dyspneic outcome. LEVEL OF EVIDENCE: 4. Laryngoscope, 127:993-997, 2017.
PubMed-ID: 27438354
http://dx.doi.org/10.1002/lary.26124

Outcome of Large Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features.
Thyroid, 27(4):512-7.
B. Xu, G. Tallini, T. Scognamiglio, B. R. Roman, R. M. Tuttle and R. A. Ghossein. 2017.
BACKGROUND: In 2016, encapsulated follicular variant of papillary thyroid carcinoma without invasion was renamed "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP) in order to reduce overtreatment of this indolent tumor. However, many endocrinologists remain uneasy about managing large (>/=4 cm) NIFTP conservatively without radioactive iodine (RAI) therapy. The objectives of this study are to characterize the clinicopathologic characteristics and outcome of large NIFTP in order to assist therapeutic decision making. METHODS: The pathology databases of four tertiary hospitals were searched for large (>/=4 cm) NIFTP. Cases with separate foci of carcinoma were excluded. Seventy-nine cases fulfilled the inclusion criteria. Among them, 56 (71%) had at least two years of clinical follow-up (FU), and 49 (62%) had four or more years of FU. The clinicopathologic characteristics were reviewed and documented by four endocrine pathologists. RESULTS: The median size of the NIFTP was 4.5 cm (range 4.0-8.0 cm). The entire capsule was sampled in 50 (63%) tumors, while in the remaining 29 (37%) cases, it was submitted representatively, with a median of 2.1 blocks per centimeter of tumor examined. Large NIFTP had a female preponderance with a male:female ratio of 1:1.8, and presented at a median age of 49 years. There were no lymph node metastases at diagnosis in any of the patients, and none of the patients (n = 25) in whom nodal tissue was available for microscopic examination had positive findings. Twenty-six (33%) underwent thyroid lobectomy alone, and 37

(47%) did not receive RAI ablation. No recurrence was observed in the entire cohort, including all 32 patients with two or more years of FU who did not receive RAI therapy (median FU: 6.7 years). Among patients with four or more years of FU, all 25 individuals without RAI therapy did not recur, with a median FU of 11.2 years. Patients with a larger tumor size tended to receive postoperative RAI ablation (p = 0.001). CONCLUSIONS: Similar to their small counterparts, large NIFTP appear to have an extremely low risk of recurrence (zero in this cohort), even when treated conservatively without RAI therapy. Surgical treatment alone, including lobectomy, appears to be adequate for large NIFTP.
PubMed-ID: 28136139
http://dx.doi.org/10.1089/thy.2016.0649

Skeletal Complications and Mortality in Thyroid Cancer: A Population-Based Study.
J Clin Endocrinol Metab, 102(4):1254-60.
P. Choksi, M. Papaleontiou, C. Guo, F. Worden, M. Banerjee and M. Haymart. 2017.
Context: Although bone is a common site for tumor metastases, the burden of bone events [bone metastases and skeletal-related events (SREs)] in patients with thyroid cancer is not well known. Objective: To measure the prevalence of bone events and their impact on mortality in patients with thyroid cancer. Patients, Design, and Setting: We identified patients diagnosed with thyroid cancer between 1991 and 2011 from the linked Surveillance Epidemiology and End Results-Medicare dataset. Multivariable logistic regression was used to identify the risk factors for bone metastases and SREs. We used Cox proportional hazards regressions to assess the impact of these events on mortality, after adjusting for patient and tumor characteristics. Results: Of the 30,063 patients with thyroid cancer, 1173 (3.9%) developed bone metastases and 1661 patients (5.5%) developed an SRE. Compared with papillary thyroid cancer, the likelihood of developing bone metastases or an SRE was higher in follicular thyroid cancer [odds ratio (OR), 2.25; 95% confidence interval (CI), 1.85 to 2.74 and OR, 1.40; 95% CI, 1.15 to 1.68, respectively] and medullary thyroid cancer (OR, 2.16; 95% CI, 1.60 to 2.86 and OR, 1.62; 95% CI, 1.23 to 2.11, respectively). The occurrence of a bone event was associated with greater risk of overall and disease-specific mortality [hazard ratio (HR), 2.14; 95% CI, 1.94 to 2.36 and HR, 1.59; 95% CI, 1.48 to 1.71, respectively]. Bone events were a poor prognostic indicator even when compared with patients with other distant metastases (P < 0.001 and P < 0.001 for overall and disease-specific mortality, respectively). Conclusions: Bone events in patients with thyroid cancer are a poor prognostic indicator. Patients with follicular and medullary thyroid cancers are at especially high risk for skeletal complications.
PubMed-ID: 28324052
http://dx.doi.org/10.1210/jc.2016-3906

Clinical Features of Early and Late Postoperative Hypothyroidism After Lobectomy.
J Clin Endocrinol Metab, 102(4):1317-24.
S. Park, M. J. Jeon, E. Song, H. S. Oh, M. Kim, H. Kwon, T. Y. Kim, S. J. Hong, Y. K. Shong, W. B. Kim, T. Y. Sung and W. G. Kim. 2017.
Context: Lobectomy is preferred in thyroid cancer to decrease surgical complications and avoid lifelong thyroid-hormone replacement. However, postoperative hypothyroidism, requiring thyroid-hormone replacement, may occur. Objective: We aimed to identify the incidence and risk factors of postoperative hypothyroidism to develop a surveillance strategy after lobectomy for papillary thyroid microcarcinoma (PTMC). Methods: This historical cohort study involved 335 patients with PTMC treated by lobectomy. Postoperative thyroid functions were measured regularly, and patients were prescribed levothyroxine according to specific criteria. Patients not satisfying hormone-replacement criteria were closely followed up. Results: Postoperative hypothyroidism occurred in 215 patients (64.2%) including 5 (1.5%) with overt hypothyroidism and 210 (62.7%) with subclinical hypothyroidism. Forty patients (11.9%) were required thyroid hormone replacement. One hundred nineteen patients (33.5%) experienced temporary hypothyroidism and spontaneously recovered to euthyroid state. High preoperative thyroid-stimulating hormone (TSH) was the most important factor predicting postoperative hypothyroidism and failure of recover from hypothyroidism (odds ratio [OR], 2.82 and 1.77; 95% confidence interval [CI], 2.07 to 3.95 and 1.22 to 2.63; P < 0.001 and 0.002, respectively). Of the 215 patients eventually developing postoperative hypothyroidism, 70 (32.6%) developed hypothyroidism after the first postoperative year. Postoperative 1-year TSH levels were able to differentiate patients developing late hypothyroidism or euthyroidism (OR, 2.29; 95% CI, 1.68 to 3.26; P < 0.001). Conclusions: Preoperative and postoperative TSH levels might be predictive for patients who develop postlobectomy hypothyroidism and identify those requiring long-term surveillance for hypothyroidism. Additionally, mild postoperative hypothyroidism cases should be followed up without immediate levothyroxine replacement with the expectation of spontaneous recovery.
PubMed-ID: 28324106
http://dx.doi.org/10.1210/jc.2016-3597

Is There a Minimum Number of Thyroidectomies a Surgeon Should Perform to Optimize Patient Outcomes?
Ann Surg, 265(2):402-7.
M. A. Adam, S. Thomas, L. Youngwirth, T. Hyslop, S. D. Reed, R. P. Scheri, S. A. Roman and J. A. Sosa. 2017.
OBJECTIVE: To determine the number of total thyroidectomies per surgeon per year associated with the lowest risk of complications. BACKGROUND: The surgeon volume-outcome association has been established for thyroidectomy; however, a threshold number of cases defining a "high-volume" surgeon remains unclear. METHODS: Adults undergoing total thyroidectomy were identified from the Health Care Utilization Project-National Inpatient Sample (1998-2009). Multivariate logistic regression with restricted cubic splines was utilized to examine the association between the number of annual total thyroidectomies per surgeon and risk of complications. RESULTS: Among 16,954 patients undergoing total thyroidectomy, 47% had thyroid cancer and 53% benign disease. Median annual surgeon volume was 7 cases; 51% of surgeons performed 1 case/y. Overall, 6% of the patients experienced complications. After adjustment, the likelihood of experiencing a complication decreased with increasing surgeon volume up to 26 cases/y ($P < 0.01$). Among all patients, 81% had surgery by low-volume surgeons (</=25 cases/y). With adjustment, patients undergoing surgery by low-volume surgeons were more likely to experience complications (odds ratio 1.51, $P = 0.002$) and longer hospital stays (+12%, $P = 0.006$). Patients had an 87% increase in the odds of having a complication if the surgeon performed 1 case/y, 68% for 2 to 5 cases/y, 42% for 6 to 10 cases/y, 22% for 11 to 15 cases/y, 10% for 16 to 20 cases/y, and 3% for 21 to 25 cases/y. CONCLUSIONS: This is the first study to identify a surgeon volume threshold (>25 total thyroidectomies/y) that is associated with improved patient outcomes. Identifying a threshold number of cases defining a high-volume thyroid surgeon is important, as it has implications for quality improvement, criteria for referral and reimbursement, and surgical education.
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http://dx.doi.org/10.1097/SLA.0000000000001688

Core-needle biopsy versus repeat fine-needle aspiration for thyroid nodules initially read as atypia/follicular lesion of undetermined significance.
Head Neck, 39(2):361-9.
Y. J. Choi, J. H. Baek, C. H. Suh, W. H. Shim, B. Jeong, J. K. Kim, D. E. Song, T. Y. Kim, K. W. Chung and J. H. Lee. 2017.
BACKGROUND: The purpose of this study was to evaluate the role of core-needle biopsy (CNB) by comparing the results of CNB and repeat fine-needle aspiration (FNA) for thyroid nodules that are initially read as atypia/follicular lesion of undetermined significance (AUS/FLUS) on FNA. METHODS: Among 2631 initial AUS/FLUS FNA results, 505 consecutive nodules (295 repeat FNAs and 210 CNBs) were retrospectively analyzed. The primary outcome was inconclusive (ie, nondiagnostic or AUS/FLUS). The secondary outcomes included inconclusive results of the subcategory, risk factors for inconclusive results, and diagnostic performance. RESULTS: CNB demonstrated significantly fewer inconclusive results than repeat FNA for the overall nodules (40.9% vs 63%; $p < .001$). Repeat FNA and group FLUS were significant risk factors for inconclusive results (odds ratio = 1.92; $p = .001$ and odds ratio = 2.08; $p < .001$, respectively). All diagnostic performances using CNB were higher than repeat FNAs. CONCLUSION: CNB is more useful than repeat FNAs for reducing inconclusive results and improving the diagnostic performance of thyroid nodules with initial AUS/FLUS FNA results. (c) 2016 Wiley Periodicals, Inc. Head Neck 39: 361-369, 2017.
PubMed-ID: 27704650
http://dx.doi.org/10.1002/hed.24597

Optimal timing for a repeat fine-needle aspiration biopsy of thyroid nodule following an initial nondiagnostic fine-needle aspiration.
Am J Surg, 213(2):433-7.
A. Deniwar, A. Y. Hammad, D. B. Ali, N. Alsaleh, M. Lahlouh, A. B. Sholl, K. Moroz, R. Aslam, T. Thethi and E. Kandil. 2017.
BACKGROUND: In the case of a nondiagnostic thyroid fine-needle aspiration (FNA) biopsy result, recent guidelines from the Bethesda system recommend repeat thyroid FNA after 3 months to prevent false-positive results. We aimed to examine our institutional data to determine whether the 3-month period affects the diagnostic yield of repeat biopsies. METHODS: A retrospective review of patient records over a 5-year period at our institution was performed. Patients who required repeat FNA due to nondiagnostic results were included. The time between the FNA biopsies, adequacy of the FNA specimens, as well as the surgical pathology diagnosis were analyzed. RESULTS: We identified 317 patients who required a repeat FNA. Of these, 96 (30.3%) patients had repeat FNAs less than 3 months after initial biopsy, while 221 (69.7%) patients had repeat FNAs in greater than 3 months. One hundred five patients were referred to our clinic with an initial nondiagnostic

biopsy from an outside institution. Repeat FNA was nondiagnostic in 35 patients (11.04%) in the total study population. There was no difference in satisfactory diagnostic yield between repeat FNAs performed greater than 3 months (201 patients, 90.95%) or less than 3 months (81 patients, 84.38%) after the initial biopsy (P = .117). Of the 35 patients with repeat nondiagnostic biopsy, 17 patients underwent diagnostic lobectomy and 3 (17.6%) patients were found to have malignant disease. CONCLUSIONS: Early (<3 months) repeat FNA does not affect diagnostic yield of the subsequent sample. Patients with suspicious thyroid nodules could therefore receive a repeat FNA as soon as needed, rather than waiting 3 months. The shortened biopsy interval would alleviate stress on patients with benign nodules and expedite surgical intervention in patients with malignancy.
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http://dx.doi.org/10.1016/j.amjsurg.2016.04.010

Parathyroid Autotransplantation During Thyroid Surgery: A Novel Technique Using a Cell Culture Nutrient Solution.
World J Surg, 41(2):457-63.
F. Fama, M. Cicciu, F. Polito, A. Cascio, M. Gioffre-Florio, A. Piquard, O. Saint-Marc and A. Sindoni. 2017.
INTRODUCTION: Parathyroid autotransplantation is an easy procedure with a low complication rate. We adopted the transplantation into the sternocleidomastoid muscle, which allows an easier and time-saving surgical procedure using the same surgical incision. METHODS: In this study, we retrospectively reviewed the records of 396 consecutive patients, who underwent total thyroidectomy for benign thyroid disease. In all cases in which a parathyroid was damaged or inadvertently removed, the gland was transplanted; before the autotransplantation, the parathyroid tissue was put in a cell culture nutrient solution for 5 min, afterward fragmented, and then was transplanted in the sternocleidomastoid muscle. To demonstrate a beneficial effect of the cell nutrient solution step, we compared data of transplanted patients with a control group of cases (n = 190) undergoing a standard immediate autotransplantation. RESULTS: We divided patients in two main groups: group A (n = 160) including subjects that underwent one or more parathyroid gland autotransplantation using the cell nutrient solution, and group B (n = 236) concerning those who were not transplanted. Among patients, 62 hypocalcemias occurred, 40 in the group A and 22 in the group B (P < 0.001): 91.9 % were transient and 8.1 % (5 patients) definitive, all pertaining to the group B. Among controls (group C), 42 hypocalcemias occurred (P = 0.616 vs. group A and P = 0.002 vs. group B) and 3/42 became definitive (P = 0.096 vs. group A and P = 0.121 vs. group B). All differences concerning pre- and postoperative calcium values were statistically significant (P < 0.001). CONCLUSIONS: We recommend the routine parathyroid autotransplantation, when a vascular damage is certain or suspected, in order to reduce the rate of permanent hypoparathyroidism, using a cell culture nutrient solution before gland transplantation.
PubMed-ID: 27734084
http://dx.doi.org/10.1007/s00268-016-3754-0

Pediatric Thyroidectomy.
Otolaryngol Head Neck Surg, 156(2):360-7.
C. Hanba, P. F. Svider, B. Siegel, A. Sheyn, M. Shkoukani, H. S. Lin and S. N. Raza. 2017.
Objectives/Hypothesis To evaluate hospital course and associated complications among pediatric patients undergoing thyroidectomy. Study Design and Setting Retrospective database review of the Kids' Inpatient Database (2009, 2012). Methods The Kids' Inpatient Database was evaluated for thyroidectomy patients for the years 2009 and 2012. Surgical procedure, patient demographics, length of stay, hospital charges (in US dollars), and surgical complications were evaluated. Results Of an estimated 1099 nationwide partial thyroidectomies and 1654 total thyroidectomies, females accounted for 73.5% and 79.1% of patients, respectively. Children <1 year of age had significantly longer hospital courses (P < .0001), and patients 1 to 5 years of age had a significantly greater length of stay than individuals 6 to 20 years of age (7.8 vs 2.1 days, P < .001). The most common complications overall included hypocalcemia, respiratory complications, vocal cord paresis/paralysis, postoperative infection, and bleeding. Vocal cord paralysis was noted in 1.7% of pediatric thyroidectomy patients. The presence of these complications among total thyroidectomy patients significantly increased one's length of stay and hospital charges. A neck dissection was reported in 22.9% of malignant thyroidectomy patients. Conclusion Nearly 20% of children who underwent total thyroidectomy experienced postoperative hypocalcemia, positing a need for the development of postoperative calcium replacement algorithms to minimize the sequelae of hypocalcemia. A greater incidence of respiratory and infectious complications among younger patients (<6 years) suggests a need for closer monitoring, possibly encompassing routine postoperative intensive care unit utilization, in an attempt to minimize these sequelae.
PubMed-ID: 28145836
http://dx.doi.org/10.1177/0194599816677527

The functional role of the pharyngeal plexus in vocal cord innervation in humans.
Eur Arch Otorhinolaryngol, 274(2):1121-8.
M. Uludag, N. Aygun and A. Isgor. 2017.
Classical understanding of the function of the pharyngeal plexus in humans is that it relies on both motor branches for innervation of the majority of pharyngeal muscles and sensory branches for the pharyngeal wall sensation. To date there has been no reported data on the role of the pharyngeal plexus in vocal cord innervation. The aim of this study is to evaluate whether or not the plexus pharyngeus contributes to the innervation of the vocal cords. One hundred twenty-five sides from 79 patients (59 female, 20 male) undergoing thyroid surgery with intraoperative neuromonitoring were prospectively evaluated. While vocal cord function was evaluated with endotracheal tube surface electrodes, cricothyroid and cricopharyngeal muscle electromyographic recordings were obtained with a pair of needle electrodes. The ipsilateral pharyngeal plexus, external branch of the superior laryngeal nerve, and recurrent laryngeal nerve were stimulated with a monopolar probe at 1 mA. With stimulation of the plexus pharyngeus on 125 operated sides, positive electromyographic waveforms were detected from five ipsilateral vocal cords (accounting for 3.2% of all vocal cords monitored and 6.3% of patients). The mean EMG amplitude of the vocal cords with stimulation of the plexus pharyngeus was 147 +/- 35.5 muV (range 110-203). In one case, the long latency time of 19.8 ms correlated with innervation by the glottic closure reflex pathway. The short latencies seen in the other four cases [3.9 +/- 1.1 ms (range 3.2-5.5)] correlated with direct innervation. In some cases, the plexus pharyngeus may contribute to vocal cord innervation by reflex or direct innervation patterns in humans.
PubMed-ID: 27812786
http://dx.doi.org/10.1007/s00405-016-4369-7

TERT Promoter Mutation Predicts Radioiodine-Refractory Character in Distant Metastatic Differentiated Thyroid Cancer.
J Nucl Med, 58(2):258-65.
X. Yang, J. Li, X. Li, Z. Liang, W. Gao, J. Liang, S. Cheng and Y. Lin. 2017.
Telomerase reverse transcriptase (TERT) promoter mutation has been reported to be associated with aggressive characteristics in differentiated thyroid cancer (DTC). This study examined the status of TERT mutation in distant metastatic DTC and evaluated the correlation between TERT mutation and radioiodine uptake, as well as that between TERT mutation and therapy response. METHODS: TERT promoter and B-Raf proto-oncogene (BRAF) V600E mutation were retrospectively examined in primary tumors of 66 patients with distant metastatic DTC. Stimulated thyroglobulin (sTg) changes, radioiodine uptake status (avid or nonavid), and other imaging evidence were analyzed to evaluate therapy response. After a median follow-up of 46.5 mo (interquartile range, 29.0-70.5 mo), therapy response was classified as either disease control or refractory. RESULTS: The prevalence of TERT mutations was 22.73% (15/66), of which C228T mutation was more prevalent (13/15) than C250T mutation (2/15). Rising sTg was noticed in 93.33% (14/15) of the TERT mutation group. Of cases negative for both mutations, 78.12% (25/32) presented with decreased sTg. TERT mutation closely correlated with a poor response to radioiodine therapy ($P < 0.001$), and all 15 patients were classified as refractory to radioiodine therapy, with a positive predictive value of 100% at the endpoint of follow-up. TERT mutation was associated with older mean age at diagnosis ($P < 0.001$), larger mean tumor diameter ($P = 0.013$), and greater likelihood of both BRAF mutation coexistence ($P = 0.044$) and radioiodine-refractory character ($P < 0.001$). In the 36 cases whose imaging results underwent semiquantitative analysis, TERT mutation significantly correlated with non-radioiodine avidity, with a much lower mean tumor-to-background ratio (obtained from postradioiodine whole-body scanning) than in TERT wild-type cases ($P < 0.001$). In addition, patients with distant metastatic DTC with TERT mutation were more likely to lose radioiodine avidity at the initial radioiodine therapy than were those with only BRAF mutation (8/8 vs. 5/11; Fisher exact test, $P = 0.018$). CONCLUSION: TERT mutation closely associates with non-radioiodine avidity in distant metastatic DTC, and when compared with BRAF mutation, TERT mutation manifested a greater negative influence on radioiodine uptake. TERT mutation could also be used as an early predictor of radioiodine-refractory cases.
PubMed-ID: 27493271
http://dx.doi.org/10.2967/jnumed.116.180240

Germline Polymorphisms of the VEGF Pathway Predict Recurrence in Nonadvanced Differentiated Thyroid Cancer.
J Clin Endocrinol Metab, 102(2):661-71.
V. Marotta, C. Sciammarella, M. Capasso, A. Testori, C. Pivonello, M. G. Chiofalo, C. Gambardella, M. Grasso, A. Antonino, A. Annunziata, P. E. Macchia, R. Pivonello, L. Santini, G. Botti, S. Losito, L. Pezzullo, A. Colao and A. Faggiano. 2017.
Context: Tumor angiogenesis is determined by host genetic background rather than environment. Germline

single nucleotide polymorphisms (SNPs) of the vascular endothelial growth factor (VEGF) pathway have demonstrated prognostic value in different tumors. Objectives: Our main objective was to test the prognostic value of germline SNPs of the VEGF pathway in nonadvanced differentiated thyroid cancer (DTC). Secondarily, we sought to correlate analyzed SNPs with microvessel density (MVD). Design: Multicenter, retrospective, observational study. Setting: Four referral centers. Patients: Blood samples were obtained from consecutive DTC patients. Genotyping was performed according to the TaqMan protocol, including 4 VEGF-A (-2578C>A, -460T>C, +405G>C, and +936C>T) and 2 VEGFR-2 (+1192 C>T and +1719 T>A) SNPs. MVD was estimated by means of CD34 staining. Outcome Measures: Rate of recurrent structural disease/disease-free survival (DFS). Difference in MVD between tumors from patients with different genotype. Results: Two hundred four patients with stage I-II DTC (mean follow-up, 73 +/- 64 months) and 240 patients with low- to intermediate-risk DTC (mean follow-up, 70 +/- 60 months) were enrolled. Two "risk" genotypes were identified by combining VEGF-A SNPs -2578 C>A, -460 T>C, and +405 G>C. The ACG homozygous genotype was protective in both stage I-II (odds ratio [OR], 0.08; 95% confidence interval [CI], 0.01 to 1.43; P = 0.018) and low- to intermediate-risk (OR, 0.14; 95% CI, 0.01 to 1.13; P = 0.035) patients. The CTG homozygous genotype was significantly associated with recurrence in stage I-II (OR, 5.47; 95% CI, 1.15 to 26.04; P = 0.018) and was slightly deleterious in low- to intermediate-risk (OR, 3.39; 95% CI, 0.8 to 14.33; P = 0.079) patients. MVD of primary tumors from patients harboring a protective genotype was significantly lower (median MVD, 76.5 +/- 12.7 and 86.7 +/- 27.9, respectively; P = 0.024). Conclusions: Analysis of germline VEGF-A SNPs could empower a prognostic approach to DTC.
PubMed-ID: 27849428
http://dx.doi.org/10.1210/jc.2016-2555

Role of surgery in the management of anaplastic thyroid carcinoma: Korean nationwide multicenter study of 329 patients with anaplastic thyroid carcinoma, 2000 to 2012.
Head Neck, 39(1):133-9.
S. K. Baek, M. C. Lee, J. H. Hah, S. H. Ahn, Y. I. Son, Y. S. Rho, P. S. Chung, Y. S. Lee, B. S. Koo, K. Y. Jung and B. J. Lee. 2017.
BACKGROUND: The Korean Society of Thyroid Head and Neck Surgery established a nationwide multicenter registry of anaplastic thyroid carcinoma (ATC) and evaluated the prognostic factors and treatment outcomes of ATC. METHODS: The present study enrolled 329 patients who were diagnosed with ATC between January 2000 and December 2012 at 19 medical centers in Korea. Survival outcomes were evaluated according to various clinical factors and treatments. RESULTS: Multivariate analysis identified age >/=70 years old, the presence of initial clinical symptoms, distant metastasis, and treatment modality as significant risk factors (p <.05). The patients who underwent curative resection and adjuvant radiotherapy (RT) or concurrent chemoradiotherapy (CRT) showed the best survival on multivariate analysis (p < 0.05). CONCLUSION: Although ATC is a lethal neoplasm, long-term survival may be acquired in cases in which the aggressive management, including curative resection or RT/concurrent CRT, is possible for therapeutic intent. (c) 2016 Wiley Periodicals, Inc. Head Neck 39: 133-139, 2017.
PubMed-ID: 27534388
http://dx.doi.org/10.1002/hed.24559

Impact of lymphocytic thyroiditis on incidence of pathological incidental thyroid carcinoma.
Head Neck, 39(1):122-7.
E. Farrell, C. Heffron, M. Murphy, G. O'Leary and P. Sheahan. 2017.
BACKGROUND: The purpose of this study was to investigate the impact of lymphocytic thyroiditis on incidence of incidental thyroid cancers. METHODS: We conducted a retrospective review of 713 consecutive patients who underwent thyroidectomies. Incidental thyroid cancer was defined as an unexpected cancer discovered on pathological examination outside the index nodule undergoing preoperative cytology. RESULTS: We excluded 65 cases because of preoperative diagnosis of thyroid cancer, and 68 because of nonincidental cancer within the index nodule. Among the remaining 580 cases, there were 43 cases (7.4%) of incidental thyroid cancers. Incidental thyroid cancers were significantly associated with moderate/severe lymphocytic thyroiditis (relative risk = 2.5; p = .03). Sixteen of 56 patients with moderate/severe lymphocytic thyroiditis had Graves' disease, none of whom had incidental thyroid cancer. The risk of incidental thyroid cancer associated with moderate/severe lymphocytic thyroiditis was significantly higher in non-Graves' than patients with Graves' disease (p = .05). CONCLUSION: The risk of incidental thyroid cancer is significantly increased in patients with moderate/severe lymphocytic thyroiditis. Moderate/severe lymphocytic thyroiditis associated with Graves' disease seems to have a lower risk of incidental thyroid cancer. (c) 2016 Wiley Periodicals, Inc. Head Neck 39: 122-127, 2017.
PubMed-ID: 27792295
http://dx.doi.org/10.1002/hed.24544

Identification of novel therapeutic targets in anaplastic thyroid carcinoma using functional genomic mRNA-profiling: Paving the way for new avenues?
Surgery, 161(1):202-11.
P. K. Jonker, G. M. van Dam, S. F. Oosting, S. Kruijff and R. S. Fehrmann. 2017.
BACKGROUND: Currently, anaplastic thyroid carcinoma has a very poor prognosis and there is an unmet need for new therapeutic options. Therefore, this study aims to identify upregulated genes in anaplastic thyroid carcinoma with known drug interactions that could serve as new therapeutic targets. METHODS: Publicly available microarray expression profiles of anaplastic thyroid carcinoma and normal thyroid tissue were collected. FGmRNA-profiling was applied, which is a recently developed method that enhances the ability to capture the downstream effects of genomic alterations on gene expression levels. Next, a comparison between FGmRNA-profiles of anaplastic thyroid carcinoma and normal thyroid samples was performed. Significantly upregulated genes in ATC were prioritized based on: 1) known interaction with antineoplastic drugs, 2) current drug development status in human, and 3) association with biologic pathways known to be involved in anaplastic thyroid carcinoma carcinogenesis. RESULTS: In the study, 25 anaplastic thyroid carcinoma and 80 normal thyroid samples were included for FGmRNA-profiling. Class comparison identified 301 significantly upregulated genes. Following prioritization, MTOR, MET, WEE1, PSMD1, MERTK, FGFR3, RARG, and ESR2 were identified as potential therapeutic targets. CONCLUSION: We prioritized 8 potential therapeutic druggable targets in anaplastic thyroid carcinoma. Ultimately, inhibition of these therapeutic targets might improve patient outcome in anaplastic thyroid carcinoma by reducing locoregional disease and distant metastases.
PubMed-ID: 27865593
http://dx.doi.org/10.1016/j.surg.2016.06.064

Prognostic Impact of Further Treatments on Distant Metastasis in Patients With Minimally Invasive Follicular Thyroid Carcinoma: Verification Using Inverse Probability of Treatment Weighting.
World J Surg, 41(1):138-45.
Y. M. Lee, Y. H. Lee, D. E. Song, W. B. Kim, T. Y. Sung, J. H. Yoon, K. W. Chung and S. J. Hong. 2017.
BACKGROUND: The aim of this study was to evaluate the prognostic impact of further treatments in minimally invasive follicular thyroid carcinoma (MIFTC) patients. METHODS: The risk factors for distant metastases were analyzed, and the impact of surgical extent on distant metastasis was verified by using weighted logistic regression models with inverse-probability of treatment weighting (IPTW). RESULTS: 166 patients including 31 males (18.7 %) and 135 females (81.3 %), with the mean age of 41.5 +/- 13.5 years, were enrolled for this study. The median follow-up period was 103.5 months (range, 13-244 months). Seven patients (4.2 %) had distant metastases during follow-up period. The presence of vascular invasion (Hazard ratio [HR] = 29.06; 95 % Confidence Interval [CI] = 3.06-209.08; p = 0.015) and extensive vascular invasion >/=4 foci (HR = 40.57; 95 % CI = 2.09-789.13; p = 0.014) were the independent risk factors for distant metastasis by multivariate analysis. Surgical extent did not influence distant metastasis. Logistic regression with IPTW also demonstrated that there were no statistically significant differences in the development of distant metastasis based on surgical extent (HR = 1.28; 95 % CI = 0.15-10.87; p = 0.823). CONCLUSIONS: The presence of extensive vascular invasion is the most powerful predictor of distant metastasis. However, it is noteworthy that further treatments do not demonstrate an advantageous effect on preventing distant metastasis during the follow-up period.
PubMed-ID: 27272481
http://dx.doi.org/10.1007/s00268-016-3608-9

Prediction of radioactive iodine remnant ablation failure in patients with differentiated thyroid cancer: A cohort study of 740 patients.
Head Neck, 39(1):109-15.
M. Prpic, D. Kust, I. Kruljac, L. S. Kirigin, T. Jukic, N. Dabelic, A. Bolanca and Z. Kusic. 2017.
BACKGROUND: The purpose of this study was to detect parameters that could serve as predictors of radioactive iodine (I-131) ablation failure in patients with low-risk and intermediate-risk differentiated thyroid carcinoma (DTC). METHODS: Our cohort study included 740 patients with DTC who received postoperative I-131 remnant ablation. Anthropometric, biochemical, and pathohistological parameters were analyzed and correlated with ablation outcome using multivariable logistic regression models. RESULTS: Treatment failure rates were higher in patients <53 years, with N1a classification, and lymph node capsular invasion. In patients with N1a disease, thyroglobulin (Tg) > 2.4 ng/mL predicted treatment failure with 93.8% sensitivity and 52.5% specificity, and in patients with N1b disease, Tg > 14.9 ng/mL with 77.8% sensitivity and 92.9% specificity. I-131 activity was not associated with treatment outcome. CONCLUSION: Patients < 53 years old, with higher Tg levels, N1a classification, and lymph node capsular invasion have a higher risk of ablation failure. Stimulated Tg is an excellent predictor of treatment failure in patients with N1 disease. (c) 2016 Wiley Periodicals, Inc. Head

Neck 39: 109-115, 2017.
PubMed-ID: 27459351
http://dx.doi.org/10.1002/hed.24550

Value of fine-needle aspiration in evaluating large thyroid nodules.
Head Neck, 39(1):32-6.
T. Raguin, O. Schneegans, J. F. Rodier, P. P. Volkmar, E. Sauleau, C. Debry, G. Debonnecaze, J. P. Ghnassia and A. Dupret-Bories. 2017.
BACKGROUND: The American Thyroid Association (ATA) recommends using ultrasound-guided fine-needle aspiration (FNA) in order to evaluate supracentimetric and suspect thyroid nodules. The purpose of this study was to evaluate the effective use of FNA before surgery for nodules over 3 cm in diameter. METHODS: In this retrospective study, we analyzed the results of ultrasound-guided FNA and postoperative histological analysis in 843 nodules >3 cm. RESULTS: The FNA was informative in 42.6%. The correlation with the final histological analysis was 94.8% for benign nodules and 71.0% for malignant nodules. The FNA had a positive predictive value of 71%, a specificity of 97%, a sensitivity of 56%, and a 4.7% rate of false-negative results. CONCLUSION: Because there is a nonnegligible FNA risk of error, notably allowing the evolution of a cancer in 1 of 20 cases, the FNA data should not delay surgical intervention for potentially suspect nodules >3 cm in diameter. (c) 2016 Wiley Periodicals, Inc. Head Neck 39: 32-36, 2017.
PubMed-ID: 27299703
http://dx.doi.org/10.1002/hed.24524

Intraoperative electrophysiologic monitoring of the recurrent laryngeal nerve during thyroid and parathyroid surgery: Experience with 1,381 nerves at risk.
Laryngoscope, 127(1):280-6.
G. W. Randolph and D. Kamani. 2017.
OBJECTIVES: The electrophysiologic responses of 1,381 recurrent laryngeal nerves (RLN) during monitored neck surgery were recorded and reviewed. STUDY DESIGN: Retrospective case series. METHODS: With institutional review board approval, we reviewed thyroid and other neck surgeries performed with intraoperative nerve monitoring (IONM) between the years 1995 and 2006. This list yielded consecutively monitored 1,381 RLNs, with over 3,000 hours of monitoring experience. All patients underwent preoperative and postoperative laryngoscopy. In an initial subset of patients, both hook-wire and endotracheal tube (ETT) surface electrodes were utilized. Normative stimulation parameters; postoperative vocal cord function prognostication using monitoring data; and false-positive, false-negative, and passive electrophysiologic responses were evaluated RESULTS: Hook-wire electrodes and ETT surface electrodes were found to have good correlation in terms of amplitude (correlation coefficient, R = 0.89). Nerve stimulation of 1 to 2 mA resulted in an ipsilateral biphasic response, with 3.3 ms mean latency and 900 muV mean amplitude. Permanent and temporary RLN paralysis rates were 0% and 0.7%, respectively. Specificity of electromyography (EMG) loss of signal (LOS) postoperative vocal cord paralysis (VCP) detection was 99.9%, and sensitivity was 33%. Negative predictive value of EMG LOS at the end of surgery in the prediction of postoperative VCP was 99.6%, whereas its positive predictive value for VCP was 75%. CONCLUSION: Intraoperative nerve monitoring of the RLN during thyroid and other neck surgeries can aid in the nerve mapping, nerve identification, and prognostication of postoperative vocal cord function, which in turn can influence the surgeon's decision to proceed to bilateral surgery. LEVEL OF EVIDENCE: 4. Laryngoscope, 127:280-286, 2017.
PubMed-ID: 27389369
http://dx.doi.org/10.1002/lary.26166

A six-genotype genetic prognostic model for papillary thyroid cancer.
Endocr Relat Cancer, 24(1):41-52.
X. Shen, R. Liu and M. Xing. 2017.
A unique prognostic role of the genetic duet of BRAF V600E and TERT promoter mutations in papillary thyroid cancer (PTC) has been recently established, but the role of RAS mutation in this genetic interplay remains to be established. Using The Cancer Genome Atlas (TCGA) data of patients with PTC from 19 medical centers, we investigated the interactions among the three mutations in clinical outcomes of PTC. We found that BRAF and RAS mutations were mutually exclusive, but both were associated with TERT promoter mutations, with the genetic duet of BRAF/RAS and TERT mutations occurring in 34/388 (8.76%) patients. BRAF/RAS or TERT mutation had no or minimal effect alone, whereas coexisting BRAF/RAS and TERT mutations had a robust synergistic effect on poor clinicopathologic outcomes of PTC, including disease recurrence and patient mortality. For example, PTC recurrence rate was 52% with coexisting BRAF V600E/RAS and TERT promoter mutations vs 6.9% with no mutation, corresponding to a HR of 8.17 (95% CI 3.09-21.58), which remained significant at 14.71

(95% CI 2.79-77.61) after adjustment for clinicopathologic factors and institution. BRAF/RAS mutation or TERT mutation alone minimally affected Kaplan-Meier patient survival curves, whereas the genetic duet was associated with a sharp curve decline. Thus, by confirming and expanding previous findings in single-institution studies, this multicenter data analysis establishes a six-genotype genetic prognostic model for poor outcomes of PTC with a risk order of genetic duet of BRAF V600E/RAS mutation and TERT mutation >>>>BRAF V600E = TERT mutation alone >RAS mutation alone = wild-type genes.
PubMed-ID: 27875244
http://dx.doi.org/10.1530/ERC-16-0402

Thyroid cancer: Redifferentiation - a 'new' option for 131I-negative DTC.
Nat Rev Endocrinol, 13(1):9-10.
F. A. Verburg and M. Luster. 2017.
PubMed-ID: 27834385
http://dx.doi.org/10.1038/nrendo.2016.182

Animal models of medullary thyroid cancer: state of the art and view to the future.
Endocr Relat Cancer, 24(1):R1-R12.
G. Vitale, G. Gaudenzi, L. Circelli, M. F. Manzoni, A. Bassi, N. Fioritti, A. Faggiano and A. Colao. 2017.
Medullary thyroid carcinoma is a neuroendocrine tumour originating from parafollicular C cells accounting for 5-10% of thyroid cancers. Increased understanding of disease-specific molecular targets of therapy has led to the regulatory approval of two drugs (vandetanib and cabozantinib) for the treatment of medullary thyroid carcinoma. These drugs increase progression-free survival; however, they are often poorly tolerated and most treatment responses are transient. Animal models are indispensable tools for investigating the pathogenesis, mechanisms for tumour invasion and metastasis and new therapeutic approaches for cancer. Unfortunately, only few models are available for medullary thyroid carcinoma. This review provides an overview of the state of the art of animal models in medullary thyroid carcinoma and highlights future developments in this field, with the aim of addressing salient features and clinical relevance.
PubMed-ID: 27799362
http://dx.doi.org/10.1530/ERC-16-0399

How Many Contralateral Carcinomas in Patients with Unilateral Papillary Thyroid Microcarcinoma are Preoperatively Misdiagnosed as Benign?
World J Surg, 41(1):129-35.
Z. G. Wu, X. Q. Yan, R. S. Su, Z. S. Ma, B. J. Xie and F. L. Cao. 2017.
BACKGROUND: The decision to perform a total thyroidectomy (TT) for unilateral papillary thyroid microcarcinoma (PTMC) with nodules in the contralateral lobe remains controversial. The aim of this study was to investigate the rate of contralateral carcinomas that are preoperatively misdiagnosed as benign. METHODS: From October 2011 to October 2015, a total of 347 patients with unilateral PTMC and contralateral benign nodules who were treated with a TT at a single institution were enrolled. All patients underwent preoperative fine needle aspiration and ultrasonography (US). Clinicopathological features such as age, sex, laterality, tumor size, central lymph node metastases, capsular invasion, TgAb and TPOAb levels, Hashimoto's thyroiditis, nodule number in both lobes according to preoperative US, and primary carcinoma number in the final postoperative pathology report were all analyzed to investigate the rate and predictive factors of contralateral carcinoma. RESULTS: A total of 100 patients (28.9 %) were diagnosed with papillary thyroid carcinoma in the contralateral lobe. A multivariate analysis showed that tumor size, nodule number in the contralateral lobe, and multifocality of the primary tumor were all independent predictive factors of contralateral carcinoma in patients with unilateral PTMC and contralateral benign nodules. CONCLUSIONS: According to our findings, the rate at which contralateral carcinomas are preoperatively misdiagnosed as benign is 28.9 %. A TT is essential for unilateral PTMC with a primary tumor size >5 mm, multifocal primary carcinomas or multifocal benign nodules in the contralateral lobe.
PubMed-ID: 27541032
http://dx.doi.org/10.1007/s00268-016-3701-0

Primary Squamous Cell Carcinoma of the Thyroid: A Population-Based Analysis.
Otolaryngol Head Neck Surg, 157(1):25-9.
J. K. Au, J. Alonso, E. C. Kuan, A. Arshi and M. A. St John. 2017.
Objectives To analyze the epidemiology and describe the prognostic indicators of patients with primary squamous cell carcinoma of the thyroid. Study Design and Setting Retrospective cohort study based on a national database. Methods The US National Cancer Institute's SEER registry (Surveillance, Epidemiology, and

End Results) was reviewed for patients with primary squamous cell carcinoma of the thyroid from 1973 to 2012. Study variables included age, sex, race, tumor size, tumor grade, regional and distant metastases, and treatment modality. Survival measures included overall survival (OS) and disease-specific survival (DSS). Results A total of 199 cases of primary squamous cell carcinoma of the thyroid were identified. Mean age at diagnosis was 68.1 years; 58.3% were female; and 79.4% were white. Following diagnosis, 46.3% of patients underwent surgery; 55.7%, radiation therapy; and 45.8%, surgery with radiation therapy. Kaplan-Meier analysis demonstrated OS and DSS of 16% and 21% at 5 years, respectively. Median survival after diagnosis was 9.1 months. Multivariate Cox regression analysis showed that predictors of OS and DSS included age (P < .001, P < .001, respectively), tumor grade (P < .001, P = .001), and tumor size (P < .001, P = .001). Surgical management was a predictor of OS but not DSS. Conclusion Squamous cell carcinoma of the thyroid is a rare malignancy with a very poor prognosis. Surgical resection confers an overall survival benefit. Age, tumor grade, and tumor size are predictors of OS and DSS.
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http://dx.doi.org/10.1177/0194599817698436

Patterns, Predictive Factors, and Prognostic Impact of Contralateral Lateral Lymph Node Metastasis in N1b Papillary Thyroid Carcinoma.
Ann Surg Oncol, 24(7):1943-50.
S. K. Kim, I. Park, N. Hur, M. Rayzah, J. H. Lee, J. H. Choe, J. H. Kim and J. S. Kim. 2017.
BACKGROUND: Although the incidence among patients with bilateral lateral lymph node metastasis (LLNM) in N1b papillary thyroid carcinoma (PTC) is reported to be as high as 40%, only a few reports have addressed the characteristics of contralateral LLNM. Therefore, this study aimed to investigate the characteristics of patients with contralateral LLNM in N1b PTC. METHODS: This study retrospectively reviewed 834 patients with N1b PTC who underwent modified radical neck dissection between January 1997 and June 2015. RESULTS: Of the 834 N1b PTC patients, unilateral LLNM was found in 728 patients (87.3%) and bilateral LLNM in 106 patients (12.7%). The independent predictors of contralateral LLNM in N1b PTC patients were male sex (adjusted odds ratio [OR], 1.647; p = 0.039), tumor larger than 4 cm (adjusted OR, 6.700; p < 0.001), multiplicity (adjusted OR, 1.754; p = 0.040), bilobar involvement (adjusted OR, 1.971; p = 0.010), and bilateral central LN metastasis (CLNM) (adjusted OR, 2.829; p = 0.025). Moreover, contralateral LLNM significantly increased the risk of overall (adjusted hazard ratio [HR], 1.943; p = 0.016) and lateral neck (adjusted HR, 2.246; p = 0.015) locoregional recurrence. CONCLUSIONS: In the preoperative period, the meticulous evaluation of contralateral lateral neck may be required for male N1b PTC patients with tumor larger than 4 cm, multiplicity, bilobar involvement, and/or bilateral CLNM. In the postoperative period, N1b PTC patients may be re-stratified according to the contralateral LLNM, and meticulous follow-up assessment is required for N1b PTC patients with contralateral LLNM.
PubMed-ID: 28160142
http://dx.doi.org/10.1245/s10434-016-5761-7

The Impact of Pathologically Positive Lymph Nodes in the Clinically Negative Neck: An Analysis of 39,301 Patients with Papillary Thyroid Cancer.
Ann Surg Oncol, 24(7):1935-42.
E. Ruel, S. Thomas, J. M. Perkins, S. A. Roman and J. A. Sosa. 2017.
PURPOSE: Management of patients with low-risk papillary thyroid cancer (PTC) with clinically uninvolved lymph nodes (cN0 LNs), but who harbor metastatic central LNs (pN1a), remains unclear. The number of central LNs examined, radioactive iodine (RAI) utilization, and survival were compared across cN0 patients based on pN stage: pN0 (negative) versus pNx (unknown) versus pN1a (pathologically positive). METHODS: Adults with a PTC >/=1 cm who were cN0 preoperatively were compared based on surgical pathology using the National Cancer Data Base (NCDB; 2003-2011), after univariate and multivariate adjustment. Overall survival (OS) was examined using Kaplan-Meier curves, the log-rank test, and Cox proportional hazards modeling. RESULTS: Overall, 39,301 patients were included; median tumor size was 1.9 cm. More LNs were examined for pN1a versus pN0 diagnosis (pN1a median = 5 LNs vs. pN0 median = 2 LNs; p < 0.0001), with a median of two central LNs found to be positive on surgical resection. Compared with pN0, pN1a patients were 78% more likely to receive RAI (odds ratio 1.78, 95% confidence interval [CI] 1.65-1.91; p < 0.0001). After adjusting for receipt of RAI, no difference in OS was observed for pN1a versus pN0 or pNx patients (p = 0.72). Treatment with RAI was associated with improved OS (hazard ratio 0.78, 95% CI 0.62-0.98, p = 0.03), but the effect of RAI did not differ based on pN stage (interaction p = 0.67). CONCLUSION: More LNs were examined for positive versus negative pN diagnosis in patients with cN0 PTC. Unsuspected central neck nodal metastases in cN0 PTC patients are associated with increased RAI utilization, but no survival difference.
PubMed-ID: 28127652
http://dx.doi.org/10.1245/s10434-016-5719-9

Features of papillary thyroid microcarcinoma associated with lateral cervical lymph node metastasis.
Clin Endocrinol (Oxf), 86(6):845-51.
M. J. Jeon, M. S. Chung, H. Kwon, M. Kim, S. Park, J. H. Baek, D. E. Song, T. Y. Sung, S. J. Hong, T. Y. Kim, W. B. Kim, Y. K. Shong, J. H. Lee and W. G. Kim. 2017.
OBJECTIVES: Papillary thyroid microcarcinoma (PTMC) has an excellent prognosis with an indolent disease course. However, some PTMCs have an aggressive course with lateral cervical lymph node (LCLN) metastasis or distant metastasis. This study aimed to evaluate the pre-operative features of PTMC associated with LCLN metastasis. DESIGN AND PATIENTS: This retrospective cohort study with a nested, matched case-control design included 199 PTMC patients with LCLN metastasis at initial surgery (N1b group) and 196 PTMC patients without any LN metastasis or persistent disease (N0 NED group) as controls; primary tumour sizes were matched. RESULTS: Compared with the N0 NED group, the N1b group was younger (<50 years) and more likely to be male (P = 0.002 and P = 0.003, respectively). On pre-operative neck ultrasonography (US), N1b group PTMCs were more commonly associated with a location in the upper lobes of the thyroid, or in the subcapsular area and microcalcifications than N0 NED group PTMCs (all P < 0.001). An increase in the number of these features was significantly associated with a higher risk of LCLN metastasis (P < 0.001). Evaluation of the clinical and pre-operative US characteristics of 26 patients with confirmed LCLN recurrence after initial treatment of clinical N0 PTMCs revealed that the distribution of the number of suspicious features in these patients was similar to that of the N1b group. CONCLUSIONS: Papillary thyroid microcarcinomas in young (<50 years) or male patients, with an upper lobe or subcapsular location, and with microcalcification have a higher risk of LCLN metastasis. Individualized management according to the number of these suspicious features may be needed for small thyroid nodules.
PubMed-ID: 28273370
http://dx.doi.org/10.1111/cen.13322

Effect of Thyroid Remnant Volume on the Risk of Hypothyroidism After Hemithyroidectomy: A Prospective Study.
Ann Surg Oncol, 24(6):1525-32.
B. H. Lang, C. K. H. Wong, K. P. Wong, K. K. Chu and T. W. H. Shek. 2017.
BACKGROUND: Hypothyroidism is a common sequel after a hemithyroidectomy. Although various risk factors leading to hypothyroidism have been reported, the effect of the contralateral lobe's volume has been understudied. This study aimed to examine the association between the preoperative contralateral lobe's volume and the risk of postoperative hypothyroidism. METHODS: During a 2-year period, 150 eligible patients undergoing a hemithyroidectomy were evaluated. The volume of the contralateral nonexcised lobe was estimated preoperatively by independent assessors on ultrasonography using the following formula: width (in cm) x depth (in cm) x length (in cm) x (pi/6), adjusted for the body surface area (BSA). Postoperative hypothyroidism was defined as serum thyroid-stimulating hormone (TSH) exceeding 4.78 mIU/L. Any significant characteristics in the univariate analysis were entered into the multivariate analysis to determine independent factors. RESULTS: After a mean follow-up period of 53.5 +/- 9.4 months, 44 patients (29.3 %) experienced postoperative hypothyroidism, and 10 of these patients required thyroxine replacement. Hypothyroidism was associated with a higher preoperative TSH level (p < 0.001), a smaller BSA-adjusted volume (p < 0.001), fewer ipsilateral nodules (p = 0.037), and the presence of thyroiditis (p = 0.050). After adjustment for thyroiditis, preoperative TSH (p < 0.001), number of ipsilateral nodules (p = 0.048), and BSA-adjusted volume (p < 0.001) were independent factors for hypothyroidism. Patients with a BSA-adjusted volume smaller than 3.2 ml had a threefold greater hypothyroidism risk than those with a BSA-adjusted volume of 3.2 ml or more (p < 0.001). CONCLUSIONS: A significant inverse association between the preoperative contralateral lobe's volume and hypothyroidism risk was observed after hemithyroidectomy. Together with a higher preoperative TSH level and fewer ipsilateral nodules, a smaller BSA-adjusted volume measured by preoperative ultrasonography independently predicted hypothyroidism.
PubMed-ID: 28058547
http://dx.doi.org/10.1245/s10434-016-5743-9

Prevalence of Contralateral Tumors in Patients with Follicular Variant of Papillary Thyroid Cancer.
J Am Coll Surg, 224(6):1021-7.
M. C. Sullivan, P. H. Graham, E. K. Alexander, D. T. Ruan, M. A. Nehs, A. A. Gawande, F. D. Moore, Jr., B. E. Howitt, K. C. Strickland, J. F. Krane, J. A. Barletta and N. L. Cho. 2017.
BACKGROUND: Thyroid lobectomy alone is being performed increasingly for patients with encapsulated follicular variant of papillary thyroid carcinoma (fvPTC). However, the prevalence of contralateral disease in these patients is unknown. We investigated the presence of synchronous disease in fvPTC to improve decision

making about the extent of surgical resection and need for surveillance. STUDY DESIGN: We performed a retrospective review of patients who underwent thyroid surgery from October 2009 to February 2013 with a diagnosis of fvPTC as their primary lesion. We collected information on patient demographics, nodule size, multifocality, fine-needle aspiration results, lymphovascular invasion, extrathyroidal extension, and lymph node metastasis. Tumors were divided into noninvasive and invasive/infiltrative fvPTC categories. Characteristics of solitary and bilateral fvPTC were compared. RESULTS: We identified 124 patients with final pathology demonstrating fvPTC. The most common fine-needle aspiration diagnosis was "suspicious for malignancy" (n = 53). Sixty-five contralateral tumors were identified in 44 of 124 patients (35.5%) and included fvPTC (n = 40), classical PTC (n = 22), tall cell PTC (n = 2), and follicular carcinoma (n = 1). Fifty contralateral tumors were 1 to 5 mm, 10 measured 6 to 9 mm, and 5 were >/=10 mm. Contralateral disease correlated significantly with lymphovascular invasion (p = 0.037) and larger primary lesions (p = 0.020). There was no significant difference noted in extrathyroidal extension or lymph node metastasis. Both noninvasive and invasive/infiltrative fvPTC demonstrated similar rates of contralateral disease. CONCLUSIONS: Bilateral disease is common in fvPTC, primarily in the form of papillary microcarcinomas. Future monitoring of the contralateral lobe should be discussed with fvPTC patients who do not undergo completion thyroidectomy.
PubMed-ID: 28017809
http://dx.doi.org/10.1016/j.jamcollsurg.2016.12.007

Risk Profile of the RET A883F Germline Mutation: An International Collaborative Study.
J Clin Endocrinol Metab, 102(6):2069-74.
J. S. Mathiesen, M. A. Habra, J. H. D. Bassett, S. M. Choudhury, S. P. Balasubramanian, T. A. Howlett, B. G. Robinson, A. P. Gimenez-Roqueplo, F. Castinetti, P. Vestergaard and K. Frank-Raue. 2017.
Context: The A883F germline mutation of the rearranged during transfection (RET) proto-oncogene causes multiple endocrine neoplasia 2B. In the revised American Thyroid Association (ATA) guidelines for the management of medullary thyroid carcinoma (MTC), the A883F mutation has been reclassified from the highest to the high-risk level, although no well-defined risk profile for this mutation exists. Objective: To create a risk profile for the A883F mutation for appropriate classification among the ATA risk levels. Design: Retrospective analysis. Setting: International collaboration. Patients: Included were 13 A883F carriers. Intervention: The intervention was thyroidectomy. Main Outcome Measures: Earliest age of MTC, regional lymph node metastases, distant metastases, age-related penetrance of MTC and pheochromocytoma (PHEO), overall and disease-specific survival, and biochemical cure rate. Results: One and three carriers were diagnosed at age 7 to 9 years (median, 7.5 years) with a normal thyroid and C-cell hyperplasia, respectively. Nine carriers were diagnosed with MTC at age 10 to 39 years (median, 19 years). The earliest age of MTC, regional lymph node metastasis, and distant metastasis was 10, 20, and 20 years, respectively. Fifty percent penetrance of MTC and PHEO was achieved by age 19 and 34 years, respectively. Five- and 10-year survival rates (both overall and disease specific) were 88% and 88%, respectively. Biochemical cure for MTC at latest follow-up was achieved in 63% (five of eight carriers) with pertinent data. Conclusions: MTC of A883F carriers seems to have a more indolent natural course compared with that of M918T carriers. Our results support the classification of the A883F mutation in the ATA high-risk level.
PubMed-ID: 28323957
http://dx.doi.org/10.1210/jc.2016-3640

TERT, BRAF, and NRAS in Primary Thyroid Cancer and Metastatic Disease.
J Clin Endocrinol Metab, 102(6):1898-907.
M. Melo, A. Gaspar da Rocha, R. Batista, J. Vinagre, M. J. Martins, G. Costa, C. Ribeiro, F. Carrilho, V. Leite, C. Lobo, J. M. Cameselle-Teijeiro, B. Cavadas, L. Pereira, M. Sobrinho-Simoes and P. Soares. 2017.
Context: Little is known about the frequency of key mutations in thyroid cancer metastases and its relationship with the primary tumor genotype. Objectives: To evaluate the frequency of TERT promoter (TERTp), BRAF, and NRAS mutations in metastatic thyroid carcinomas, analyzing primary thyroid tumors, lymph node metastases (LNMs), and distant metastases. Design and Patients: Mutation analysis was performed in 437 tissue samples from 204 patients, mainly with papillary thyroid carcinomas (PTCs; n = 180), including 196 LNMs and 56 distant metastases. All the distant metastases included corresponded to radioiodine-refractory metastatic tissue. Results: We found the following mutation frequency in primary PTCs, LNMs, and distant metastases, respectively: TERTp: 12.9%, 10.5%, and 52.4%; BRAF: 44.6%, 41.7%, and 23.8%; and NRAS: 1.2%, 1.3%, and 14.3%. There was a significant concordance between the primary tumor genotype and the corresponding LNM for all the genes, in particular BRAF-mutated PTC. The overall concordance between primary tumors and respective distant metastases was low. In the group of patients with PTCs, we found a high frequency of TERTp mutations and a low frequency of BRAF mutations in distant metastases, in comparison with the paired primary tumors. When present in distant metastases, BRAF mutations frequently coexisted with TERTp mutations.

Conclusions: When the genotype of primary tumors is compared with the genotype of LNMs, the concordance is high for all the genes studied. On the other hand, distant metastases show an enrichment in TERTp mutations and a decrease in BRAF mutations. TERTp mutations may play a role in distant metastases.
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http://dx.doi.org/10.1210/jc.2016-2785

The utility of the Bethesda category and its association with BRAF mutation in the prediction of papillary thyroid cancer stage.
Langenbecks Arch Surg, 402(2):227-34.
A. Beisa, M. Kvietkauskas, V. Beisa, M. Stoskus, E. Ostaneviciute, E. Jasiunas, L. Griskevicius and K. Strupas. 2017.
PURPOSE: This study aims to determine the utility of the Bethesda category and its association with BRAF mutation in prediction of the papillary thyroid cancer (PTC) stage. METHODS: A prospective study analyzed patients who had ultrasound-suspicious thyroid nodules, underwent FNA and cytological examination, and were classified according to the Bethesda system. Patients from Undetermined Significance Or Follicular Lesion Of Undetermined Significance (AUS/FLUS), Follicular Neoplasm or Suspicious for a Follicular Neoplasm (FN/SFN), Suspicious for Malignant Cells (SMC), and Positive for Malignant Cells (PMC) groups were examined for the BRAF mutation and had a thyroid surgery. Demographical and histological features and stage of the disease were evaluated for PTC patients in accordance with the Bethesda category and its association with BRAF mutation. RESULTS: Three hundred eight of all patients underwent operation. One hundred forty-three (46.4%) of them were diagnosed with PTC. In 14 (9.8%) PTC cases, FNA biopsies were classified as AUS/FLUS, 23 (16.1%) as FN/SFN, 41 (28.7%) as SMC, and 65 (45.5%) as PMC. I-II stages of PTC were diagnosed for 88 (61.5%) patients and III-IVA for 55 (38.5%). Patients from the SMC and PMC groups had larger tumors, higher incidence of lymph node metastases, classical PTC type, B-type Raf (BRAF) positive, and III-IVA stage cancer, than patients from the AUS/FLUS and FN/SFN groups. When comparing 27 (18.9%) BRAF-negative patients from the AUS/FLUS and FN/SFN groups with 116 (81.1%) BRAF-negative patients from the SMC and PMC groups and all BRAF-positive patients, the prediction of more aggressive histological features and stage was slightly improved. CONCLUSIONS: Higher Bethesda categories are associated with higher stages of PTC. Association of the Bethesda category with BRAF mutation can slightly improve the value of stage prediction.
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http://dx.doi.org/10.1007/s00423-017-1560-2

Hypoparathyroidism after total thyroidectomy in patients with previous gastric bypass.
Langenbecks Arch Surg, 402(2):273-80.
R. A. Droeser, J. Ottosson, A. Muth, H. Hultin, K. Lindwall-Ahlander, A. Bergenfelz and M. Almquist. 2017.
PURPOSE: Case reports suggest that patients with previous gastric bypass have an increased risk of severe hypocalcemia after total thyroidectomy, but there are no population-based studies. The prevalence of gastric bypass before thyroidectomy and the risk of hypocalcemia after thyroidectomy in patients with previous gastric bypass were investigated. METHODS: By cross-linking The Scandinavian Quality Registry for Thyroid, Parathyroid and Adrenal Surgery with the Scandinavian Obesity Surgery Registry patients operated with total thyroidectomy without concurrent or previous surgery for hyperparathyroidism were identified and grouped according to previous gastric bypass. The risk of treatment with intravenous calcium during hospital stay, and with oral calcium and vitamin D at 6 weeks and 6 months postoperatively was calculated by using multiple logistic regression in the overall cohort and in a 1:1 nested case-control analysis. RESULTS: We identified 6115 patients treated with total thyroidectomy. Out of these, 25 (0.4 %) had undergone previous gastric bypass surgery. In logistic regression, previous gastric bypass was not associated with treatment with i.v. calcium (OR 2.05, 95 % CI 0.48-8.74), or calcium and/or vitamin D at 6 weeks (1.14 (0.39-3.35), 1.31 (0.39-4.42)) or 6 months after total thyroidectomy (1.71 (0.40-7.32), 2.28 (0.53-9.75)). In the nested case-control analysis, rates of treatment for hypocalcemia were similar in patients with and without previous gastric bypass. CONCLUSION: Previous gastric bypass surgery was infrequent in patients undergoing total thyroidectomy and was not associated with an increased risk of postoperative hypocalcemia.
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http://dx.doi.org/10.1007/s00423-016-1517-x

Prognostic Significance of the Proportion of Tall Cell Components in Papillary Thyroid Carcinoma.
World J Surg, 41(3):742-7.
Y. Ito, M. Hirokawa, A. Miyauchi, T. Higashiyama, M. Kihara and A. Miya. 2017.
AIM: Tall cell variant (TCV) of papillary thyroid carcinoma (PTC) shows a poorer prognosis than conventional PTC. The World Health Organization (WHO) classification defines TCV as the tall cell component (TCC) in

>/=50% of PTC lesions. We investigated whether and how the proportion of TCC affects the prognosis of patients with PTC with TCC. PATIENTS AND METHODS: Seventy patients with TCC in >/=30% of their PTC lesions and 210 age- and gender-matched controls with no TCC who underwent locally curative surgery at Kuma Hospital (2006-2014) were enrolled. The 70 PTC patients were divided into two categories: TCC >/=50% (TCC-major, n = 19) and TCC 30-49% (TCC-minor, n = 51). We performed univariate and multivariate analyses of the relationships between disease-free survival (DFS) and variables including the TCC proportion in 276 patients who had no distant metastases at surgery (median follow-up 64 months). RESULTS: In the univariate analysis, TCC-major, TCC-minor, old age (>/=65 years), clinical node metastasis, significant extrathyroid extension (Ex), and high Ki-67 labeling index (>/=5%) significantly affected the DFS. In the multivariate analysis, TCC-major and Ex independently affected the DFS, but TCC-minor did not. In an analysis excluding TCC-major patients, TCC-minor was not an independent prognostic factor for DFS. CONCLUSIONS: Studies or larger patient series with longer follow-ups are necessary, but we speculate that in PTC with TCC, TCC-major significantly and independently affects the DFS, whereas TCC-minor does not. Our findings indicate that the WHO definition of TCV is appropriate and that the prognostic impact of TCC-minor is limited.
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http://dx.doi.org/10.1007/s00268-016-3784-7

Role of immediate recurrent laryngeal nerve reconstruction in surgery for thyroid cancers with fixed vocal cords.
Head Neck, 39(3):427-31.
S. Iwaki, T. Maeda, M. Saito, N. Otsuki, M. Takahashi, E. Wakui, H. Shinomiya, K. Morimoto, H. Inoue, H. Masuoka, A. Miyauchi and K. I. Nibu. 2017.
BACKGROUND: Quality of voice after immediate recurrent laryngeal nerve (RLN) reconstruction in thyroid cancers has not been thoroughly studied. METHODS: Thirteen patients with fixed vocal cords (fixed vocal cord group) and 8 patients with intact or impaired mobile vocal cords (mobile vocal cord group) who had immediate RLN reconstruction simultaneously with total thyroidectomy, and patients who had arytenoid adduction and thyroplasty for vocal cord paralysis caused by previous surgery (arytenoid adduction thyroplasty group) were enrolled in this study. RESULTS: Preoperative phonation efficiency index was significantly lower (p = .008) in the fixed vocal cord group than in the mobile vocal cord group. One year after surgery, all voice parameters of the patients in the fixed vocal cord group had improved, compared with their preoperative data. The fixed vocal cord group had attained satisfactory voice qualities equivalent to those of the mobile vocal cord group in terms of various voice parameters. CONCLUSION: The present results support the idea that immediate RLN reconstruction at the time of surgery for thyroid cancers may spare the need for subsequent arytenoid adduction thyroplasty even in the patients with preoperatively fixed vocal cords. (c) 2016 Wiley Periodicals, Inc. Head Neck 39: 427-431, 2017.
PubMed-ID: 27997055
http://dx.doi.org/10.1002/hed.24627

The need of prophylactic central lymph node dissection is controversial in terms of postoperative thyroglobulin follow-up of patients with cN0 papillary thyroid cancer.
Langenbecks Arch Surg, 402(2):235-42.
M. H. Korkmaz, B. Ocal, G. Saylam, E. Cakal, O. Bayir, E. Tutal and E. C. Tatar. 2017.
PURPOSE: The objective of this study was to investigate whether prophylactic central lymph node dissection (pCLND) facilitates postoperative thyroglobulin (Tg) follow-up in the patients with papillary thyroid carcinoma (PTC). We also questioned whether radioactive iodine (RAI) remnant ablation provides any further advantage in this regard. METHODS: The records of patients with low-intermediate risk PTC who underwent either only total thyroidectomy (TT) or TT in conjunction with pCLND were reviewed. Adjuvant RAI ablation was performed depending on tumor diameter, multifocality, the presence of positive lymph nodes and adverse histopathologic features. Pre-ablative and post-ablative Tg levels, post-operative complications and clinico-pathological characteristics were compared between the two groups (TT alone and TT with pCLND). RESULTS: Among the 302 patients, TT was performed in 140 (46.4%) and TT with pCLND in 162 (53.6%). More than half of all patients in both groups had papillary microcarcinoma (58.0% and 53,1%, respectively). Postoperatively, the median preablative Tg level was higher in the TT only group than that of the TT with pCLND group (0.96 vs 0.27 ng/ml, respectively). The post-ablative Tg levels were undetectable in both groups at the last follow-up visit. Also, a subgroup of patients (19.5%) who did not receive RAI ablation all became athyroglobulinemic at one year after surgery. CONCLUSIONS: Although performing pCLND with TT seems to have an advantage over TT alone as to achieve lower Tg levels in the early post-operative period, Tg levels become comparable following RAI ablation. On the other hand, the patients who have not been treated with adjuvant RAI ablation, also became athyroglobulinemic regardless of the surgical method.

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http://dx.doi.org/10.1007/s00423-017-1556-y

The electrophysiology of thyroid surgery: electrophysiologic and muscular responses with stimulation of the vagus nerve, recurrent laryngeal nerve, and external branch of the superior laryngeal nerve.
Laryngoscope, 127(3):764-71.
W. Liddy, S. R. Barber, M. Cinquepalmi, B. M. Lin, S. Patricio, N. Kyriazidis, C. Bellotti, D. Kamani, S. Mahamad, H. Dralle, R. Schneider, G. Dionigi, M. Barczynski, C. W. Wu, F. Y. Chiang and G. Randolph. 2017.
OBJECTIVES/HYPOTHESIS: Correlation of physiologically important electromyographic (EMG) waveforms with demonstrable muscle activation is important for the reliable interpretation of evoked waveforms during intraoperative neural monitoring (IONM) of the vagus nerve, recurrent laryngeal nerve (RLN), and external branch of the superior laryngeal nerve (EBSLN) in thyroid surgery. STUDY DESIGN: Retrospective chart review. METHODS: Data were reviewed retrospectively for thyroid surgery patients with laryngeal nerve IONM from January to December, 2015. EMG responses to monopolar stimulation of the vagus/RLN and EBSLN were recorded in bilateral vocalis, cricothyroid (CTM), and strap muscles using endotracheal tube-based surface and intramuscular hook electrodes, respectively. Target muscles for vagal/RLN and EBSLN stimulation were the ipsilateral vocalis and CTM, respectively. All other recording channels were nontarget muscles. RESULTS: Fifty surgical sides were identified in 37 subjects. All target muscle mean amplitudes were significantly higher than in nontarget muscles. With vagal/RLN stimulation, target ipsilateral vocalis mean amplitude was 1,095.7 muV (mean difference range = -814.1 to -1,078 muV, P < .0001). For EBSLN stimulation, target ipsilateral CTM mean amplitude was 6,379.3 muV (mean difference range = -6,222.6 to -6,362.3 muV, P < .0001). Target muscle large-amplitude EMG responses correlated with meaningful visual or palpable muscular responses, whereas nontarget EMG responses showed no meaningful muscle activation. CONCLUSIONS: Target and nontarget laryngeal muscles are differentiated based on divergence of EMG response directly correlating with presence or absence of visual and palpable muscle activation. Low-amplitude EMG waveforms in nontarget muscles with neural stimulation can be explained by the concept of far-field artifactual waveforms and do not correspond to a true muscular response. The surgeon should be aware of these nonphysiologic waveforms when interpreting and applying IONM during thyroid surgery. LEVEL OF EVIDENCE: 4 Laryngoscope, 127:764-771, 2017.
PubMed-ID: 27374859
http://dx.doi.org/10.1002/lary.26147

Failure of fragmented parathyroid gland autotransplantation to prevent permanent hypoparathyroidism after total thyroidectomy.
Langenbecks Arch Surg, 402(2):281-7.
L. Lorente-Poch, J. Sancho, J. L. Munoz, L. Gallego-Otaegui, C. Martinez-Ruiz and A. Sitges-Serra. 2017.
PURPOSE: Parathyroid autotransplantation during total thyroidectomy leads to higher rates of postoperative hypocalcaemia. It has been argued, however, that it prevents permanent hypoparathyroidism. The impact of autografted normal parathyroid gland fragments on long-term parathyroid status has not been assessed properly. To clarify this, the short- and long-term parathyroid function was assessed in patients with three glands remaining in situ after total thyroidectomy, in whom the fourth gland was either autotransplanted (Tx) or accidentally resected (AR). METHODS: Consecutive patients (n = 669) undergoing first-time total thyroidectomy were prospectively studied recording the number of parathyroid glands remaining in situ: PGRIS =4-(glands autografted + glands in the specimen). The study was focused on the subgroup of 186 patients with three parathyroid glands remaining in situ as a result of either accidental resection (AR, n = 76) or autotransplantation into the sternocleidomastoid muscle (Tx, n = 110). Prevalence of postoperative hypocalcaemia, protracted, and permanent hypoparathyroidism were compared between the two groups. Demographic, disease-related, laboratory, and surgical variables were recorded. All patients were followed for at least 1 year. RESULTS: Both groups were comparable in terms of disease and extent of surgery. Mean postoperative serum calcium was the same (AR: 1.97 +/- 0.2 vs Tx: 1.97 +/- 0.22 mmol/L). Rates of protracted (AR: 24% vs Tx: 25.5%) and permanent hypoparathyroidism (AR: 5.3% vs Tx: 7.3%) were similar in both groups. CONCLUSIONS: The prevalence of parathyroid failure syndromes after total thyroidectomy was similar whether a parathyroid gland was inadvertently excised or autotransplanted. Autotransplantation did not influence the permanent hypoparathyroidism rate.
PubMed-ID: 28064342
http://dx.doi.org/10.1007/s00423-016-1548-3

The advantages of extended subplatysmal dissection in thyroid surgery-the "mobile window" technique.
Langenbecks Arch Surg, 402(2):257-63.
T. Runge, R. Inglin, P. Riss, A. Selberherr, R. M. Kaderli, D. Candinas and C. A. Seiler. 2017.
PURPOSE: Minimal access thyroidectomy, using various techniques, is widely known, but respective data on thyroidectomy for thyroid cancer with lymphadenectomy is scarce. The present study aims to evaluate the feasability of extended subplatysmal dissection in combination with a small incision ("mobile window" technique). METHODS: A retrospective study was performed analysing data from 93 patients. All patients suffered from thyroid carcinoma and underwent (total) thyroidectomy, bilateral cervico-central (levels VI and VII) and functional lateral neck dissection (levels II to V) on the side of the malignancy. In group A, consisting of 47 patients, the operation was performed by a traditional Kocher incision (minimal range 6-7 cm), in 46 patients (group B) a mini-incision (</=4 cm) was made. Intra- and postoperative morbidity as well as oncological accuracy were assessed. RESULTS: There was no significant difference between the two groups comparing postoperative pathological diagnosis, intra- and postoperative complications and the number of removed lymph nodes. However, operating time was slightly longer in group A and thyroid weight was heavier in group B. CONCLUSIONS: Extended subplatymsal dissection allows thyroidectomy and even lateral lymphadenectomy for thyroid carcinoma via "mobile" mini-incision. The procedure is safe, of equivalent oncological accuracy compared to traditional incision and the cosmetic results are excellent.
PubMed-ID: 28050728
http://dx.doi.org/10.1007/s00423-016-1545-6

Are large thyroid nodules classified as benign on fine needle aspiration more likely to harbor cancer?
Am J Surg, 213(3):464-6.
H. Shi, I. Bobanga and C. R. McHenry. 2017.
INTRODUCTION: Our aim was to investigate whether benign thyroid nodules >/= 4 cm have a higher malignancy rate. METHODS: A retrospective review of patients with a nodule and a benign FNAB who underwent thyroidectomy was completed. Patients were divided into two groups; nodule size: < 4 cm or >/=4 cm, and clinical factors, nodule size and rates of malignancy were compared. RESULTS: 337 patients underwent thyroidectomy: 99 had nodules <4 cm (2.8 +/- 0.58 cm) and 238 had nodules >/= 4 cm (5.9 +/- 1.97 cm). Seven (2.1%) patients had cancer, 2 (2.0%) with a nodule < 4 cm and 5 (2.1%) with a nodule >/= 4 cm (p = 0.962). There was no difference in clinical factors between groups (p > 0.05). CONCLUSION: There is no difference in rates of malignancy for nodules < 4 cm or >/= 4 cm. Thus, thyroidectomy should not be recommended based solely on nodule size.
PubMed-ID: 28057295
http://dx.doi.org/10.1016/j.amjsurg.2016.10.028

Low-risk papillary microcarcinoma of the thyroid: A review of active surveillance trials.
Eur J Surg Oncol,
Y. Ito, A. Miyauchi and H. Oda. 2017.
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

Patterns of Treatment Failure in Anaplastic Thyroid Carcinoma.
Thyroid, 27(5):672-81.
S. N. Rao, M. Zafereo, R. Dadu, N. L. Busaidy, K. Hess, G. J. Cote, M. D. Williams, W. N. William, V. Sandulache, N. Gross, G. B. Gunn, C. Lu, R. Ferrarotto, S. Y. Lai and M. E. Cabanillas. 2017.
BACKGROUND: Anaplastic thyroid cancer (ATC) is one of the most lethal forms of cancer with a high mortality rate. Current guidelines support surgery for resectable ATC followed by external beam radiation therapy (EBRT) with or without chemotherapy. Treatment for those who are unresectable is palliative. Our goal was to examine first-line therapies as well as the role of genomic profiling in an effort better understand how to approach ATC. METHODS: This is a retrospective study of ATC patients who were seen at our institution from January 2013 to October 2015. Median overall survival (OS) and time to treatment failure (TTF) were calculated by the Kaplan-Meier method. RESULTS: Fifty-four patients were included. Median age at diagnosis was 63 years and 29/54 (54%) were women. The majority had stage IVC disease at diagnosis (50%), followed by IVB (32%), and IVA (18%). Approximately 93% had somatic gene testing. Initial treatment was surgery in 23 patients, EBRT with or without radiosensitizing chemotherapy in 29 patients, and systemic chemotherapy in 2 patients. Nineteen patients had all three treatment modalities. For the entire cohort, median OS was 11.9 months with 39% survival at 1 year and median TTF was 3.8 months. The majority of patients (74%) developed new distant metastasis or progression of existing metastatic disease. Patients who received trimodal therapy consisting of surgery, EBRT, and chemotherapy had a median OS of 22.1 months versus 6.5 months in those who received dual therapy with EBRT and chemotherapy ($p = 0.0008$). The TTF was the same in the two groups (7.0 and 6.5 months, respectively). Men were three times more likely to die from ATC than women ($p = 0.0024$). No differences in OS or TTF were noted based on tumor size (5 cm cutoff), age (60 years cutoff), or presence of any mutation. There was a trend toward shorter TTF in patients with somatic mutations in TP53. CONCLUSION: Patients with ATC amenable to aggressive tri-modal therapy demonstrate improved survival. The short TTF, due primarily to distant metastatic disease, highlights the potential opportunity for improved outcomes with earlier initiation of systemic therapy including adjuvant or neoadjuvant therapy.
PubMed-ID: 28068873
http://dx.doi.org/10.1089/thy.2016.0395

Staged Surgery for Advanced Thyroid Cancers: Safety and Oncologic Outcomes of Neural Monitored Surgery.
Otolaryngol Head Neck Surg, 156(5):816-21.
B. Salari, R. J. Hammon, D. Kamani and G. W. Randolph. 2017.
Objective Thyroidectomy with extensive multicompartment bilateral neck dissections for advanced-stage thyroid cancer may lead to increased risk of complications, including bilateral recurrent laryngeal nerve (RLN) paralysis and hypoparathyroidism. A planned staged approach derived from a detailed preoperative radiographic map is associated with a low complication profile. This study evaluates oncologic results and safety of neural monitored, staged thyroid cancer surgery for management of advanced thyroid cancer. Study Design Case series with chart review. Setting Tertiary care center. Subjects and Methods With institutional review board approval, 35 consecutive patients with advanced thyroid malignancy and extensive nodal disease managed with staged surgery between January 2004 and May 2013 by the senior author (G.W.R.) were identified, and the oncologic and surgical outcomes were reviewed. Results In total, 37.2% of patients had stage III or IV disease, with extrathyroidal extension in 71.4%, vascular invasion in 51.4%, and RLN invasion in 17% of patients. A total of 34% patients had positive lymph nodes in more than 5 nodal compartments; the average positive lymph node yield was 17, and extranodal extension was present in 51%. Three patients had RLN sacrifice, and there were no other cases of temporary or permanent RLN paralysis; permanent hypoparathyroidism and chyle leak occurred in one patient each. Locoregional recurrence occurred in 5.7% of patients after a 147-week mean follow-up. In patients with papillary thyroid carcinoma, median postoperative nonstimulated and stimulated thyroglobulin levels were 0.2 and 0.75 ng/mL, respectively. Conclusion A neural monitored, staged surgical approach was conducted without significant adverse events in this small sample and represents and effective alternative strategy option to simultaneous bilateral surgery in the management of thyroid cancer with extensive neck metastases.
PubMed-ID: 28374646
http://dx.doi.org/10.1177/0194599817697189

Parathyroids

Meta-Analyses

- None -

Randomized controlled trials

- None -

Consensus Statements/Guidelines

- None -

Other Articles

Intraoperative Parathyroid Hormone Levels at 5 min Can Identify Multigland Disease.
Ann Surg Oncol, 24(3):733-8.
A. Alhefdhi, K. Ahmad, R. Sippel, H. Chen and D. F. Schneider. 2017.
BACKGROUND: Intraoperative parathyroid hormone (IOPTH) monitoring is crucial in the treatment of primary hyperparathyroidism (PHPT). Often, the 5 min IOPTH levels fall, but not by the requisite 50 %. In such cases, the surgeon must decide whether to wait for additional levels or to continue exploration. This study aimed to evaluate the 5 min drop in IOPTH for distinguishing single adenomas (SA) from multigland disease. METHODS: A retrospective analysis of a prospectively collected database was performed on PHPT patients who underwent initial curative parathyroidectomy between 2001 and 2013. Those with familial disease and those taking lithium or undergoing concomitant thyroidectomy were excluded from the analysis. For cases of double adenomas (DA) or hyperplasia (HA), the IOPTH values indicating additional glands were analyzed. RESULTS: The inclusion criteria were met by 1021 patients: 817 patients with SA (82.2 %), 99 patients with DA (10 %), and 78 with HA (7.9 %). The SA patients exhibited a 56.6 +/- 4.9 % decline in IOPTH at 5 min compared with 21.3 +/- 4.5 % of the DA patients and 22.5 +/- 4.3 % of the HA patients ($p < 0.01$). Post hoc comparisons showed that the 5 min decrease in the SA group was significantly greater than in either the DA group or the HA group ($p < 0.01$). A 5 min percentage decline of 35 % best distinguished SA from multiglandular disease (85.3 vs. 24.9 %). CONCLUSION: The data suggest that when IOPTH level does not drop by at least 35 % at 5 min after excision, the surgeon should consider further exploration rather than wait for additional levels.
PubMed-ID: 27743228
http://dx.doi.org/10.1245/s10434-016-5617-1

Normohormonal primary hyperparathyroidism is a distinct form of primary hyperparathyroidism.
Surgery, 161(1):62-9.
M. K. Applewhite, M. G. White, J. Tseng, M. K. Mohammed, F. Mercier, E. L. Kaplan, P. Angelos, T. Vokes and R. H. Grogan. 2017.
BACKGROUND: Normohormonal primary hyperparathyroidism presents diagnostic and intraoperative challenges, and current literature is conflicting about management. We aim to better define normohormonal primary hyperparathyroidism in order to improve the care for these patients. METHODS: In the study, 516 consecutive patients undergoing parathyroidectomy for primary hyperparathyroidism were divided into 2 groups: classic primary hyperparathyroidism (classic primary hyperparathyroidism, increased serum levels of calcium, and parathyroid hormone) and normohormonal primary hyperparathyroidism (hypercalcemia, normal serum levels of parathyroid hormone). We evaluated inter-group differences in presentation, gland weight, pathology, and complications. RESULTS: The normohormonal primary hyperparathyroidism group was comprised of 116 (22.5%) patients. Mean serum levels of parathyroid hormone and calcium were 62.1 pg/mL +/- 10.1 and 10.6

mg/dL +/- 0.63 in normohormonal primary hyperparathyroidism, and 142 +/- 89.0pg/mL and 11.0 +/- 0.88 (both P < .01) for classic primary hyperparathyroidism. Nephrolithiasis was more common in normohormonal primary hyperparathyroidism. Multigland hyperplasia was more common in normohormonal primary hyperparathyroidism 23 (19.8%) vs 44 (11%; P = .04). Concordant imaging studies were less likely in normohormonal primary hyperparathyroidism (82 [73.2%] vs 337 [87.1%; P < .01]), had a lesser total gland weight (531.8 mg +/- 680.0 vs 1,039.6 mg +/- 1,237.3; P < .01), and lesser 2-week parathyroid hormone (32.5 pg/mL +/- 18.95 vs 41.0 pg/mL +/- 27.8; P = .01). There was no difference in hypoparathyroidism (parathyroid hormone <15 pg/mL; P = .93) at 2 weeks postoperatively. CONCLUSION: Normohormonal primary hyperparathyroidism represents 22.5% of our primary hyperparathyroidism population, which is greater than reported previously. It is a distinct disease process from classic primary hyperparathyroidism in presentation, imaging, and operative findings. More hyperplasia and a lesser gland weight make it challenging to resect the ideal amount of tissue. Studies with long-term follow-up are needed to determine optimal operative management.
PubMed-ID: 27866715
http://dx.doi.org/10.1016/j.surg.2016.03.038

Cost-benefit analysis of the intraoperative parathyroid hormone assay in primary hyperparathyroidism.
Head Neck, 39(2):241-6.
B. Badii, F. Staderini, C. Foppa, L. Tofani, I. Skalamera, G. Fiorenza, E. Qirici, F. Cianchi and G. Perigli. 2017.
BACKGROUND: The purpose of this study was to evaluate the usefulness of the routine intraoperative intact parathyroid hormone (IOPTH) assay, the role of unilateral and bilateral cervical exploration and of preoperative imaging, and to do a cost-benefit analysis in parathyroidectomy for primary hyperparathyroidism. METHODS: Two hundred sixty-four patients who underwent operations between January 2000 and March 2015 were retrospectively divided into 2 groups. RESULTS: Group A (IOPTH) was composed of 64 patients. Ultrasonography and technetium-99m-sestamibi (MIBI) identified the adenoma in 38 cases. Bilateral exploration was performed in 43 patients; of which 2 failures occurred. The IOPTH false-negative rate was 18.4%. The average cost was euro1297.30. Group B (without IOPTH) was composed of 200 patients. Ultrasonography and MIBI identified the adenoma in 113 cases. Bilateral exploration was performed in 129 patients; of which 2 failures occurred. The average cost was euro618.75. CONCLUSION: The IOPTH assay should be used only in few selected cases because of its high cost. The experience of the team is essential to obtain a high cure rate. (c) 2016 Wiley Periodicals, Inc. Head Neck 39: 241-246, 2017.
PubMed-ID: 27557453
http://dx.doi.org/10.1002/hed.24567

Is intraoperative parathyroid hormone monitoring necessary for primary hyperparathyroidism with concordant preoperative imaging?
Am J Surg, 213(3):484-8.
I. D. Bobanga and C. R. McHenry. 2017.
BACKGROUND: The purpose of this study was to determine if intraoperative parathyroid hormone (PTH) monitoring is necessary in patients with concordant ultrasound and sestamibi imaging. METHODS: Clinical factors, intraoperative findings and outcome were correlated with imaging results in patients with primary hyperparathyroidism who underwent parathyroidectomy with concordant ultrasound and sestamibi imaging. RESULTS: There were 127 patients with primary hyperparathyroidism and concordant imaging who underwent parathyroidectomy. Seven patients (5.5%) had intraoperative findings that were discordant with imaging: 2 (1.6%) had an adenoma at a different location, 2 (1.6%) had double adenomas and 3 (2.4%) had asymmetric hyperplasia. Gland weight and preoperative PTH levels were greater for patients with concordant operative and imaging findings ($p < 0.05$). CONCLUSION: Six percent of patients with concordant ultrasound and sestamibi imaging had unexpected intraoperative findings. Intraoperative PTH monitoring remains a necessary adjunct even with concordant imaging to ensure identification of abnormal parathyroid glands and cure of hyperparathyroidism.
PubMed-ID: 28017299
http://dx.doi.org/10.1016/j.amjsurg.2016.11.035

Concentration of serum calcium is not correlated with symptoms or severity of primary hyperparathyroidism: An examination of 20,081 consecutive adults.
Surgery, 161(1):98-106.
D. Boone, D. Politz, J. Lopez, J. Mitchell, K. Parrack and J. Norman. 2017.
BACKGROUND: Guidelines for operative treatment of primary hyperparathyroidism include calcium levels >1 mg/dL above normal. We sought to determine whether greater calcium concentrations were associated with increased symptoms or disease severity. METHODS: A retrospective review of a prospectively maintained

database of adults undergoing parathyroidectomy for primary hyperparathyroidism, grouped according to greatest preoperative calcium level: those patients with calcium concentrations between 10.0 and 11.0 mg/dL and those with >11.0 mg/dL. We compared subjective symptoms and objective measures of disease severity. RESULTS: The review included 20,081 adults who were split nearly evenly between calcium concentrations between 10.0 and 11.0 (10,430, 51.9%) and those with >11.0 mg/dL (9,651, 48.1%). In both groups, an absence of symptoms related to primary hyperparathyroidism was uncommon (<5%). All subjective and objective measures of disease severity were nearly identical with no significant differences (percentages for calcium concentrations between 10.0 and 11.0 and those with >11.0 mg/dL, respectively), including fatigue (72% for both groups), heartburn (37% vs 34%), bone pain (50% vs 48%), sleep disturbances (68% vs 65%), osteoporosis (40% in both groups), kidney stones (21% vs 22%), chronic kidney disease with glomerular filtration rate <60 (29% vs 32%), and hypertension (50% vs 53%). CONCLUSION: Serum calcium concentrations of greater than or less than 11 mg/dL are unrelated to symptoms and disease severity in primary hyperparathyroidism. There is no evidence to support a serum calcium threshold in parathyroidectomy guidelines.
PubMed-ID: 27863777
http://dx.doi.org/10.1016/j.surg.2016.09.012

Ultrasound based focused neck exploration for primary hyperparathyroidism.
Am J Surg, 213(3):452-5.
S. J. Bradley and K. F. Knodle. 2017.
OBJECTIVE: We review our experience with focused neck exploration (FNE) based on ultrasound (USN) alone, in patients with primary hyperparathyroidism (PHP) and negative sestamibi scans (SES). METHODS: 124 patients with PHP were evaluated for FNE and studied with SES and USN. 53 patients (43%) had a negative SES. 49 of those patients (92%) were selected for FNE based on USN criteria of a single abnormal gland, .5 cm or greater, as determined by an experienced surgeon-sonographer. RESULTS: 40 of 49 patients (82%) selected on USN criteria alone underwent successful FNE. Of the 9 patients who required neck exploration 6 (12%) were incorrectly localized, 2 (4%) were found to have hyperplasia, and 1 (2%) was correctly localized but not found on the initial exploration. US had a 97.5% sensitivity and a 25% specificity as a diagnostic test for single adenomas, both within the 95% confidence interval. Of those glands successfully imaged by USN, image size correlated well with the measured size of the adenoma at path, on average within 0.40 cm (Standard deviation 0.30 cm). CONCLUSION: We feel our data show that USN provides reliable information in patient selection for FNE. The literature supports SES as a more reliable study when positive for parathyroid adenoma, but false negative rates of 30-40% have been reported. Routine use of preoperative US by experienced surgeon-sonographers would result in more patients selected for FNE vs. routine neck exploration with expected benefits.
PubMed-ID: 27939023
http://dx.doi.org/10.1016/j.amjsurg.2016.11.025

Association between clinical variables and mortality after parathyroidectomy in maintenance hemodialysis patients.
Am J Surg, 213(1):140-5.
J. B. Chen, F. F. Chou, C. H. Yang and M. S. Hua. 2017.
BACKGROUND: We investigated factors associated with all-cause mortality and cardiovascular disease (CVD)-associated mortality after parathyroidectomy (PTX) in patients on maintenance hemodialysis (HD). METHODS: Our study population consisted of 161 consecutive HD patients who underwent PTX before 2009 and 354 consecutive HD patients without PTX as controls from those visiting the Kaohsiung Chang Gung Memorial Hospital, Taiwan between 2009 and 2013. All-cause and CVD mortality with clinical variables were compared in PTX and non-PTX HD patients. RESULTS: PTX patients had significantly lower all-cause and CVD mortality than controls. Multivariate logistic regression analyses showed PTX patients had a lower odds ratio for all-cause mortality than those without (odds ratio = .35, 95% confidence interval = .16 to .74). Association analysis based on clinical variables revealed patients with higher hemoglobin, albumin, creatinine, and HD adequacy index-Kt/V levels had significantly decreased risk of all-cause mortality. CONCLUSIONS: PTX in HD patients reduces the risk of death.
PubMed-ID: 27469221
http://dx.doi.org/10.1016/j.amjsurg.2016.03.012

Primary hyperparathyroidism with normal baseline intraoperative parathyroid hormone: A challenging population.
Surgery, 161(2):493-8.
M. Javid, G. Callender, C. Quinn, T. Carling, P. Donovan and R. Udelsman. 2017.
BACKGROUND: Patients with primary hyperparathyroidism and baseline intraoperative parathyroid hormone

levels in the normal range are challenging. This study compares the predictive value of a commonly used intraoperative parathyroid hormone algorithm, a software model for cure prediction, and surgeon judgment in this population. METHODS: This was a retrospective review of consecutive patients who underwent parathyroidectomy for primary hyperparathyroidism at a single institution from March 2013 to October 2014. RESULTS: Of 541 operative patients, 114 (21.1%) had a mean normal baseline intraoperative parathyroid hormone of </=69 pg/mL (median 59.0 +/- 10.3; range 26-69). Of the 114 patients, 93 (81.6%) were women, median age was 61 years (range 18-88). Overall, 107/108 (99.1%) patients were cured; 47 (41.2%) patients had single adenomas, 16 (14%) had double adenomas, and 51 (44.7%) had multigland hyperplasia. Using the 50% decline algorithm, a correct prediction was made in 86 (75.4%) patients. Using the computer software, a correct prediction was made in 88 (77.2%) patients. Surgeon judgment, however, was 99.1% accurate. CONCLUSION: Patients with normal baseline intraoperative parathyroid hormone have a high incidence of multigland disease (58.8%), greater than reported previously. Current software modeling and the 50% decline algorithm are insufficient to predict cure in this population; intraoperative parathyroid hormone interpretation combined with operative findings and surgical judgment yield optimal outcomes.
PubMed-ID: 27712879
http://dx.doi.org/10.1016/j.surg.2016.08.018

The utility of repeat sestamibi scans in patients with primary hyperparathyroidism after an initial negative scan.
Surgery, 161(6):1651-8.
V. D. Krishnamurthy, S. Sound, A. K. Okoh, P. Yazici, H. Yigitbas, D. Neumann, K. Doshi and E. Berber. 2017.
BACKGROUND: We analyzed the utility of repeated sestambi scans in patients with primary hyperparathyroidism and its effects on operative referral. METHODS: We carried out a retrospective review of patients with primary hyperparathyroidism who underwent repeated sestambi scans exclusively within our health system between 1996-2015. Patient demographic, presentation, laboratory, imaging, operative, and pathologic data were reviewed. Univariate analysis with JMP Pro v12 was used to identify factors associated with conversion from an initial negative to a subsequent positive scan. RESULTS: After exclusion criteria (including reoperations), we identified 49 patients in whom 59% (n = 29) of subsequent scans remained negative and 41% (n = 20) converted to positive. Factors associated with an initial negative to a subsequent positive scan included classic presentation and second scans with iodine subtraction (P = .04). Nonsurgeons were less likely to order an iodine-subtraction scan (P < .05). Fewer patients with negative imaging were referred to surgery (33% vs 100%, P = .005), and median time to operation after the first negative scan was 25 months (range 1.4-119). Surgeon-performed ultrasonography had greater sensitivity and positive predictive value than repeated sestamibi scans. CONCLUSION: Negative sestambi scans decreased and delayed operative referral. Consequently, we identified several process improvement initiatives, including education regarding superior institutional imaging. Combining all findings, we created an algorithm for evaluating patients with primary hyperparathyroidism after initially negative sestamibi scans, which incorporates surgeon-performed ultrasonography.
PubMed-ID: 28108033
http://dx.doi.org/10.1016/j.surg.2016.11.019

Indocyanine green fluorescence angiography for quantitative evaluation of in situ parathyroid gland perfusion and function after total thyroidectomy.
Surgery, 161(1):87-95.
B. H. Lang, C. K. Wong, H. T. Hung, K. P. Wong, K. L. Mak and K. B. Au. 2017.
BACKGROUND: Because the fluorescent light intensity on an indocyanine green fluorescence angiography reflects the blood perfusion within a focused area, the fluorescent light intensity in the remaining in situ parathyroid glands may predict postoperative hypocalcemia risk after total thyroidectomy. METHODS: Seventy patients underwent intraoperative indocyanine green fluorescence angiography after total thyroidectomy. Any parathyroid glands with a vascular pedicle was left in situ while any parathyroid glands without pedicle or inadvertently removed was autotransplanted. After total thyroidectomy, an intravenous 2.5 mg indocyanine green fluorescence angiography was given and real-time fluorescent images of the thyroid bed were recorded using the SPY imaging system (Novadaq, Ontario, Canada). The fluorescent light intensity of each indocyanine green fluorescence angiography as well as the average and greatest fluorescent light intensity in each patient were calculated. Postoperative hypocalcemia was defined as adjusted calcium <2.00 mmol/L within 24 hours. RESULTS: The fluorescent light intensity between discolored and normal-looking indocyanine green fluorescence angiographies was similar (P = .479). No patients with a greatest fluorescent light intensity >150% developed postoperative hypocalcemia while 9 (81.8%) patients with a greatest fluorescent light intensity </=150% did. Similarly, no patients with an average fluorescent light intensity >109% developed PH while 9

(30%) with an average fluorescent light intensity </=109% did. The greatest fluorescent light intensity was more predictive than day-0 postoperative hypocalcemia (P = .027) and % PTH drop day-0 to 1 (P < .001). CONCLUSION: Indocyanine green fluorescence angiography is a promising operative adjunct in determining residual parathyroid glands function and predicting postoperative hypocalcemia risk after total thyroidectomy.
PubMed-ID: 27839936
http://dx.doi.org/10.1016/j.surg.2016.03.037

How long should we follow patients after apparently curative parathyroidectomy?
Surgery, 161(1):54-61.
I. Lou, C. Balentine, S. Clarkson, D. F. Schneider, R. S. Sippel and H. Chen. 2017.
BACKGROUND: Little is known about the long-term recurrence risk for primary hyperparathyroidism after immediately "curative" parathyroidectomy. This study aimed to evaluate the risk of recurrent hyperparathyroidism in the 10 years after operation. METHOD: We retrospectively identified patients with sporadic primary hyperparathyroidism undergoing initial parathyroidectomy between November 1, 2000 and June 30, 2005. Recurrence was defined as serum calcium >10.2 mg/dL after 6 months from operation. Kaplan-Meier estimates and Cox proportional hazards were used to evaluate disease-free survival and predictors of recurrence. RESULTS: We evaluated 196 patients with a 14.8% 10-year recurrence rate. Median time to recurrence was 6.3 years (interquartile range 3.4-10.8 years), and 34.5% of all recurrences were identified >10 years after operation. There was no difference in recurrence between open and minimally invasive operation (P = .448). Double adenomas (P = .006), intraoperative parathyroid hormone drop <70% (P = .015), and young age (P = .032) were predictive of disease recurrence. Multivariable analysis demonstrated that older age was protective against recurrence (hazard ratio 0.97, 95% confidence interval 0.94-0.99, P = .034), while double adenomas (hazard ratio 3.52, 95% confidence interval 1.23-10.08, P = .019) were an independent predictor for recurrence. CONCLUSION: The long-term recurrence rate for sporadic primary hyperparathyroidism after "curative" parathyroidectomy is likely greater than reported. With over one-third of our institutional recurrences at >10 years after the initial operation, long-term follow-up is essential.
PubMed-ID: 27863779
http://dx.doi.org/10.1016/j.surg.2016.05.049

The changing pattern of diagnosing primary hyperparathyroidism in young patients.
Am J Surg, 213(1):146-50.
I. Lou, D. F. Schneider, R. S. Sippel, H. Chen and D. M. Elfenbein. 2017.
BACKGROUND: Primary hyperparathyroidism (PHPT) is increasing in adults but rarely reported in young patients where routine blood work is obtained more judiciously. We aim to determine how PHPT is currently being diagnosed in young patients and examine surgical outcomes. METHOD: We retrospectively analyzed PHPT patients 24 years of age or less who underwent parathyroidectomy from 2001 to 2014. Patients were divided into 2 time periods: 2001 to 2007 (A) and 2008 to 2014 (B). Incidentally, diagnosed patients lacked objective symptoms of PHPT and had no family history. RESULTS: Forty young patients met inclusion criteria: 16 in group A and 24 in group B. Those in group A compared with group B had similar mean age, preoperative calcium, and parathyroid hormone (P > .05). Incidental diagnosis was more common in the contemporary group (42% vs 25%, P = .001). CONCLUSIONS: Current diagnosis of PHPT in young patients is increasingly incidental. This trend may be attributed to the more liberal use of labs in younger patients.
PubMed-ID: 27392754
http://dx.doi.org/10.1016/j.amjsurg.2016.03.019

Prevertebral cervical approach: a pure endoscopic surgical technique for posterior mediastinum parathyroid adenomas.
Surg Endosc, 31(4):1930-5.
J. M. Martos-Martinez, C. Sacristan-Perez, M. Perez-Andres, V. M. Duran-Munoz-Cruzado, V. Pino-Diaz and F. J. Padillo-Ruiz. 2017.
BACKGROUND: Parathyroid gland mediastinal ectopia is an unusual but challenging condition in surgical management of hyperparathyroidism. Posterior mediastinum parathyroid ectopia is rare, and glands need to be removed either with a broad open cervical or thoracic approach. In recent years, several minimally invasive approaches to mediastinal parathyroid glands have been described, but for posterior mediastinum adenomas, proposed techniques are transthoracic. METHODS: The aim of this paper is to describe, to our best knowledge for the first time, a standardized pure endoscopic cervical technique to approach posterior mediastinal parathyroid adenomas which we have used in three patients. RESULTS: The technique was applied in three patients which excellent surgical, postoperative, and cosmetic results. CONCLUSIONS: Endoscopic prevertebral approach is a feasible, sure and inexpensive standardized pure endoscopic cervical approach to posterior

mediastinal parathyroid adenomas, which may result in a less aggressive surgical option when compared with thoracic approaches.
PubMed-ID: 27553796
http://dx.doi.org/10.1007/s00464-016-5197-y

Efficacy and safety of ultrasound-guided radiofrequency ablation of hyperplastic parathyroid gland for secondary hyperparathyroidism associated with chronic kidney disease.
Head Neck, 39(3):564-71.
C. Peng, Z. Zhang, J. Liu, H. Chen, X. Tu, R. Hu, J. Ni, N. Weng, H. Pang and Z. Xue. 2017.
BACKGROUND: The purpose of this study was to determine if ultrasound-guided radiofrequency ablation (RFA) of hyperplastic parathyroid glands could be used to treat secondary hyperparathyroidism (HPT) in patients with chronic kidney disease. METHODS: RFA of the hyperplastic parathyroid glands was performed in 34 patients with secondary HPT. Intact parathyroid hormone (iPTH), calcium, and phosphorus were measured. The outcome was based on the ablation extent (ie, 4, 3, and 1-2 glands). RESULTS: The iPTH, calcium, and phosphorus levels decreased in all groups after RFA. One year after ablation, these parameters remained significantly lower in the 4-gland ablation group compared with the 3-gland and 1 to 2-gland groups. The same tendency was observed for the symptom score. The iPTH levels of <272 pg/mL on the day after ablation was the best predictor for maintaining parathyroid hormone (PTH) levels in a reasonable range 1 year after ablation. CONCLUSIONS: RFA of hyperplastic parathyroid glands for treating secondary HPT is feasible in selected patients. (c) 2016 Wiley Periodicals, Inc. Head Neck 39: 564-571, 2017.
PubMed-ID: 28032671
http://dx.doi.org/10.1002/hed.24657

SPECT/CT's Advantage for Preoperative Localization of Small Parathyroid Adenomas in Primary Hyperparathyroidism.
Clin Nucl Med, 42(2):e109-e14.
P. Sandqvist, I. L. Nilsson, P. Gryback, A. Sanchez-Crespo and A. Sundin. 2017.
PURPOSES: The aims of this study were to assess the performance of Tc-sestamibi SPECT/CT, with diagnostic CT quality, compared with SPECT alone for preoperative localization of parathyroid adenomas and to assess the influence of adenoma weight on the correct adenoma lateralization with SPECT/CT and with SPECT alone. METHODS: Two hundred forty-nine consecutive patients, biochemically diagnosed with primary hyperparathyroidism, were examined with a combined SPECT/CT scanner. Subsequently, 200 patients with confirmed histopathology and biochemical cure after parathyroidectomy were included in this study (16 with multiglandular disease). For each patient, the SPECT-alone data were analyzed first. Thereafter, the CT information was added, and a new evaluation was performed with the combined data. In addition, for each patient, the diagnostic confidence with each method was graded on a scale based on the presence of different image features. The preoperative diagnostic findings were then compared with the surgical and histopathologic reports. RESULTS: The distribution of adenoma weights showed a peak at 210 mg, with a median at 338 mg. The sensitivity and specificity (multiglandular disease included) for correct classification of adenomas were significantly higher for SPECT/CT, 83% and 96%, respectively, than for SPECT alone, 80% and 93% ($P < 0.01$). Below 210 mg, the differences between SPECT/CT and SPECT alone in accurate adenoma lateralization were more prominent. Sixty-seven percent of all adenomas were graded with the highest confidence score with SPECT/CT compared with 53% with SPECT. CONCLUSIONS: SPECT/CT yields fewer false-positive findings than SPECT alone. The advantage of SPECT/CT over SPECT alone was most apparent for correct lateralization of small adenomas (<210 mg).
PubMed-ID: 27819859
http://dx.doi.org/10.1097/RLU.0000000000001447

"Silent" kidney stones in "asymptomatic" primary hyperparathyroidism-a comparison of multidetector computed tomography and ultrasound.
Langenbecks Arch Surg, 402(2):289-93.
A. Selberherr, M. Hormann, G. Prager, P. Riss, C. Scheuba and B. Niederle. 2017.
PURPOSE: The purpose of this study was to demonstrate the high number of kidney stones in primary hyperparathyroidism (PHPT) and the low number of in fact "asymptomatic" patients. METHODS: Forty patients with PHPT (28 female, 12 male; median age 58 (range 33-80) years; interquartile range 17 years [51-68]) without known symptoms of kidney stones prospectively underwent multidetector computed tomography (MDCT) and ultrasound (US) examinations of the urinary tract prior to parathyroid surgery. Images were evaluated for the presence and absence of stones, as well as for the number of stones and sizes in the long axis. The MDCT and US examinations were interpreted by two experienced radiologists who were blinded to all clinical and

biochemical data. Statistical analysis was performed using the Wilcoxon signed-rank test. RESULTS: US revealed a total of 4 kidney stones in 4 (10 %) of 40 patients (median size 6.5 mm, interquartile range 11.5 mm). MDCT showed a total of 41 stones (median size was 3 mm, interquartile range 2.25 mm) in 15 (38 %) of 40 patients. The number of kidney stones detected with MDCT was significantly higher compared to US (p = 0.00124). CONCLUSIONS: MDCT is a highly sensitive method for the detection of "silent" kidney stones in patients with PHPT. By widely applying this method, the number of asymptomatic courses of PHPT may be substantially reduced. MDCT should be used primarily to detect kidney stones in PHPT and to exclude asymptomatic PHPT.
PubMed-ID: 27734157
http://dx.doi.org/10.1007/s00423-016-1520-2

Prognostic Scoring System to Risk Stratify Parathyroid Carcinoma.
J Am Coll Surg,
A. M. Silva-Figueroa, K. R. Hess, M. D. Williams, C. N. Clarke, I. Christakis, P. H. Graham, E. G. Grubbs, J. E. Lee, N. L. Busaidy and N. D. Perrier. 2017.
BACKGROUND: Parathyroid carcinoma is a rare endocrine malignancy that lacks an established system for risk categorization. This study evaluated a prognostic scoring system for recurrence-free survival (RFS) of patients with parathyroid carcinoma. STUDY DESIGN: Patients diagnosed and confirmed to have parathyroid carcinoma and who were treated between 1980 and 2016 at The University of Texas MD Anderson Cancer Center were studied retrospectively. Univariate and multivariate Cox proportional hazards regression analyses of RFS were conducted. A prognostic scoring system was created based on multivariate analysis. RESULTS: Sixty-eight patients were evaluated. After a median follow-up of 4.6 years, 26 patients experienced a recurrence. The Kaplan-Meier RFS rates were 85% at 1 year (95% CI 77% to 95%), 67% at 2 years (95% CI 55% to 81%), and 51% at 10 years (95% CI 36% to 72%) after initial operation. Multivariate analysis demonstrated that age older than 65 years, serum calcium level >15 mg/dL, and vascular invasion were negatively correlated with RFS rate. Combining these adverse variables into a prognostic scoring system, we stratified patients into 3 risk groups: low (0 variable; 2-year RFS rate, 93%), moderate (1 variable; 2-year RFS rate, 72%), and high (2 variables; 2-year RFS rate, 27%) (p = 0.001 [log-rank test]; concordance index, 0.70; 95% CI 0.47 to 0.92). CONCLUSIONS: A prognostic scoring system using vascular invasion, age, and serum calcium level at initial parathyroidectomy can be used to predict RFS. This categorization might be helpful for clinical decisions relative to the timing and use of adjuvant therapy. Comprehensive validation using multiple cohorts will be needed to confirm applicability.
PubMed-ID: 28427885
http://dx.doi.org/10.1016/j.jamcollsurg.2017.01.060

Inadvertent parathyroidectomy during total thyroidectomy and central neck dissection for papillary thyroid carcinoma.
Surgery, 161(3):712-9.
A. Sitges-Serra, L. Gallego-Otaegui, S. Suarez, L. Lorente-Poch, A. Munne and J. J. Sancho. 2017.
BACKGROUND: The main drawback of central neck lymph node dissection is postoperative parathyroid failure. Little information is available concerning inadvertent resection of the parathyroid glands in this setting and its relationship to postoperative hypoparathyroidism. Our aim was to determine the prevalence of inadvertent parathyroidectomy during total thyroidectomy and central neck dissection for papillary thyroid cancer and its impact on short-and long-term parathyroid function. METHODS: This was a prospective observational study of consecutive patients undergoing first-time total thyroidectomy with a central neck dissection for papillary carcinoma >10 mm. Prevalence and risk factors for inadvertent parathyroidectomy were recorded. Serum calcium and intact parathyroid hormone concentrations were determined 24 hours after operation and then periodically in patients developing postoperative hypocalcemia. All patients were followed for a minimum of one year. RESULTS: Whole gland (n = 33) or microscopic parathyroid fragments (n = 14) were identified in 47/170 (28%) operative specimens. The lower parathyroid glands were involved more often. Variables influencing inadvertent parathyroidectomy were extrathyroidal extension of the tumor and therapeutic lymphadenectomy. Neither lateral neck dissection nor the number of lymph nodes retrieved affected the rate of inadvertent parathyroid resection. Postoperative hypocalcemia and permanent hypoparathyroidism were more frequent after inadvertent parathyroidectomy (64% vs 46% and 15% vs 4%; P </= .03 each). CONCLUSION: Inadvertent parathyroidectomy during total thyroidectomy with central neck dissection for papillary thyroid carcinoma is common and involves the inferior glands more frequently in patients with extended resections and clinical N1a disease. Inadvertent resection of parathyroid glands is associated with greater rates of postoperative hypocalcemia and permanent hypoparathyroidism.
PubMed-ID: 27743717
http://dx.doi.org/10.1016/j.surg.2016.08.021

Hypoparathyroidism: Less Severe Hypocalcemia With Treatment With Vitamin D2 Compared With Calcitriol.
J Clin Endocrinol Metab, 102(5):1505-10.
E. A. Streeten, Y. Mohtasebi, M. Konig, L. Davidoff and K. Ryan. 2017.
Context: Options for chronic treatment of hypoparathyroidism include calcitriol, recombinant human parathyroid hormone, and high-dose vitamin D (D2). D2 is used in a minority of patients because of fear of prolonged hypercalcemia and renal toxicity. There is a paucity of recent data about D2 use in hypoparathyroidism. Objective: Compare renal function, hypercalcemia, and hypocalcemia in patients with hypoparathyroidism treated chronically with either D2 (D2 group) or calcitriol. Design, Setting, and Patients: A retrospective study of patients with hypoparathyroidism treated at the University of Maryland Hospital. Participants were identified by a billing record search with diagnosis confirmed by chart review. Thirty patients were identified; 16 were treated chronically with D2, 14 with calcitriol. Data were extracted from medical records. Main Outcome Measures: Serum creatinine and calcium, hospitalizations, and emergency department (ED) visits for hypercalcemia and hypocalcemia. Results: D2 and calcitriol groups were similar in age (58.9 +/- 16.7 vs 50.9 +/- 22.6 years, P = 0.28), sex, and treatment duration (17.8 +/- 14.2 vs 8.5 +/- 4.4 years, P = 0.076). Hospitalization or ED visits for hypocalcemia occurred in none of the D2 group vs four of 14 in the calcitriol group (P = 0.03); three in the calcitriol group had multiple ED visits. There were no differences between D2 and calcitriol groups in hospitalizations or ED visits for hypercalcemia, serum creatinine or calcium, or kidney stones. Conclusion: We found less morbidity from hypocalcemia in hypoparathyroid patients treated chronically with D2 compared with calcitriol and found no difference in renal function or morbidity from hypercalcemia. Treatment with D2 should be considered in patients with hypoparathyroidism, particularly in those who experience recurrent hypocalcemia.
PubMed-ID: 28324108
http://dx.doi.org/10.1210/jc.2016-3712

Thiazide Treatment in Primary Hyperparathyroidism-A New Indication for an Old Medication?
J Clin Endocrinol Metab, 102(4):1270-6.
G. Tsvetov, D. Hirsch, I. Shimon, C. Benbassat, H. Masri-Iraqi, A. Gorshtein, D. Herzberg, T. Shochat, I. Shraga-Slutzky and T. Diker-Cohen. 2017.
Context: There is no therapy for control of hypercalciuria in nonoperable patients with primary hyperparathyroidism (PHPT). Thiazides are used for idiopathic hypercalciuria but are avoided in PHPT to prevent exacerbating hypercalcemia. Nevertheless, several reports suggested that thiazides may be safe in patients with PHPT. Objective: To test the safety and efficacy of thiazides in PHPT. Design: Retrospective analysis of medical records. Setting: Endocrine clinic at a tertiary hospital. Patients: Fourteen male and 58 female patients with PHPT treated with thiazides. Interventions: Data were compared for each patient before and after thiazide administration. Main Outcome Measures: Effect of thiazide on urine and serum calcium levels. Results: Data are given as mean +/- standard deviation. Treatment with hydrochlorothiazide 12.5 to 50 mg/d led to a decrease in mean levels of urine calcium (427 +/- 174 mg/d to 251 +/- 114 mg/d; P < 0.001) and parathyroid hormone (115 +/- 57 ng/L to 74 +/- 36 ng/L; P < 0.001), with no change in serum calcium level (10.7 +/- 0.4 mg/dL off treatment, 10.5 +/- 1.2 mg/dL on treatment, P = 0.4). Findings were consistent over all doses, with no difference in the extent of reduction in urine calcium level or change in serum calcium level by thiazide dose. Conclusion: Thiazides may be effective even at a dose of 12.5 mg/d and safe at doses of up to 50 mg/d for controlling hypercalciuria in patients with PHPT and may have an advantage in decreasing serum parathyroid hormone level. However, careful monitoring for hypercalcemia is required.
PubMed-ID: 28388724
http://dx.doi.org/10.1210/jc.2016-2481

Impact of the Introduction of Calcimimetics on Timing of Parathyroidectomy in Secondary and Tertiary Hyperparathyroidism.
Ann Surg Oncol, 24(1):15-22.
W. Y. van der Plas, A. F. Engelsman, A. Ozyilmaz, A. N. van der Horst-Schrivers, K. Meijer, G. M. van Dam, R. A. Pol, M. H. de Borst and S. Kruijff. 2017.
BACKGROUND: Hyperparathyroidism (HPT), both secondary and tertiary, is common in patients with end-stage renal disease, and is associated with severe bone disorders, cardiovascular complications, and increased mortality. Since the introduction of calcimimetics in 2004, treatment of HPT has shifted from surgery to predominantly medical therapy. OBJECTIVE: The aim of this study was to evaluate the impact of this change of management on the HPT patient population before undergoing (sub-)total parathyroidectomy (PTx). METHODS: Overall, 119 patients with secondary or tertiary HPT undergoing PTx were included in a retrospective, single-center cohort. Group A, who underwent PTx before January 2005, was compared with group B, who underwent

PTx after January 2005. Patient characteristics, time interval between HPT diagnosis and PTx, and postoperative complications were compared. RESULTS: Group A comprised 70 (58.8 %) patients and group B comprised 49 (41.2 %) patients. The median interval between HPT diagnosis and PTx was 27 (interquartile range [IQR] 12.5-48.0) and 49 (IQR 21.0-75.0) months for group A and B, respectively (p = 0.007). Baseline characteristics were similar among both groups. The median preoperative serum parathyroid hormone (PTH) level was 936 pg/mL (IQR 600-1273) for group A versus 1091 pg/mL (IQR 482-1373) for group B (p = 0.38). PTx resulted in a dramatic PTH reduction (less than twofold the upper limit: A, 80.0 %; B, 85.4 %), and postoperative complication rates were low in both groups (A: 7.8 %; B: 10.2 %) [p = 0.66]. CONCLUSIONS: The introduction of calcimimetics in 2004 is associated with a significant 2-year delay of surgery with continuously elevated preoperative PTH levels, while parathyroid surgery, even in a fragile population, is considered a safe and effective procedure.
PubMed-ID: 27459979
http://dx.doi.org/10.1245/s10434-016-5450-6

Is C-11 Methionine PET/CT Able to Localise Sestamibi-Negative Parathyroid Adenomas?
World J Surg, 41(4):980-5.
T. Weber, M. Gottstein, S. Schwenzer, A. Beer and M. Luster. 2017.
BACKGROUND: Patients with primary hyperparathyroidism (pHPT) and a negative preoperative Tc-99 sestamibi (MIBI) scintigraphy are considered to have a higher risk of persistent disease. The aim of this study was to assess whether additional imaging with C-11 methionine positron emission tomography/computed tomography (Met-PET/CT) is able to localise sestamibi-negative hyperfunctioning parathyroid glands. METHODS: In 50 patients (38 females, 12 males, age 13-81 years) with pHPT and negative localisation procedures such as ultrasound and sestamibi, a Met-PET/CT was performed before parathyroid surgery. The results of Met-PET/CT were analysed prospectively and compared with intraoperative and histopathological findings. 22% of the patients underwent previous parathyroid and/or thyroid surgery. RESULTS: Met-PET/CT correctly located a single-gland adenoma in 33 of 45 (73%) patients with pHPT. In 5 patients with multiglandular disease, Met-PET/CT detected at least one hyperfunctional parathyroid gland in 4 patients (80%). In 3 patients with double adenomas, 5 of 6 parathyroids were correctly located. Overall, 40 of 57 (70%) hyperfunctioning glands were identified with Met-PET/CT. Met-PET/CT was false-negative in 12 of 50 (24%) patients and false-positive in only one case (2%). Postoperatively, 48 of 50 patients (96%) were cured. CONCLUSIONS: Additional pre-interventional imaging with Met-PET/CT was able to identify hyperfunctioning parathyroid glands in 74% of patients with pHPT and negative sestamibi scans, thus enabling successful parathyroid surgery.
PubMed-ID: 27834016
http://dx.doi.org/10.1007/s00268-016-3795-4

Adrenals

Meta-Analyses

- None -

Randomized controlled trials

- None –

Consensus Statements/Guidelines

European Society of Endocrine Surgeons (ESES) and European Network for the Study of Adrenal Tumours (ENSAT) recommendations for the surgical management of adrenocortical carcinoma.
Br J Surg, 104(4):358-76.
S. Gaujoux and R. Mihai. 2017.
BACKGROUND: Radical surgery provides the best chance of cure for adrenocortical carcinoma (ACC), but perioperative surgical care for these patients is yet to be standardized. METHODS: A working group appointed jointly by ENSAT and ESES used Delphi methodology to produce evidence-based recommendations for the perioperative surgical care of patients with ACC. Papers were retrieved from electronic databases. Evidence and recommendations were classified according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system, and were discussed until consensus was reached within the group. RESULTS: Twenty-five recommendations for the perioperative surgical care of patients with ACC were formulated. The quality of evidence is low owing to the rarity of the disease and the lack of prospective surgical trials. Multi-institutional prospective cohort studies and prospective RCTs are urgently needed and should be strongly encouraged. CONCLUSION: The present evidence-based recommendations provide comprehensive advice on the optimal perioperative care for patients undergoing surgery for ACC.
PubMed-ID: 28199015
http://dx.doi.org/10.1002/bjs.10414

Other Articles

SDHB mutation status and tumor size but not tumor grade are important predictors of clinical outcome in pheochromocytoma and abdominal paraganglioma.
Surgery, 161(1):230-9.
Y. Assadipour, S. M. Sadowski, M. Alimchandani, M. Quezado, S. M. Steinberg, N. Nilubol, D. Patel, T. Prodanov, K. Pacak and E. Kebebew. 2017.
BACKGROUND: A staging/prognostic system has long been desired to better categorize pheochromocytoma/paraganglioma which can be very aggressive in the setting of SDHB mutations. METHODS: A retrospective analysis was conducted of clinical characteristics and outcomes including results of genetic testing, tumor recurrence/metastasis, Ki67/MIB1% staining, and tumor mitotic index in patients with pheochromocytoma/paraganglioma. RESULTS: Patients with SDHB mutation presented at younger age (33.0 years old vs 49.6 years old, P < .001), had increased local recurrence and distant metastases (47.6% vs 9.1%, P < .001, and 56.3% vs 9.1%, P < .001, respectively), and lesser median disease-free interval (89.8 months, 95% confidence interval 36.0-96.4 vs not reached, P < .001). SDHB mutation, greatest tumor diameter, and open operative resection were associated with a greater rate of local recurrence and distant metastases (P < .006 each). SDHB mutation and tumor diameter were independent risk factors for local recurrence (P </= .04 each) and metastases. Ki67% and mitotic index were not associated with SDHB mutation (P >/= .09 each), local recurrence (P = .48, P = .066, respectively), metastases (P >/= .22 each), or disease-free interval (P >/= .19 each). CONCLUSION: SDHB status and primary tumor size are more predictive of patient outcome than Ki67% or mitotic index and should be part of any clinically relevant, prognostic scoring system.

PubMed-ID: 27839933
http://dx.doi.org/10.1016/j.surg.2016.05.050

Pediatric patients with pheochromocytoma and paraganglioma should have routine preoperative genetic testing for common susceptibility genes in addition to imaging to detect extra-adrenal and metastatic tumors.
Surgery, 161(1):220-7.
B. Babic, D. Patel, R. Aufforth, Y. Assadipour, S. M. Sadowski, M. Quezado, N. Nilubol, T. Prodanov, K. Pacak and E. Kebebew. 2017.
BACKGROUND: Pediatric pheochromocytomas and paragangliomas are rare with limited data on the optimal management approach. The aim of this study was to determine the role of genetic testing and imaging to detect extra-adrenal and/or metastatic tumors in pediatric pheochromocytomas and paragangliomas. METHODS: We performed a retrospective study of 55 patients diagnosed at </=21 years of age with pheochromocytomas and paragangliomas with analysis of data on genetic testing and multimodal imaging. RESULTS: Eighty percent of patients (n = 44/55) had a germline mutation. The majority were found to have either VHL (38%) or SDHB (25%) mutation. Pheochromocytoma was present in 67% (n = 37/55) of patients and was bilateral in 51% (n = 19/37). The majority of patients with bilateral pheochromocytomas had VHL (79%). Abdominal paragangliomas was present in 22% (n = 12/55), head and neck paragangliomas in 11% (n = 6/55), and thoracic paragangliomas in 2 of 55 patients. For paragangliomas, SDHx accounted for 72% (n = 13/18) of mutations. The rate of malignancy was 16% (n = 9/55), 56% of whom had SDHB mutations. In two-thirds of patients, functional imaging identified either extra-adrenal paragangliomas and/or metastatic disease. CONCLUSION: The majority of pediatric patients with pheochromocytomas and paragangliomas have detectable germline mutations. Therefore, we suggest strongly that all pediatric patients with pheochromocytomas and paragangliomas undergo genetic testing and imaging to detect extra-adrenal paragangliomas and metastatic disease to guide treatment and follow-up.
PubMed-ID: 27865588
http://dx.doi.org/10.1016/j.surg.2016.05.059

Long-Term Outcomes of Adjuvant Mitotane Therapy in Patients With Radically Resected Adrenocortical Carcinoma.
J Clin Endocrinol Metab, 102(4):1358-65.
A. Berruti, S. Grisanti, A. Pulzer, M. Claps, F. Daffara, P. Loli, M. Mannelli, M. Boscaro, E. Arvat, G. Tiberio, S. Hahner, B. Zaggia, F. Porpiglia, M. Volante, M. Fassnacht and M. Terzolo. 2017.
Context: In 2007, a retrospective case-control study provided evidence that adjuvant mitotane prolongs recurrence-free survival (RFS) in patients with radically resected adrenocortical carcinoma (ACC). Objective and Design: We aimed to confirm the prognostic role of adjuvant mitotane in the same series after 9 additional years of follow-up. Setting, Patients, and Interventions: One hundred sixty-two ACC patients who did not recur or die after a landmark period of 3 months were considered. Forty-seven patients were enrolled in four Italian centers where adjuvant mitotane was routinely recommended (mitotane group), 45 patients in four Italian centers where no adjuvant strategy was undertaken (control group 1), and 70 German patients left untreated after surgery (control group 2). Main Outcome Measures: The primary aim was RFS, the secondary was overall survival. Results: An increased risk of recurrence was found in both control cohorts [group 1: hazard ratio (HR) = 2.98; 95% confidence interval (CI), 1.75 to 5.09; P < 0.0001; group 2: HR = 2.61; 95% CI, 1.56 to 4.36; P < 0.0001] compared with the mitotane group. The risk of death was higher in control group 1 (HR = 2.03; 95% CI, 1.17 to 3.51; P = 0.011) but not in control group 2 (HR = 1.60; 95% CI, 0.94 to 2.74; P = 0.083), which had better prognostic factors and more aggressive treatment of recurrences than control group 1. The benefit of adjuvant mitotane on RFS was observed regardless of the hormone secretory status. Conclusions: Adjuvant mitotane is associated with prolonged RFS, without any apparent influence by the tumor secretory status. The retrospective nature of the study is a major limitation.
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http://dx.doi.org/10.1210/jc.2016-2894

Pheochromocytoma and paraganglioma in patients with neurofibromatosis type 1.
Clin Endocrinol (Oxf), 86(1):141-9.
L. M. Gruber, D. Erickson, D. Babovic-Vuksanovic, G. B. Thompson, W. F. Young, Jr. and I. Bancos. 2017.
OBJECTIVE: Individuals with neurofibromatosis type 1 (NF1) are at an increased risk of developing a pheochromocytoma or paraganglioma (PHEO/PGL). However, the best case detection strategy is unknown. Our objectives were to describe the prevalence, clinical presentation and outcomes of PHEO/PGL associated with NF1 and formulate case detection testing recommendations for PHEO/PGL. DESIGN: A retrospective cohort

study from 1959 to 2015, Tertiary medical centre. PATIENTS AND MEASUREMENTS: We studied 41 patients with NF1 and PHEO/PGL who were identified using the PHEO/PGL and NF1 databases: 3289 and 1415 patients, respectively. Our main outcome measures were prevalence of PHEO/PGL in NF1 and occurrence of bilateral, recurrent, or metastatic disease and method of PHEO/PGL detection (symptoms vs incidental vs biochemical case detection testing). RESULTS: The prevalence of PHEO/PGL in patients with NF1 was 2.9%. The 41 patients included 23 men (56%) and 18 women. The median age at diagnosis was 41.0 years (range 14-67). The median tumour size was 3.4 cm (range 0.8-9.5). Bilateral PHEO was identified in 17% (n = 7) of patients, all women. Metastatic or recurrent disease occurred in 7.3% (n = 3). In the last 25 years, PHEO/PGL was diagnosed after incidental finding on computed imaging in 31% of patients (n = 11). Only three patients (7.3%) had PHEO/PGL discovered because of biochemical case detection testing. CONCLUSION: We recommend patients with NF1 have biochemical case detection testing for PHEO/PGL every 3 years starting at age 10 to 14 years. Biochemical case detection testing should also be carried out prior to elective surgical procedures and conception.
PubMed-ID: 27460956
http://dx.doi.org/10.1111/cen.13163

Performance of 18F-FDG PET/CT in the Characterization of Adrenal Masses in Noncancer Patients: A Prospective Study.
J Clin Endocrinol Metab, 102(7):2465-72.
C. Guerin, F. Pattou, L. Brunaud, J. C. Lifante, E. Mirallie, M. Haissaguerre, D. Huglo, P. Olivier, C. Houzard, C. Ansquer, E. Hindie, A. Loundou, C. Archange, A. Tabarin, F. Sebag, K. Baumstarck and D. Taieb. 2017.
Context: Few prospective studies have evaluated the role of 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) in the characterization of adrenal masses. Objective: To assess the performance of 18F-FDG PET/CT in the malignancy diagnosis of adrenal masses in noncancer patients. Design: Prospective multicenter study. Material and Methods: The study population consisted of 87 patients (87 adrenal masses) referred to endocrine surgeons: 56 with mass diameter >/=40 mm and 31 with a diameter <40 mm and of indeterminate nature based on unenhanced and washout CT attenuation densities. Fourteen patients had hypercortisolism. Adrenal masses were characterized by 18F-FDG PET/CT. Histology was the gold standard for the diagnosis of malignancy. In the absence of pathological proof (n = 23), the nature of the lesion was based on the 12-month imaging follow-up. Results: Fifteen adrenal masses were classified as malignant (including 11 adrenocortical carcinomas) and 72 as benign. Compared with benign lesions, malignant lesions were larger in size (P = 0.003), had higher unenhanced densities (P = 0.002), lower relative washout values (P = 0.007), and higher 18F-FDG uptake parameters (P < 10-3). The optimal threshold value of (Tumor SUVmax:Liver SUVmax) the ratio for malignancy was >1.5 with sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 86.7%, 86.1%, 56.5%, 96.9%, and 86.2%, respectively. Conclusions: Our results show that 18F-FDG PET/CT complements adrenal washout CT in the evaluation of adrenal masses and should be recommended in the evaluation of large and/or indeterminate adrenal masses.
PubMed-ID: 28431167
http://dx.doi.org/10.1210/jc.2017-00254

Preoperative alpha-blockade in phaeochromocytoma and paraganglioma: is it always necessary?
Clin Endocrinol (Oxf), 86(3):309-14.
M. Isaacs and P. Lee. 2017.
Resection of phaeochromocytoma and paraganglioma (PPGL) is traditionally preceded by alpha-blockade to prevent complications of haemodynamic instability intraoperatively. While there is general agreement on preoperative alpha-blockade for classic PPGLs presenting with hypertension, it is less clear whether alpha-blockade is necessary in predominantly dopamine-secreting tumours, normotensive PPGLs, as well as tumours that appear to be biochemically 'silent'. Preoperative management of these 'atypical' PPGLs is challenging and the treatment approach must be individualized, carefully weighing the risk of intraoperative hypertension against the possibility of orthostatic and prolonged postoperative hypotension. Consideration of antihypertensive medication pharmacology in the light of catecholamine physiology and PPGL secretory profile will facilitate the formulation of individualized preoperative preparatory strategies.
PubMed-ID: 27864838
http://dx.doi.org/10.1111/cen.13284

Scoring system for the diagnosis of bilateral primary aldosteronism in the outpatient setting before adrenal venous sampling.
Clin Endocrinol (Oxf), 86(4):467-72.
H. Kobayashi, A. Haketa, T. Ueno, Y. Ikeda, Y. Hatanaka, S. Tanaka, H. Otsuka, M. Abe, N. Fukuda and M.

Soma. 2017.
OBJECTIVE: The only reliable method for subtyping primary aldosteronism (PA) is adrenal venous sampling (AVS), which is costly and time-consuming. Considering the limited availability of AVS, it would be helpful to obtain information on the diagnosis of bilateral hyperaldosteronism (BHA) from routine tests. We aimed to establish new, simple criteria for outpatients to diagnose BHA from PA before AVS. DESIGN: We retrospectively analysed 82 patients who were diagnosed with PA and underwent AVS. Thirty-seven patients were diagnosed with unilateral hyperaldosteronism (UHA), and 36 with BHA and nine were undetermined. Among the variables that were significantly different between UHA and BHA in the univariate analysis, we chose three variables to be included in multivariate logistic regression models and constructed a subtype prediction score. RESULTS: The subtype prediction score was calculated as follows: 3 points for no adrenal nodules on computed tomography imaging, 2 for serum potassium of >/=3.5 mmol/l and 2 for aldosterone-to-renin ratio of <490 after a captopril challenge test. Receiver operating characteristic curve analysis for the ability to discriminate BHA from UHA showed that a score of 7 points had 50% sensitivity and 100% specificity and a score of 5 points had 67% sensitivity and 94% specificity (area under the curve: 0.922; 95% CI: 0.863-0.980). CONCLUSIONS: Our new, simple criteria specifically distinguished BHA from UHA in the outpatient setting before AVS. Furthermore, not only endocrinologists but also general internists can use this convenient, safe scoring system.
PubMed-ID: 27862131
http://dx.doi.org/10.1111/cen.13278

Adrenocortical carcinoma with inferior vena cava tumor thrombus.
Surgery, 161(1):240-8.
D. V. Laan, C. A. Thiels, A. Glasgow, K. B. Wise, G. B. Thompson, M. L. Richards, D. R. Farley, M. J. Truty and T. J. McKenzie. 2017.
BACKGROUND: The safety, efficacy, and prognostic implications of resection of adrenocortical carcinoma with inferior vena cava tumor thrombus are poorly described. METHODS: A retrospective review was performed during a 30-year period on patients who underwent resection of locally advanced, nonmetastatic adrenocortical carcinoma. We compared patients with and without inferior vena cava tumor thrombus, examining perioperative characteristics, completeness of resection, mortality, and survival. RESULTS: We identified 65 patients who underwent resection of locally advanced (T4N0 and T4N1) adrenocortical carcinoma (28 patients with inferior vena cava tumor thrombus, 37 noninferior vena cava tumor thrombus). Rate of complete resection, adjuvant chemotherapy, and short-term postoperative morbidity was similar between groups. Overall survival was similar at 12-months. At 24 months overall survival was less in the inferior vena cava tumor thrombus group (59% vs 30%, P = .04). Differential survival through 60-month follow-up favored the noninferior vena cava tumor thrombus group (36% vs 0%, P = .001). Subgroup analysis including only patients with complete resection demonstrates similar survival at 24-months but at 36-months survival favored the noninferior vena cava tumor thrombus patients (65% vs 29%, P = .047) and this continued through 60 months (40% vs 0%, P = .049). CONCLUSION: Attempt at complete resection of adrenocortical carcinoma with inferior vena cava tumor thrombus seems justified particularly as short-term safety and survival are similar to patients without inferior vena cava tumor thrombus. However, survival beyond 36-months is limited in patients with inferior vena cava tumor thrombus. Patients being evaluated for resection in the setting of inferior vena cava tumor thrombus should be selected carefully.
PubMed-ID: 27866717
http://dx.doi.org/10.1016/j.surg.2016.07.040

Hypertension Cure Following Laparoscopic Adrenalectomy for Hyperaldosteronism is not Universal: Trends Over Two Decades.
World J Surg, 41(4):986-90.
T. Namekawa, T. Utsumi, T. Tanaka, M. Kaga, H. Nagano, T. Kono, K. Kawamura, N. Kamiya, T. Imamoto, H. Suzuki and T. Ichikawa. 2017.
BACKGROUND: Laparoscopic adrenalectomy has been established as a standard surgical method for unilateral primary aldosteronism. Meanwhile, the background characteristics of the patients undergoing adrenalectomy have changed over the last 20 years. The aim of this study was to investigate the changes in hypertension cure rates after laparoscopic adrenalectomy during the last two decades. METHODS: This retrospective clinical study included 176 patients who underwent unilateral laparoscopic adrenalectomy for primary aldosteronism from 1995 to 2015. The patients were divided into two groups by decade. The patients' baseline characteristics and the hypertension cure rates were compared between the two groups. Additionally, the values were re-examined based on predictive model predicting postoperative hypertension cure. RESULTS: The hypertension cure rate decreased significantly from 51.8 to 31.1%. The following variables were significantly different between the two groups: age, sex, body mass index, history of diabetes mellitus, preoperative systolic and diastolic blood

pressures, potassium level, and plasma renin activity. CONCLUSIONS: This study showed that the number of patients with unfavorable conditions for hypertension cure after adrenalectomy has recently increased. The treatment goal for primary aldosteronism is not only to cure the hypertension but also to prevent organ disorders due to inappropriate aldosterone levels. Therefore, we recommend laparoscopic adrenalectomy for unilateral primary aldosteronism, even if hypertension is not always cured postoperatively. However, clinicians need to fully explain the postoperative hypertension outcomes to primary aldosteronism patients.
PubMed-ID: 27872977
http://dx.doi.org/10.1007/s00268-016-3822-5

Peptide Receptor Radionuclide Treatment and (131)I-MIBG in the management of patients with metastatic/progressive phaeochromocytomas and paragangliomas.
J Surg Oncol, 115(4):425-34.
K. Nastos, V. T. F. Cheung, C. Toumpanakis, S. Navalkissoor, A. M. Quigley, M. Caplin and B. Khoo. 2017.
BACKGROUND AND OBJECTIVES: Radionuclide therapy has been used to treat patients with progressive/metastatic paragangliomas (PGLs) and phaeochromocytomas (PCCs). The aim of the present study is to retrospectively compare the therapeutic outcomes of these modalities in patients with progressive/metastatic PCCs and PGLs. METHODS: Patients with progressive/metastatic PGLs and PCCs that were subjected to radionuclide treatment in our department were retrieved from our department's database for the period 1998-2013. Overall survival (OS), progression free survival (PFS), event free survival (EFS), and response to treatment were calculated. Treatment toxicity was documented. RESULTS: Twenty-two patients with progressive/metastatic PGLs or PCCs were treated with either (131)I-MIBG, (90)Y-DOTATATE or (177)Lu-DOTATATE. A total of 30 treatments were administered (16 treatments with (131)I-MIBG, 2 with (177)Lu-DOTATATE, and 12 with (90)Y-DOTATATE. Patients treated with PRRT had increased PFS and response to treatment compared to (131)I-MIBG treated patients ($P < 0.05$). However, difference in OS was non significant ($P = 0.09$). There was no difference in major toxicities between groups. When comparing only patients with PGLs, OS, PFS, EFS, and response to treatment were significantly higher in the PRRT treatment group. CONCLUSION: PRRT treatment offers increased OS, PFS, EFS, and response to treatment compared to (131)I-MIBG therapy in patients with progressive/malignant PGLs.
PubMed-ID: 28166370
http://dx.doi.org/10.1002/jso.24553

Characteristics of Pediatric vs Adult Pheochromocytomas and Paragangliomas.
J Clin Endocrinol Metab, 102(4):1122-32.
C. Pamporaki, B. Hamplova, M. Peitzsch, A. Prejbisz, F. Beuschlein, H. Timmers, M. Fassnacht, B. Klink, M. Lodish, C. A. Stratakis, A. Huebner, S. Fliedner, M. Robledo, R. O. Sinnott, A. Januszewicz, K. Pacak and G. Eisenhofer. 2017.
Context: Pheochromocytomas and paragangliomas (PPGLs) in children are often hereditary and may present with different characteristics compared with adults. Hereditary PPGLs can be separated into cluster 1 and cluster 2 tumors due to mutations impacting hypoxia and kinase receptor signaling pathways, respectively. Objective: To identify differences in presentation of PPGLs between children and adults. Design: A retrospective cross-sectional clinical study. Setting: Seven tertiary medical centers. Patients: The study included 748 patients with PPGLs, including 95 with a first presentation during childhood. Genetic testing was available in 611 patients. Other data included locations of primary tumors, presence of recurrent or metastatic disease, and plasma concentrations of metanephrines and 3-methoxytyramine. Results: Children showed higher ($P < 0.0001$) prevalence than adults of hereditary (80.4% vs 52.6%), extra-adrenal (66.3% vs 35.1%), multifocal (32.6% vs 13.5%), metastatic (49.5% vs 29.1%), and recurrent (29.5% vs 14.2%) PPGLs. Tumors due to cluster 1 mutations were more prevalent among children than adults (76.1% vs 39.3%; $P < 0.0001$), and this paralleled a higher prevalence of noradrenergic tumors, characterized by relative lack of increased plasma metanephrine, in children than in adults (93.2% vs 57.3%; $P < 0.0001$). Conclusions: The higher prevalence of hereditary, extra-adrenal, multifocal, and metastatic PPGLs in children than adults represents interrelated features that, in part, reflect the lower age of disease presentation of noradrenergic cluster 1 than adrenergic cluster 2 tumors. The differences in disease presentation are important to consider in children at risk for PPGLs due to a known mutation or previous history of tumor.
PubMed-ID: 28324046
http://dx.doi.org/10.1210/jc.2016-3829

Assessment of the Aldosteronona resolution score as a predictive resolution score of hypertension after adrenalectomy for aldosteronoma in French patients.
Langenbecks Arch Surg, 402(2):309-14.
L. Pasquier, M. Kirouani, F. Fanget, C. Nomine, C. Caillard, V. Arnault, J. B. Finel, N. Christou, M. Mathonnet, C. Tresallet, A. Hamy, L. de Calan, L. Brunaud, F. Menegaux, J. C. Lifante, J. B. Hardouin, D. Drui, E. Mirallie and C. Blanchard. 2017.
PURPOSE: Aldosteronoma Resolution Score (ARS) is a predictive score for cure of hypertension after adrenalectomy for hyperaldosteronism and has been validated in American patients. The aim of the study was to validate this score in a French population. METHOD: Data concerning patients operated from 2002 to 2015 in 7 French University Hospitals were retrospectively collected. Diagnosis of Aldosterone-producing adenoma (APA) was confirmed with clinical and biochemical hyperaldosteronism and adrenal nodule on CT scan. Adrenal venous sampling was performed when CT failed to identify laterality. ARS is based on four variables: female sex, BMI </=25 kg/m2, duration of hypertension </=6 years, number of antihypertensive medications </=2. One point is attributed for the first three and 2 points for the last. Patients were considered as cured if they had no hypertension and no antihypertensive medications at least 6 months after surgery. Patients with bilateral adrenal hyperplasia were excluded. RESULTS: This multicenter study included 310 patients with APA. ARS and follow-up were obtained in 257 patients. 46.6% of patients were cured and potassium serum level was normalized in 97.7%. In multivariate analysis, odds ratio for female sex, BMI </=25 kg/m2, duration of hypertension </=6 years, and number of antihypertensive medications </=2 were 1.60 (p = 0.09), 1.77 (p = 0.04), 1.28 (p = 0.4), 3.41 (p < 0.001), respectively. Cure rate were, respectively, 22.2, 41.4 and 74% for patients with a score ARS 0-1, 2-3, 4-5. The area under the curve (AUC) of ARS was 0.715. CONCLUSION: ARS is not a predictive score efficient enough in a French population maybe due to different metabolic data and genetic conditions.
PubMed-ID: 28111697
http://dx.doi.org/10.1007/s00423-017-1557-x

Selective Versus Non-selective alpha-Blockade Prior to Laparoscopic Adrenalectomy for Pheochromocytoma.
Ann Surg Oncol, 24(1):244-50.
R. W. Randle, C. J. Balentine, S. C. Pitt, D. F. Schneider and R. S. Sippel. 2017.
BACKGROUND: The optimal preoperative alpha-blockade strategy is debated for patients undergoing laparoscopic adrenalectomy for pheochromocytomas. We evaluated the impact of selective versus non-selective alpha-blockade on intraoperative hemodynamics and postoperative outcomes. METHODS: We identified patients having laparoscopic adrenalectomy for pheochromocytomas from 2001 to 2015. As a marker of overall intraoperative hemodynamics, we combined systolic blood pressure (SBP) > 200, SBP < 80, SBP < 80 and >200, pulse > 120, vasopressor infusion, and vasodilator infusion into a single variable. Similarly, the combination of vasopressor infusion in the post-anesthesia care unit (PACU) and the need for intensive care unit (ICU) admission provided an overview of postoperative support. RESULTS: We identified 52 patients undergoing unilateral laparoscopic adrenalectomy for pheochromocytoma. Selective alpha-blockade (i.e. doxazosin) was performed in 35 % (n = 18) of patients, and non-selective blockade with phenoxybenzamine was performed in 65 % (n = 34) of patients. Demographics and tumor characteristics were similar between groups. Patients blocked selectively were more likely to have an SBP < 80 (67 %) than those blocked with phenoxybenzamine (35 %) (p = 0.03), but we found no significant difference in overall intraoperative hemodynamics between patients blocked selectively and non-selectively (p = 0.09). However, postoperatively, patients blocked selectively were more likely to require additional support with vasopressor infusions in the PACU or ICU admission (p = 0.02). Hospital stay and complication rates were similar. CONCLUSION: Laparoscopic adrenalectomy for pheochromocytoma is safe regardless of the preoperative alpha-blockade strategy employed, but patients blocked selectively may have a higher incidence of transient hypotension during surgery and a greater need for postoperative support. These differences did not result in longer hospital stay or increased complications.
PubMed-ID: 27561909
http://dx.doi.org/10.1245/s10434-016-5514-7

Impact of Surgical Resection of the Primary Tumor on Overall Survival in Patients With Metastatic Pheochromocytoma or Sympathetic Paraganglioma.
Ann Surg,
A. Roman-Gonzalez, S. Zhou, M. Ayala-Ramirez, C. Shen, S. G. Waguespack, M. A. Habra, J. A. Karam, N. Perrier, C. G. Wood and C. Jimenez. 2017.
OBJECTIVE: To determine whether primary tumor resection in patients with metastatic pheochromocytoma or paraganglioma (PPG) is associated with longer overall survival (OS). BACKGROUND: Patients with metastatic PPG have poor survival outcomes. The impact of surgical resection of the primary tumor on OS is not known.

METHODS: We retrospectively studied patients with metastatic PPG treated at the University of Texas, MD Anderson Cancer Center from January 2000 through January 2015. Kaplan-Meier analysis with log-rank tests was used to compare OS among patients undergoing primary tumor resection and patients not treated surgically. Propensity score method was applied to adjust for selection bias using demographic, clinical, biochemical, genetic, imaging, and pathologic information. RESULTS: A total of 113 patients with metastatic PPG were identified. Eighty-nine (79%) patients had surgery and 24 (21%) patients did not. Median OS was longer in patients who had surgery than in patients who did not [148 months, 95% confidence interval (CI) 112.8-183.2 months vs 36 months, 95% CI 27.2-44.8 months; P < 0.001].Fifty-three (46%) patients had synchronous metastases; of these patients, those who had surgery had longer OS than those who did not (85 months, 95% CI 64.5-105.4 months vs 36 months, 95% CI 29.7-42.3 months; P < 0.001). Patients who had surgery had a similar ECOG performance status to the ones who did not (P = 0.1798, two sample t test; P = 0.2449, Wilcoxon rank sum test). Univariate and propensity score analysis confirmed that patients treated with surgery had longer OS than those not treated surgically irrespective of age, race, primary tumor size and location, number of metastatic sites, and genetic background (log-rank P < 0.001).In patients with hormonally active tumors (70.8%), the symptoms of catecholamine excess improved after surgery. However, the tumor burden was a more important determinant of OS than hormonal secretion. CONCLUSIONS: Primary tumor resection in patients with metastatic PPG appeared to be associated with improved OS. In patients with hormonally active tumors, surgical resection led to better blood pressure control.
PubMed-ID: 28257320
http://dx.doi.org/10.1097/SLA.0000000000002195

Anatomical Variations of the Venous Drainage from the Left Adrenal Gland: An Anatomical Study.
World J Surg, 41(4):991-6.
M. Siebert, Y. Robert, R. Didier, A. Minster, W. M'Sallaoui, A. Bellier and P. C. Chaffanjon. 2017.
BACKGROUND: For radiologists, the venous drainage of adrenal glands is a key to the technique of selective adrenal venous sampling. For endocrine surgeons, it is key to adrenalectomy for carcinoma and pheochromocytoma. This study aims to demonstrate direct anastomosis between the left adrenal vein, the diaphragmatic circulation and the azygos system. Anatomical textbooks only offer very little information concerning the left adrenal vein (LAV) and its potential anastomosis with the reno-lumbo-azygo trunk (RLAT) and the diaphragmatic circulation. METHODS: Between November 2014 and October 2015 in the LADAF (French Alps Anatomy Laboratory), we dissected 44 formalin-fixed adult cadavers. RESULTS: We found no direct anastomosis between the left adrenal vein and the reno-azygo-lumbar trunk and two anastomoses (4.5%) between the adrenal capsular vein and azygos system. A lumbo-azygo trunk has been found 38 times (86.3%), drained 35 times (79.5%) into the left renal vein and 3 times (6.8%) into the left genital vein. An inferior phrenic vein ending into an adrenal vein was highlighted in all cases, 6 times (13.7%) in a double adrenal vein and 38 times (86.3%) in a single one. CONCLUSIONS: No connections have been found between left adrenal vein and the RLAT, and frequency of the IPV is discordant with the literature. However, our findings concerning the capsular vessels' anastomosis with the azygos system, inferior diaphragmatic flow and double adrenal vein could have two clinical applications: Firstly, the ligation of the adrenal vein solely is not enough to entirely interrupt the adrenal vein drainage, and secondly, sampling of hormones in the LAV could be underestimated because of the risk of dilution.
PubMed-ID: 27853815
http://dx.doi.org/10.1007/s00268-016-3817-2

Surgery for recurrent adrenocortical carcinoma: A multicenter retrospective study.
Surgery, 161(1):249-56.
G. Simon, F. Pattou, E. Mirallie, J. C. Lifante, C. Nomine, V. Arnault, L. de Calan, C. Caillard, B. Carnaille, L. Brunaud, N. Laplace, R. Caiazzo and C. Blanchard. 2017.
BACKGROUND: Adrenocortical carcinoma is a rare neoplasm with a high rate of recurrence. We studied the impact of surgery on the survival in recurrent adrenocortical carcinoma patients. METHODS: We performed a retrospective review of patients with recurrent adrenocortical carcinoma, managed in 5 French University Hospitals between 1980 and 2014. We compared surgery and medical management for ACC recurrence. RESULTS: Fifty-nine patients were included, 46 of whom had an initial R0 resection. Twenty-nine patients underwent reoperation for recurrence, while 30 had nonoperative treatments. Operated patients had a greater median overall survival after recurrence than nonoperated patients (91 vs 15 months; P < .001). Patients operated on for local or distant recurrence had similar overall survival (110 vs 91 months; P = .81). In nonoperated patients, types of medical managements did not impact survival. Surgery for recurrence (P = .037) and a disease-free interval between initial resection and recurrence >12 months (P = .059) were both prognostic factors for improved survival, whereas age, stage, and tumor size (P >/= .2 each) were not. A Ki67 <25% tended

to be associated with better overall survival (P = .051). CONCLUSION: Both surgery for recurrence and disease-free interval between the initial resection of an adrenocortical carcinoma and recurrence >12 months are associated with better overall survival.
PubMed-ID: 27855966
http://dx.doi.org/10.1016/j.surg.2016.08.058

Surgical Treatment of Malignant Pheochromocytoma and Paraganglioma: Retrospective Case Series.
Ann Surg Oncol, 24(6):1546-50.
V. Strajina, B. M. Dy, D. R. Farley, M. L. Richards, T. J. McKenzie, K. C. Bible, F. G. Que, D. M. Nagorney, W. F. Young and G. B. Thompson. 2017.
INTRODUCTION: Pheochromocytoma and paraganglioma (PPGL) are rare neoplasms; about 10% are malignant. Literature regarding possible benefit from resection is extremely limited. METHODS: A 20 year review of all patients undergoing surgery for malignant PPGL at the Mayo Clinic Rochester Campus between 1994 and June 2014 was performed. RESULTS: We identified 34 patients undergoing surgery for malignant PPGL. Median follow up was 6 and 5 years survival was 90% (median 11 years). Complete resection (R0) was achieved in 14 patients (41%). Median disease-free survival was 4.6 years for patients with R0 resection (up to 12 years). Only eight patients (23%) were disease-free on last follow up. Elevated preoperative fractionated metanephrines or catecholamines were documented in 23 patients (68%); these normalized in 13 of 23 patients (56%) postoperatively-with symptom relief in 15 of 18 preoperatively symptomatic patients (79%). Among 23 patients with hormone-producing tumors, significant reduction in number of antihypertensive medications was also noted postoperatively; 11 patients have remained off all antihypertensives, 6 required 1 medication, 1 required 2, while 5 required full blockade with phenoxybenzamine and a beta-adrenergic blocker. CONCLUSION: Surgery plays a significant role in the management of selected malignant PPGL. Resection can be effective in normalizing or significantly reducing levels of catecholamines and metanephrines, and can improve hormone-related symptoms and hypertension. Surgical resection, either complete or incomplete, is associated with durable survival despite a high rate of tumor recurrence.
PubMed-ID: 28058556
http://dx.doi.org/10.1245/s10434-016-5739-5

A registry-based study of thyroid paraganglioma: histological and genetic characteristics.
Endocr Relat Cancer, 22(2):191-204.
E. von Dobschuetz, H. Leijon, C. Schalin-Jantti, F. Schiavi, M. Brauckhoff, M. Peczkowska, G. Spiazzi, S. Dematte, M. E. Cecchini, P. Sartorato, J. Krajewska, K. Hasse-Lazar, K. Roszkowska-Purska, E. Taschin, A. Malinoc, L. A. Akslen, J. Arola, D. Lange, A. Fassina, G. Pennelli, M. Barbareschi, J. Luettges, A. Prejbisz, A. Januszewicz, T. Strate, B. Bausch, F. Castinetti, B. Jarzab, G. Opocher, C. Eng and H. P. Neumann. 2015.
The precise diagnosis of thyroid neoplasias will guide surgical management. Primary thyroid paraganglioma has been rarely reported. Data on prevalence, immunohistochemistry (IHC), and molecular genetics in a systematic series of such patients are pending. We performed a multinational population-based study on thyroid paraganglioma and analyzed prevalence, IHC, and molecular genetics. Patients with thyroid paraganglioma were recruited from the European-American-Head-and-Neck-Paraganglioma-Registry. Demographic and clinical data were registered. Histopathology and IHC were re-investigated. All patients with thyroid paraganglioma underwent molecular genetic analyses of the SDHA, SDHB, SDHC, SDHD, SDHAF2, VHL, RET, TMEM127, and MAX genes. Analyses included Sanger sequencing and multiplex ligation-dependent probe amplification (MLPA) for detection of large rearrangements. Of 947 registrants, eight candidates were initially identified. After immunohistochemical analyses of these eight subjects, 5 (0.5%) were confirmed to have thyroid paraganglioma. IHC was positive for chromogranin, synaptophysin, and S-100 and negative for calcitonin in all five thyroid paragangliomas, whereas the three excluded candidate tumors stained positive for pan-cytokeratin, a marker excluding endocrine tumors. Germline variants, probably representing mutations, were found in four of the five confirmed thyroid paraganglioma cases, two each in SDHA and SDHB, whereas the excluded cases had no mutations in the tested genes. Thyroid paraganglioma is a finite entity, which must be differentiated from medullary thyroid carcinoma, because medical, surgical, and genetic management for each is different. Notably, approximately 80% of thyroid paragangliomas are associated with germline variants, with implications for additional tumors and a potential risk for the family. As opposed to sporadic tumors, surgical management and extent of resection are different for heritable tumors, each guided by the precise gene involved.
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http://dx.doi.org/10.1530/ERC-14-0558

NET

Meta-Analyses

Systematic Review of the Role of Targeted Therapy in Metastatic Neuroendocrine Tumors.
Neuroendocrinology, 104(3):209-22.
A. Lee, D. L. Chan, M. H. Wong, B. T. Li, S. Lumba, S. J. Clarke, J. Samra and N. Pavlakis. 2017.
BACKGROUND: Targeted therapies [interferon (IFN), vascular endothelial growth factor (VEGF) inhibitors, and somatostatin analogs (SSA)] have become an integral part of the neuroendocrine tumor (NET) treatment paradigm. We systematically reviewed the available literature to assess the overall beneficial and negative effects of targeted therapy on progression-free survival (PFS), overall survival (OS), response rate (RR), and toxicity. METHODS: Randomized controlled trials (RCT) were identified from MEDLINE, Embase, other major databases, and an electronic search of major conferences. Abstract review, quality assessment, and data abstraction were performed independently by 2 investigators. Meta-analyses were conducted using the generic inverse variance method with a random-effects model, with studies pooled according to drug class and/or control arm for clinical homogeneity. RESULTS: Fifteen RCT [SSA, n = 2; mammalian target of rapamycin (mTOR)/VEGF inhibitors, n = 4; IFN, n = 3; targeted therapy added to everolimus, n = 2, and other, n = 4] investigating 2,790 patients were included. Overall, targeted agents improved PFS (HR 0.54; 95% CI 0.40-0.73) but not OS (HR 0.86; 95% CI 0.72-1.01). SSA improved PFS (HR 0.41; 95% CI 0.29-0.58) but not OS (HR 1.00; 95% CI 0.58-1.74). mTOR/VEGF inhibitors improved PFS (HR 0.48; 95% CI 0.32-0.72) but not OS (HR 0.82; 95% CI 0.58-1.17). Targeted therapies added to everolimus or IFN did not improve either PFS or OS. The RR overall was improved (OR 2.85; 95% CI 1.77-4.59) but toxicity was increased (meta-analysis not performed). CONCLUSIONS: The addition of targeted therapies improves PFS but not OS in NET. The evidence is strongest for VEGF inhibitors and SSA. There is an ongoing need for well-designed RCT to inform the optimal use of targeted therapies in NET.
PubMed-ID: 27082107
http://dx.doi.org/10.1159/000446115

Systematic review of active surveillance versus surgical management of asymptomatic small non-functioning pancreatic neuroendocrine neoplasms.
Br J Surg, 104(1):34-41.
S. Partelli, R. Cirocchi, S. Crippa, L. Cardinali, V. Fendrich, D. K. Bartsch and M. Falconi. 2017.
BACKGROUND: The incidence of asymptomatic, sporadic, small non-functioning pancreatic neuroendocrine neoplasms (NF-PNENs) has increased in recent decades. Conservative treatment has been advocated for these tumours. The aim of this study was systematically to evaluate the literature on active surveillance and to compare this with surgical management for asymptomatic sporadic small NF-PNENs. METHODS: PubMed, Embase and the Cochrane Library were searched systematically for studies that compared the active surveillance of asymptomatic, sporadic, small NF-PNENs with surgical management. PRISMA guidelines for systematic reviews were followed. RESULTS: After screening 3915 records, five retrospective studies with a total of 540 patients were included. Of these, 327 patients (60.6 per cent) underwent active surveillance and 213 (39.4 per cent) had surgery. There was wide variation in the tumour diameter threshold considered as inclusion criterion (2 cm to any size). The median length of follow-up ranged from 28 to 45 months. Measurable tumour growth was observed in 0-51.0 per cent of patients. Overall, 46 patients (14.1 per cent) underwent pancreatic resection after initial conservative treatment. In most patients the reason was an increase in tumour size (19 of 46). There were no disease-related deaths in the active surveillance group in any of the studies. CONCLUSION: This systematic review suggests that active surveillance of patients affected by sporadic, small, asymptomatic NF-PNENs may be a good alternative to surgical treatment.
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http://dx.doi.org/10.1002/bjs.10312

Randomized controlled trials

Telotristat Ethyl, a Tryptophan Hydroxylase Inhibitor for the Treatment of Carcinoid Syndrome.
J Clin Oncol, 35(1):14-23.
M. H. Kulke, D. Horsch, M. E. Caplin, L. B. Anthony, E. Bergsland, K. Oberg, S. Welin, R. R. Warner, C. Lombard-Bohas, P. L. Kunz, E. Grande, J. W. Valle, D. Fleming, P. Lapuerta, P. Banks, S. Jackson, B. Zambrowicz, A. T. Sands and M. Pavel. 2017.
Purpose Preliminary studies suggested that telotristat ethyl, a tryptophan hydroxylase inhibitor, reduces bowel movement (BM) frequency in patients with carcinoid syndrome. This placebo-controlled phase III study evaluated telotristat ethyl in this setting. Patients and Methods Patients (N = 135) experiencing four or more BMs per day despite stable-dose somatostatin analog therapy received (1:1:1) placebo, telotristat ethyl 250 mg, or telotristat ethyl 500 mg three times per day orally during a 12-week double-blind treatment period. The primary end point was change from baseline in BM frequency. In an open-label extension, 115 patients subsequently received telotristat ethyl 500 mg. Results Estimated differences in BM frequency per day versus placebo averaged over 12 weeks were -0.81 for telotristat ethyl 250 mg (P < .001) and 0.69 for telotristat ethyl 500 mg (P < .001). At week 12, mean BM frequency reductions per day for placebo, telotristat ethyl 250 mg, and telotristat ethyl 500 mg were -0.9, -1.7, and -2.1, respectively. Responses, predefined as a BM frequency reduction >/= 30% from baseline for >/= 50% of the double-blind treatment period, were observed in 20%, 44%, and 42% of patients given placebo, telotristat ethyl 250 mg, and telotristat ethyl 500 mg, respectively. Both telotristat ethyl dosages significantly reduced mean urinary 5-hydroxyindole acetic acid versus placebo at week 12 (P < .001). Mild nausea and asymptomatic increases in gamma-glutamyl transferase were observed in some patients receiving telotristat ethyl. Follow-up of patients during the open-label extension revealed no new safety signals and suggested sustained BM responses to treatment. Conclusion Among patients with carcinoid syndrome not adequately controlled by somatostatin analogs, treatment with telotristat ethyl was generally safe and well tolerated and resulted in significant reductions in BM frequency and urinary 5-hydroxyindole acetic acid.
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http://dx.doi.org/10.1200/JCO.2016.69.2780

Consensus Statements/Guidelines

Consensus Statement on next-generation-sequencing-based diagnostic testing of hereditary phaeochromocytomas and paragangliomas.
Nat Rev Endocrinol, 13(4):233-47.
R. A. Toledo, N. Burnichon, A. Cascon, D. E. Benn, J. P. Bayley, J. Welander, C. M. Tops, H. Firth, T. Dwight, T. Ercolino, M. Mannelli, G. Opocher, R. Clifton-Bligh, O. Gimm, E. R. Maher, M. Robledo, A. P. Gimenez-Roqueplo and P. L. Dahia. 2017.
Phaeochromocytomas and paragangliomas (PPGLs) are neural-crest-derived tumours of the sympathetic or parasympathetic nervous system that are often inherited and are genetically heterogeneous. Genetic testing is recommended for patients with these tumours and for family members of patients with hereditary forms of PPGLs. Due to the large number of susceptibility genes implicated in the diagnosis of inherited PPGLs, next-generation sequencing (NGS) technology is ideally suited for carrying out genetic screening of these individuals. This Consensus Statement, formulated by a study group comprised of experts in the field, proposes specific recommendations for the use of diagnostic NGS in hereditary PPGLs. In brief, the study group recommends target gene panels for screening of germ line DNA, technical adaptations to address different modes of disease transmission, orthogonal validation of NGS findings, standardized classification of variant pathogenicity and uniform reporting of the findings. The use of supplementary assays, to aid in the interpretation of the results, and sequencing of tumour DNA, for identification of somatic mutations, is encouraged. In addition, the study group launches an initiative to develop a gene-centric curated database of PPGL variants, with annual re-evaluation of variants of unknown significance by an expert group for purposes of reclassification and clinical guidance.
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http://dx.doi.org/10.1038/nrendo.2016.185

Other Articles

Phase II clinical trial of pasireotide long-acting repeatable in patients with metastatic neuroendocrine tumors.
Endocr Relat Cancer, 22(1):1-9.
M. Cives, P. L. Kunz, B. Morse, D. Coppola, M. J. Schell, T. Campos, P. T. Nguyen, P. Nandoskar, V. Khandelwal and J. R. Strosberg. 2015.
Pasireotide long-acting repeatable (LAR) is a novel somatostatin analog (SSA) with avid binding affinity to somatostatin receptor subtypes 1, 2, 3 (SSTR1,2,3) and 5 (SSTR5). Results from preclinical studies indicate that pasireotide can inhibit neuroendocrine tumor (NET) growth more robustly than octreotide in vitro. This open-label, phase II study assessed the clinical activity of pasireotide in treatment-naive patients with metastatic grade 1 or 2 NETs. Patients with metastatic pancreatic and extra-pancreatic NETs were treated with pasireotide LAR (60 mg every 4 weeks). Previous systemic therapy, including octreotide and lanreotide, was not permitted. Tumor assessments were performed every 3 months using Response Evaluation Criteria in Solid Tumors (RECIST) criteria. The primary endpoint was progression-free survival (PFS). The secondary endpoints included overall survival (OS), overall radiographic response rate (ORR), and safety. Twenty-nine patients were treated with pasireotide LAR (60 mg every 4 weeks) and 28 were evaluable for response. The median PFS was 11 months. The most favorable effect was observed in patients with low hepatic tumor burden, normal baseline chromogranin A, and high tumoral SSTR5 expression. Median OS has not been reached; the 30-month OS rate was 70%. The best radiographic response was partial response in one patient (4%), stable disease in 17 patients (60%), and progressive disease in ten patients (36%). Although grade 3/4 toxicities were rare, pasireotide LAR treatment was associated with a 79% rate of hyperglycemia including 14% grade 3 hyperglycemia. Although pasireotide appears to be an effective antiproliferative agent in the treatment of advanced NETs, the high incidence of hyperglycemia raises concerns regarding its suitability as a first-line systemic agent in unselected patients. SSTR5 expression is a potentially predictive biomarker for response.
PubMed-ID: 25376618
http://dx.doi.org/10.1530/ERC-14-0360

Prognostic factors in ectopic Cushing's syndrome due to neuroendocrine tumors: a multicenter study.
Eur J Endocrinol, 176(4):451-9.
M. V. Davi, E. Cosaro, S. Piacentini, G. Reimondo, N. Albiger, G. Arnaldi, A. Faggiano, G. Mantovani, N. Fazio, A. Piovesan, E. Arvat, F. Grimaldi, L. Canu, M. Mannelli, A. G. Ambrogio, F. Pecori Giraldi, C. Martini, A. Lania, M. Albertelli, D. Ferone, M. C. Zatelli, D. Campana, A. Colao, C. Scaroni, M. Terzolo, L. De Marinis, S. Cingarlini, R. Micciolo and G. Francia. 2017.
OBJECTIVE: Evidence is limited regarding outcome of patients with ectopic Cushing's syndrome (ECS) due to neuroendocrine tumors (NETs). DESIGN: We assessed the prognostic factors affecting the survival of patients with NETs and ECS. METHODS: Retrospective analysis of clinicopathological features, severity of hormonal syndrome, treatments from a large cohort of patients with NETs and ECS collected from 17 Italian centers. RESULTS: Our series included 110 patients, 58.2% female, with mean (+/-s.d.) age at diagnosis of 49.5 +/- 15.9 years. The main sources of ectopic ACTH were bronchial carcinoids (BC) (40.9%), occult tumors (22.7%) and pancreatic (p)NETs (15.5%). Curative surgery was performed in 56.7% (70.2% of BC, 11% of pNETs). Overall survival was significantly higher in BC compared with pNETs and occult tumors (P = 0.033) and in G1-NETs compared with G2 and G3 (P = 0.007). Negative predictive factors for survival were severity of hypercortisolism (P < 0.02), hypokalemia (P = 0.001), diabetes mellitus (P = 0.0146) and distant metastases (P < 0.001). Improved survival was observed in patients who underwent NET removal (P < 0.001). Adrenalectomy improved short-term survival. CONCLUSIONS: Multiple factors affect prognosis of ECS patients: type of NET, grading, distant metastases, severity of hypercortisolism, hypokalemia and diabetes mellitus. BCs have the highest curative surgical rate and better survival compared with occult tumors and pNETs. Hypercortisolism plays a primary role in affecting outcome and quality of life; therefore, prompt and vigorous treatment of hormonal excess by NET surgery and medical therapy should be a key therapeutic goal. In refractory cases, adrenalectomy should be considered as it affects outcome positively at least in the first 2 years.
PubMed-ID: 28183788
http://dx.doi.org/10.1530/EJE-16-0809

Aggressive Surgical Approach to the Management of Neuroendocrine Tumors: A Report of 1,000 Surgical Cytoreductions by a Single Institution.
J Am Coll Surg, 224(4):434-47.
E. A. Woltering, B. A. Voros, D. T. Beyer, Y. Z. Wang, R. Thiagarajan, P. Ryan, A. Wright, R. A. Ramirez, M. J. Ricks and J. P. Boudreaux. 2017.

BACKGROUND: Neuroendocrine tumors (NETs) are rare neoplasms. Our group has treated more than 2,000 NET patients and has performed more than 1,000 surgical cytoreductive procedures. STUDY DESIGN: Records of 834 NET patients who underwent surgical cytoreduction at our institution were reviewed. Demographic information, intraoperative findings, extent of disease, complications, and survival rates were calculated. RESULTS: Eight hundred patients underwent 1,001 cytoreductive operations. Sixty-five percent had small bowel primaries. One hundred and thirty-eight patients presented with an unknown primary site, which was localized intraoperatively in 89% of these cases. The intraoperative complication rate was 9%. The incidence of intraoperative carcinoid crisis was 1%. Mean +/- SD operative time was 368 +/- 146 minutes. Mean +/- SD hospital stay was 9 +/- 10 days. Minor postoperative complications occurred after 43% of procedures and major postoperative complications were noted after 19% of procedures. The 30-day postoperative mortality rate was 2%. Median overall survival (OS) for patients with pancreatic NETs was 124 months. The 5-, 10-, and 20-year OS rates for patients with pancreatic NETs were 67%, 51%, and 36%, respectively. The life expectancy difference (between OS and actuarial survival) after surgical cytoreduction for patients with pancreatic NETs was 16.6 years. Median OS for patients with small bowel NETs was 161 months. The 5-, 10-, and 20-year OS rates for patients with small bowel NETs were 84%, 67% and 31%, respectively. The life expectancy difference after surgical cytoreduction for patients with small bowel NETs was 11.7 years. CONCLUSIONS: Surgical cytoreduction in NET patients has low morbidity and mortality rates and results in prolonged survival. We believe that surgical cytoreduction should play a major role in the care of patients with NETs.
PubMed-ID: 28088602
http://dx.doi.org/10.1016/j.jamcollsurg.2016.12.032

Vascularity and Tumor Size are Significant Predictors for Recurrence after Resection of a Pancreatic Neuroendocrine Tumor.
Ann Surg Oncol, 24(8):2363-70.
Y. Yamamoto, Y. Okamura, S. Uemura, T. Sugiura, T. Ito, R. Ashida, Y. Kato, K. Ohgi, M. Yamada, K. Sasaki, T. Aramaki and K. Uesaka. 2017.
BACKGROUND: It is difficult to identify patients at high risk of recurrence after pancreatectomy for pancreatic neuroendocrine tumor (PNET) using only the grading classification, especially the G2 category, which includes both benign and low- and high-grade malignant tumors. METHODS: Forty-one patients with PNET who underwent pancreatectomy were enrolled in this study. We defined the computed tomography (CT) ratio as the CT value of the tumor divided by that of non-tumorous pancreatic parenchyma using the late arterial phase dynamic CT. The optimal cut-off values for CT ratio and tumor size were determined using p-values that were calculated using the log-rank test. RESULTS: The optimal cut-off values of CT ratio and tumor size for dividing patients into groups according to the greatest difference in disease-free survival (DFS) were 0.85 ($p < 0.001$) and 3.0 cm ($p < 0.001$), respectively. In analysis using Spearman's correlation coefficient, CT ratio ($p = 0.007$) and tumor size ($p = 0.003$) were individually associated with the Ki-67 proliferative index. Cox proportional hazard analysis identified that a CT ratio <0.85 ($n = 10$, $p = 0.006$) and tumor size >/=3.0 cm ($n = 13$, $p = 0.023$) were independent prognostic factors associated with DFS. All patients in the CT ratio >/=0.85 and tumor size <3.0 cm group ($n = 23$, including seven patients with G2 disease) did not develop recurrence after surgery. On the other hand, 5-year DFS in the CT ratio <0.85 and tumor size >/=3.0 cm group ($n = 5$, including three patients with G2 disease) was zero. CONCLUSIONS: PNETs with a CT ratio <0.85 and tumor size >/=3.0 cm should be considered as having a high risk of recurrence after pancreatectomy.
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http://dx.doi.org/10.1245/s10434-017-5823-5

Assessing the role of primary tumour resection in patients with synchronous unresectable liver metastases from pancreatic neuroendocrine tumour of the body and tail. A propensity score survival evaluation.
Eur J Surg Oncol, 43(2):372-9.
E. Bertani, N. Fazio, D. Radice, C. Zardini, G. Spinoglio, A. Chiappa, D. Ribero, R. Biffi, S. Partelli and M. Falconi. 2017.
BACKGROUND: The role of primary tumour surgery in pancreatic neuroendocrine tumours (PNETs) with unresectable liver metastases is controversial and international guidelines do not recommend surgery in such cases. Resectability of the primary tumour has never been considered in outcome comparisons between operated and non-operated patients. METHODS: From two institutional prospective databases of patients affected by PNET and unresectable liver metastases, 63 patients who underwent a left-pancreatectomy at diagnosis were identified and compared with a group of 30 patients with a potentially resectable but not-resected primary tumour located in the body or tail. The endpoint was overall survival (OS). RESULTS: The two groups significantly differed at baseline with regard to liver tumour burden Ki-67 labelling index, site of pancreas, results

of the 18FDG PET-CT and age. In the operated patients, surgical morbidity comprised 7 cases of pancreatic fistula. Postoperative mortality was nil. Median OS for patients undergoing left-pancreatectomy was 111 months vs 52 for the non operated patients (p = 0.003). At multivariate analysis after propensity score adjustment, no surgery as well as liver tumour burden>25% and higher Ki-67 index were associated with an increased risk of death during follow-up. In patients with unresectable primary tumour, OS was similar in comparison to that in the resectable but non-resected patients, and significantly worse than that in the resected patients (p = 0.032). CONCLUSION: In PNETs located in the body or tail and diffuse liver metastases distal pancreatectomy may be justified in selected patients. Randomized studies may be safely proposed in future on this topic.
PubMed-ID: 27742480
http://dx.doi.org/10.1016/j.ejso.2016.09.011

Primary tumour resection may improve survival in functional well-differentiated neuroendocrine tumours metastatic to the liver.
Eur J Surg Oncol, 43(2):380-7.
D. Citterio, S. Pusceddu, A. Facciorusso, J. Coppa, M. Milione, R. Buzzoni, M. Bongini, F. deBraud and V. Mazzaferro. 2017.
BACKGROUND: Functional well-differentiated neuroendocrine tumours (NET) with liver metastases represent a therapeutic challenge with few alternative options in guidelines. In these patients, the role of surgical resection of the primary tumour is controversial. PATIENTS AND METHODS: From a regional registry collecting somatostatin analogue (SSA)-treated tumours from 1979 to 2005, a series of 139 patients presenting with symptomatic, liver-metastatic, well-differentiated NET (G1-G2, mitoses: </=20, Ki-67: </=20%) was prospectively collected and retrospectively analysed. Surgery on either the primary tumour or liver metastases was chosen: 1) when low perioperative risk was predictable; 2) in presence of an impending risk of obstruction, bleeding, or perforation; or 3) if liver metastases were suitable of curative or subtotal (>90%) tumour removal. Impact of the most relevant clinico-pathological parameters on survival was studied. RESULTS: Median follow-up was 127 months and median survival was 94 months, with 138 vs. 37 months in resected vs. non-resected primary NET (p < 0.001), respectively. In the univariate analysis, prolonged survival was significantly associated with primary tumour resection (p < 0.001), resection of liver metastases (p = 0.002), site of primary (carcinoid vs. pancreatic, p = 0.018), basal chromogranin-A (CgA) <200 ng/mL (p = 0.001), and absence of diarrhea (p = 0.012). Multivariate analysis showed that primary tumour resection was an independent positive prognostic factor (HR = 3.17; 95% CI: 1.77-5.69, p < 0.001), whereas diarrhea, basal CgA >/=200 ng/mL, and high tumour load were independent negative prognostic factors. Also, in 103 patients with non-resectable liver metastases, primary tumour resection was significantly associated with prolonged survival (median 137 vs. 32 months, p < 0.0001). CONCLUSIONS: Primary tumour resection may improve survival in functional well-differentiated NET with liver metastases.
PubMed-ID: 27956320
http://dx.doi.org/10.1016/j.ejso.2016.10.031

Long-term outcomes in patients with multiple endocrine neoplasia type 1 and pancreaticoduodenal neuroendocrine tumours.
Clin Endocrinol (Oxf), 86(2):199-206.
D. Donegan, N. Singh Ospina, R. Rodriguez-Gutierrez, Z. Al-Hilli, G. B. Thompson, B. L. Clarke and W. F. Young, Jr. 2017.
BACKGROUND: In patients with multiple endocrine neoplasia type 1 (MEN-1), pancreaticoduodenal (PD) neuroendocrine tumours (NETs) are associated with early mortality, yet the best treatment strategy remains uncertain. AIM: To assess patient important outcomes (mortality and metastasis) of PD-NETs and predictors of outcomes in patients with MEN-1. METHODS: Retrospective cohort of patients with MEN-1 who attended the Mayo Clinic, Rochester, MN from 1997 to 2014. RESULTS: We identified 287 patients with MEN-1; 199 (69%) patients had 217 PD-NETs. Among those with a PD-NETs, 129 (65%) had surgery of which 90 (70%) had their primary surgery performed at Mayo Clinic. The median postoperative follow-up was 8 years during which 13 (14%) patients died. The mean (+/-standard deviation) age of death was 51 (+/-9) years. Tumour size, metastasis at surgery or tumour type were not predictive of mortality, but for every year older at surgery, the odds of metastasis increased by 6%. Surgery was not performed in 70 (35%) patients. Among those who were observed/medically managed without known metastatic disease, mean tumour growth was 0.02 cm/year (range, -0.13-0.4 cm/year). Four patients (7%) died at a median age of 77 (range, 51-89) years. CONCLUSION: PD-NETs are common in patients with MEN-1 and are associated with early mortality even after surgical intervention. Active surveillance is a viable option in nonaggressive PD-NETs, although definitive factors identifying such patients are lacking. Therefore, counselling regarding risks and benefits of current treatment options remains integral to the care of patients with MEN-1.

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http://dx.doi.org/10.1111/cen.13264

Clinical signs of fibrosis in small intestinal neuroendocrine tumours.
Br J Surg, 104(1):69-75.
K. Daskalakis, A. Karakatsanis, P. Stalberg, O. Norlen and P. Hellman. 2017.
BACKGROUND: In patients with small intestinal neuroendocrine tumours (SI-NETs), serotonin and other cytokines released from tumour cells may induce fibrosis, leading to carcinoid heart disease and abdominal fibrotic reactions. The aim of this study was to assess the prevalence, clinical complications and management of this reaction in the abdomen. METHODS: This was a retrospective cohort study of patients with SI-NETs diagnosed between 1985 and 2015. Clinical data, outcomes, radiological findings, and surgical and radiological interventions were reviewed. RESULTS: A total of 824 patients were diagnosed with SI-NETs in the study interval. Clinically significant abdominal signs and symptoms of fibrosis occurred in 36 patients. Of these, 20 had critically symptomatic central mesenteric fibrosis causing obstruction of mesenteric vessels, and 16 had retroperitoneal fibrosis causing obstructive uropathy with hydronephrosis. Extensive fibrosis causing mesenteric vessel obstruction and/or obstructive uropathy was more often associated with symptomatic and advanced disease encompassing lymph node metastases in the mesenteric root, para-aortic lymph node metastases, as well as liver metastases and peritoneal carcinomatosis. Palliative intervention in terms of superior mesenteric vein stenting or resection of central mesenteric metastases and/or percutaneous nephrostomy and J stent treatment was beneficial in the majority of the patients. CONCLUSION: Extensive abdominal fibrosis associated with clinically significant symptoms of intestinal ischaemia and/or obstructive uropathy was linked to advanced disease in patients with SI-NETs. Prompt recognition and minimally invasive intervention was effective in disease palliation.
PubMed-ID: 27861745
http://dx.doi.org/10.1002/bjs.10333

Localization of Insulinoma Using 68Ga-DOTATATE PET/CT Scan.
J Clin Endocrinol Metab, 102(1):195-9.
P. Nockel, B. Babic, C. Millo, P. Herscovitch, D. Patel, N. Nilubol, S. M. Sadowski, C. Cochran, P. Gorden and E. Kebebew. 2017.
Context: Reliable localization of insulinoma is critical for successful treatment. Objective: This study compared the accuracy of 68Gallium DOTA-(Tyr3)-octreotate (Ga-DOTATATE) positron emission tomography (PET)/computed tomography (CT) to anatomic imaging modalities, selective arterial secretagogue injection (SASI), and intraoperative ultrasound (IO ultrasound) and palpation for localizing insulinoma in patients who were biochemically cured. Design, Setting, and Patients: We conducted a retrospective analysis of 31 patients who had an insulinoma. The results of CT, magnetic resonance imaging (MRI), ultrasound, IO ultrasound, 68Ga-DOTATATE PET/CT, SASI, and operative findings were analyzed. Intervention, Main Outcome Measures, and Results: The insulinomas were correctly localized in 17 out of 31 (55%) patients by CT, in 17 out of 28 (61%) by MRI, in 6 out of 28 (21%) by ultrasound, and in 9 out of 10 (90%) by 68Ga-DOTATATE. In 29 of 31 patients (93.5%) who had IO ultrasound, an insulinoma was successfully localized. Thirty patients underwent SASI, and the insulinoma was regionalized in 28 out of 30 patients (93%). In 19 out of 23 patients (83%), manual palpation identified insulinoma. In patients who had all 4 noninvasive imaging studies, CT was concordant with 68Ga-DOTATATE in 6 out of 9 patients (67%), MRI in 8 out of 9 (78%), ultrasound in 0 out of 9; the lesion was only seen by 68Ga-DOTATATE in 1 out of 9 (11%). Conclusions: 68Ga-DOTATATE PET/CT identifies most insulinomas and may be considered as an adjunct imaging study when all imaging studies are negative and when a minimally invasive surgical approach is planned.
PubMed-ID: 27805844
http://dx.doi.org/10.1210/jc.2016-3445

Utility of FDG-PET Imaging for Risk Stratification of Pancreatic Neuroendocrine Tumors in MEN1.
J Clin Endocrinol Metab, 102(6):1926-33.
E. R. Kornaczewski Jackson, O. P. Pointon, R. Bohmer and J. R. Burgess. 2017.
Context: Patients with multiple endocrine neoplasia type 1 (MEN1) are at high risk of malignant pancreatic neuroendocrine tumors (pNETs). Structural imaging is typically used to screen for pNETs but is suboptimal for stratifying malignant potential. Objective: To determine the utility of fluorodeoxyglucose (18F) positron emission tomography/computed tomography (18F-FDG PET/CT) for predicting the malignant potential of pNETs in MEN1. Design: Retrospective observational study. Setting: Tertiary referral hospital. Patients: Forty-nine adult patients with MEN1 carrying a common MEN1 mutation who underwent 18F-FDG PET/CT for MEN1 surveillance between 1 January 2010 and 30 September 2016. Interventions: Structural and functional imaging (magnetic

resonance imaging, CT, ultrasonography, and 18F-FDG PET/CT) and surgical histopathology. Main Outcome Measures: pNET size, behavior, and histopathology. Results: Twenty-five (51.0%) of 49 patients studied had pancreatic lesions on structural imaging. Five (25%) of these had 18F-FDG-PET-avid lesions. In addition, two had solitary FDG-avid liver lesions, and one a pancreatic focus without structural correlate. Eight patients with pNETs underwent surgery (three FDG-avid lesions and five nonavid pNETs). The Ki-67 index was >/=5% in FDG-avid pNETs and <2% in nonavid pNETs. Overall, six of the eight (75%) patients with FDG-avid hepatopancreatic lesions harbored aggressive or metastatic NETs compared with one of 41 patients (2.4%) without hepatopancreatic FDG avidity [P < 0.001; sensitivity; 85.7% (95% confidence interval [CI], 48.7% to 99.3%); specificity, 95.2% (95% CI, 84.2% to 99.2%)]. Conclusion: 18F-FDG PET/CT is an effective screening modality in MEN1 for identifying pNETs of increased malignant potential. Surgical resection is recommended for FDG-avid pNETs.
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http://dx.doi.org/10.1210/jc.2016-3865

Well-Differentiated, Non-Functional, Non-Ampullary Duodenal Neuroendocrine Tumors: Toward Defining Evaluation and Management.
World J Surg, 41(3):844-50.
T. Weatherall, J. Denbo, J. Sharpe, M. Martin, T. O'Brien, R. Gupta, K. Groshart, S. Behrman and P. Dickson.
2017.
INTRODUCTION: Nonfunctional, non-ampullary duodenal neuroendocrine tumors (dNETs) are rare neoplasms, and specific treatment recommendations are less clear than for other NETs. MATERIALS AND METHODS: We performed a retrospective review of patients (pts) with a diagnosis of dNET, excluding hormonally functional, ampullary, and high-grade tumors. Clinical data were evaluated to identify factors that might impact clinical staging and predictors of metastases. RESULTS: Thirty-six pts were identified. Surgical resection was performed in 28 and endoscopic resection in 8. LNs were included in specimens of 19/28 (68 %) pts who underwent surgical resection (median #LNs 5, range 1-12). Of these 19 pts, 5 (26 %) were found to be LN+. Of LN+ pts, all had tumors </=2 cm. When compared to LN- pts, LN+ pts were more likely to have muscularis propria (MP) invasion (80 vs. 23 %, p = 0.04). Tumor size, tumor grade, lymphovascular invasion, and multifocality were similar between LN+ and LN- patients. No pt was found to have distant metastases. Heterogeneity in clinical staging modalities and small number of pts evaluated prohibited meaningful analysis of most appropriate preoperative imaging. At a median follow-up of 25 months (range 9-139), no patient developed recurrence or experienced disease-specific death. CONCLUSIONS: Non-functional, non-ampullary dNETs, particularly those with MP invasion, have a propensity to metastasize to regional LNs. However, these neoplasms appear to have a favorable prognosis. Further evaluation of preoperative imaging is required to better determine most appropriate clinical staging. A suggested workup and management strategy for prospective evaluation is proposed.
PubMed-ID: 27743074
http://dx.doi.org/10.1007/s00268-016-3770-0

General

Meta-Analyses

- None -

Randomized controlled trials

Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors.
N Engl J Med, 376(2):125-35.
J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P. L. Kunz, M. H. Kulke, H. Jacene, D. Bushnell, T. M. O'Dorisio, R. P. Baum, H. R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srirajaskanthan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Oberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J. L. Erion, P. Ruszniewski, D. Kwekkeboom and E. Krenning. 2017.
BACKGROUND: Patients with advanced midgut neuroendocrine tumors who have had disease progression during first-line somatostatin analogue therapy have limited therapeutic options. This randomized, controlled trial evaluated the efficacy and safety of lutetium-177 (177Lu)-Dotatate in patients with advanced, progressive, somatostatin-receptor-positive midgut neuroendocrine tumors. METHODS: We randomly assigned 229 patients who had well-differentiated, metastatic midgut neuroendocrine tumors to receive either 177Lu-Dotatate (116 patients) at a dose of 7.4 GBq every 8 weeks (four intravenous infusions, plus best supportive care including octreotide long-acting repeatable [LAR] administered intramuscularly at a dose of 30 mg) (177Lu-Dotatate group) or octreotide LAR alone (113 patients) administered intramuscularly at a dose of 60 mg every 4 weeks (control group). The primary end point was progression-free survival. Secondary end points included the objective response rate, overall survival, safety, and the side-effect profile. The final analysis of overall survival will be conducted in the future as specified in the protocol; a prespecified interim analysis of overall survival was conducted and is reported here. RESULTS: At the data-cutoff date for the primary analysis, the estimated rate of progression-free survival at month 20 was 65.2% (95% confidence interval [CI], 50.0 to 76.8) in the 177Lu-Dotatate group and 10.8% (95% CI, 3.5 to 23.0) in the control group. The response rate was 18% in the 177Lu-Dotatate group versus 3% in the control group (P<0.001). In the planned interim analysis of overall survival, 14 deaths occurred in the 177Lu-Dotatate group and 26 in the control group (P=0.004). Grade 3 or 4 neutropenia, thrombocytopenia, and lymphopenia occurred in 1%, 2%, and 9%, respectively, of patients in the 177Lu-Dotatate group as compared with no patients in the control group, with no evidence of renal toxic effects during the observed time frame. CONCLUSIONS: Treatment with 177Lu-Dotatate resulted in markedly longer progression-free survival and a significantly higher response rate than high-dose octreotide LAR among patients with advanced midgut neuroendocrine tumors. Preliminary evidence of an overall survival benefit was seen in an interim analysis; confirmation will be required in the planned final analysis. Clinically significant myelosuppression occurred in less than 10% of patients in the 177Lu-Dotatate group. (Funded by Advanced Accelerator Applications; NETTER-1 ClinicalTrials.gov number, NCT01578239 ; EudraCT number 2011-005049-11 .).
PubMed-ID: 28076709
http://dx.doi.org/10.1056/NEJMoa1607427

Consensus Statements/Guidelines

- None -

Other Articles

177Lu-Dotatate for Midgut Neuroendocrine Tumors.
N Engl J Med, 376(14):1390-1.
M. S. Hofman, M. Michael and R. J. Hicks. 2017.
PubMed-ID: 28382815
http://dx.doi.org/10.1056/NEJMc1701616

Endocrine surgery fellowship graduates past, present, and future: 8 years of early job market experiences and what program directors and trainees can expect.
Surgery, 161(1):289-96.
V. D. Krishnamurthy, J. Gutnick, R. Slotcavage, J. Jin, E. Berber, A. Siperstein and J. J. Shin. 2017.
BACKGROUND: Given the increasing number of endocrine surgery fellowship graduates, we investigated if expectations and job opportunities changed over time. METHODS: American Association of Endocrine Surgeons (AAES) fellowship graduates, surgery department chairs, and physician recruiters were surveyed. Univariate analysis was performed with JMP Pro 12 software. RESULTS: We identified 141 graduates from 2008-2015; survey response rate was 72% (n = 101). Compared to earlier graduates, fewer academic opportunities were available for the recent graduates who intended to join them (P = .001). Unlike earlier graduates, recent graduates expected to also perform elective general surgery, which ultimately represented a greater percentage of their practices (both P < .05). Interview offers increased for recent graduates, but job offers decreased. Overall, 84% of graduates matched their intended practice type and 98% reported being satisfied. Reponses from graduates, department chairs, and physician recruiters highlighted opportunities to improve mentor involvement, job search strategies, and online job board utilization. CONCLUSION: The endocrine surgery job market has diversified resulting in more graduates entering nonacademic practices and performing general surgery. This rapid evolution supports future analyses of the job market and opportunities for job creation. Almost every graduate reported job satisfaction, which encourages graduates to consider joining both academic and nonacademic practices equally.
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http://dx.doi.org/10.1016/j.surg.2016.06.069

Diagnostic value of chromogranin A in pancreatic neuroendocrine tumors depends on tumor size: A prospective observational study from a single institute.
Surgery, 162(1):120-30.
E. Jun, S. C. Kim, K. B. Song, D. W. Hwang, J. H. Lee, S. H. Shin, S. M. Hong, K. M. Park and Y. J. Lee. 2017.
BACKGROUND: Chromogranin A has recently been recommended as the most practical tumor marker in patients with pancreatic neuroendocrine tumors. However, the diagnostic effectiveness of circulating chromogranin A levels remains controversial. Here, we aimed to assess the clinical diagnostic value of plasma chromogranin A levels for pancreatic neuroendocrine tumors. METHODS: Between June 2012 and June 2015, 110 consecutive patients with a suspected pancreatic neuroendocrine tumor were prospectively enrolled. We evaluated the diagnostic value of the chromogranin A assay for differentiating pancreatic neuroendocrine tumors from other tumors. The plasma chromogranin A levels in the pancreatic neuroendocrine tumor patients were examined according to various clinicopathologic factors. RESULTS: A total of 65 patients were diagnosed as having pancreatic neuroendocrine tumors, whereas 45 had other tumors. The median chromogranin A level in pancreatic neuroendocrine tumor cases was higher than that in cases of other tumors (pancreatic neuroendocrine tumors: 126.62 ng/mL, other tumors: 69.82 ng/mL). The sensitivity, specificity, and accuracy of the chromogranin A assay for pancreatic neuroendocrine tumor diagnosis were 49.2%, 77.8%, and 60.9%, respectively. The chromogranin A levels after operative resection were reduced or were confirmed as being within the normal range (78.9%) in most cases. Moreover, the chromogranin A level in pancreatic neuroendocrine tumors cases was correlated with tumor size based on comparisons with other tumors in the pancreas (P = .038). The sensitivity, specificity, and accuracy of the chromogranin A assay for large tumors were greater, at 64.3%, 100.0%, and 81.5%, respectively. CONCLUSION: In clinical settings, the identification of pancreatic neuroendocrine tumors is vital for the development of therapeutic strategies. In large pancreatic tumors, the measurement of chromogranin A levels is very useful for distinguishing pancreatic neuroendocrine tumors from other tumors in the pancreas.
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http://dx.doi.org/10.1016/j.surg.2017.01.019

Optimizing Outpatient Pain Management After Thyroid and Parathyroid Surgery: A Two-Institution Experience.
Ann Surg Oncol, 24(7):1951-7.
I. Lou, T. B. Chennell, S. C. Schaefer, H. Chen, R. S. Sippel, C. Balentine, D. F. Schneider and J. Moalem. 2017.
BACKGROUND: Thyroidectomy and parathyroidectomy are the most commonly performed endocrine operations, and are increasingly being completed on a same-day basis; however, few data exist regarding the outpatient postoperative pain requirement of these patients. We aimed to describe the outpatient narcotic medication needs for patients undergoing thyroid and parathyroid surgery, and to identify predictors of higher requirement. METHOD: We examined patients undergoing thyroid and parathyroid surgery at two large academic institutions from 1 January-30 May 2014. Prospective data were collected on pain scores and the oral morphine equivalents (OMEQs) taken by these patients by their postoperative visit. RESULTS: Overall, 313 adult patients underwent thyroidectomy or parathyroidectomy during the study period; 83% of patients took ten or fewer OMEQs, and 93% took 20 or fewer OMEQs. Patients who took more than ten OMEQs were younger ($p < 0.001$) and reported significantly higher overall mean pain scores at their postoperative visit ($p < 0.001$) than patients who took fewer than ten OMEQs. A multivariate model was constructed on pre- and intraoperative factors that may predict use of more than ten OMEQs postoperatively. Age <45 years ($p = 0.002$), previous narcotic use ($p = 0.037$), and whether parathyroid or thyroid surgery was performed ($p = 0.003$) independently predicted the use of more than ten OMEQs after surgery. A subgroup analysis was then performed on thyroidectomy-only patients. CONCLUSION: Overall, 93% of patients undergoing thyroidectomy and parathyroidectomy require 20 or fewer OMEQs by their postoperative visit. We therefore recommend these patients be discharged with 20 OMEQs, both to minimize waste and increase patient safety.
PubMed-ID: 28160140
http://dx.doi.org/10.1245/s10434-017-5781-y

Operation for insulinomas in multiple endocrine neoplasia type 1: When pancreatoduodenectomy is appropriate.
Surgery, 161(3):727-34.
F. Tonelli, F. Giudici, G. Nesi, G. Batignani and M. L. Brandi. 2017.
BACKGROUND: Distal pancreatectomy is the most frequent operation for insulinomas complicating multiple endocrine neoplasia type 1 insulinoma, although there are conditions for which a different operative approach might be preferable. In this article, we report the operative experience of a referral center for multiple endocrine neoplasia type 1 insulinoma. METHODS: Twelve patients underwent operations between 1992 and 2015: 8 underwent a distal pancreatic resection, and 4 underwent a pancreatoduodenectomy. Enucleation of other macroadenomas present in the remnant pancreas was performed in 9 out of these 12 patients. RESULTS: Operative complications (2 pancreatic fistulas and 2 cases of pancreatitis) occurred in 4 of the 8 distal pancreatic resections. In 1 patient, reoperation was required to resolve the complications of the first operation. At pathologic analysis, multiple insulinomas were found in 5 patients, lymph-nodal metastasis positive for insulin in 2 patients, multiple nonfunctioning pancreatic tumors in all patients, glucagonoma in 4 patients, and gastrinoma in the duodenum or lymph nodes in 4 patients. All the patients were treated successfully for the hypoglycemic/hyperinsulinemic syndrome with no clinical recurrence at a mean follow-up of 85 months (range 4-242 months). Recurrent nonfunctioning pancreatic tumor macroadenomas in the remnant pancreas occurred in only 1 of the 12 patients, and no progression of the gastrinomas was observed. None of the patients developed diabetes mellitus. CONCLUSION: Resection of the most severely affected part of the pancreas, whether left or right, associated with enucleation of concomitant macroadenomas in the preserved pancreas is recommended for the treatment of hypoglycemic/hyperinsulinemic syndrome and to prevent malignant progression of nonfunctioning pancreatic tumors in patients with multiple endocrine neoplasia type 1. If the head of the pancreas is the most affected site and the Zollinger-Ellison syndrome is concomitant, then pancreatoduodenectomy should be preferred over distal pancreatectomy.
PubMed-ID: 27863775
http://dx.doi.org/10.1016/j.surg.2016.09.017

Management of MEN1 Related Nonfunctioning Pancreatic NETs: A Shifting Paradigm: Results From the DutchMEN1 Study Group.
Ann Surg,
S. Nell, H. M. Verkooijen, C. R. Pieterman, W. W. de Herder, A. R. Hermus, O. M. Dekkers, A. N. van der Horst-Schrivers, M. L. Drent, P. H. Bisschop, B. Havekes, I. H. Borel Rinkes, M. R. Vriens and G. D. Valk. 2017.
OBJECTIVE: To assess if surgery for Multiple Endocrine Neoplasia type 1 (MEN1) related nonfunctioning pancreatic neuroendocrine tumors (NF-pNETs) is effective for improving overall survival and preventing liver

metastasis. BACKGROUND: MEN1 leads to multiple early-onset NF-pNETs. The evidence base for guiding the difficult decision who and when to operate is meager. METHODS: MEN1 patients diagnosed with NF-pNETs between 1990 and 2014 were selected from the DutchMEN1 Study Group database, including > 90% of the Dutch MEN1 population. The effect of surgery was estimated using time-dependent Cox analysis with propensity score restriction and adjustment. RESULTS: Of the 152 patients, 53 underwent surgery and 99 were managed by watchful waiting. In the surgery group, tumors were larger and faster-growing, patients were younger, more often male, and were more often treated in centers that operated more frequently. Surgery for NF-pNETs was not associated with a significantly lower risk of liver metastases or death, [adjusted hazard ratio (HR) = 0.73 (0.25-2.11)]. Adjusted HR's after stratification by tumor size were: NF-pNETs <2 cm = 2.04 (0.31-13.59) and NF-pNETs 2-3 cm = 1.38 (0.09-20.31). Five out of the 6 patients with NF-pNETs >3 cm managed by watchful waiting developed liver metastases or died compared with 6 out of the 16 patients who underwent surgery. CONCLUSIONS: MEN1 patients with NF-pNETs <2 cm can be managed by watchful waiting, hereby avoiding major surgery without loss of oncological safety. The beneficial effect of a surgery in NF-pNETs 2 to 3 cm requires further research. In patients with NF-pNETs >3 cm, watchful waiting seems not advisable.
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http://dx.doi.org/10.1097/SLA.0000000000002183

Long-term Follow-up of MEN1 Patients Who Do Not Have Initial Surgery for Small </=2 cm Nonfunctioning Pancreatic Neuroendocrine Tumors, an AFCE and GTE Study: Association Francophone de Chirurgie Endocrinienne & Groupe d'Etude des Tumeurs Endocrines.
Ann Surg,
F. Triponez, S. M. Sadowski, F. Pattou, C. Cardot-Bauters, E. Mirallie, M. Le Bras, F. Sebag, P. Niccoli, S. Deguelte, G. Cadiot, G. Poncet, J. C. Lifante, F. Borson-Chazot, P. Chaffanjon, O. Chabre, F. Menegaux, E. Baudin, P. Ruszniewski, H. Du Boullay and P. Goudet. 2017.
OBJECTIVE: To report long-term follow-up of patients with multiple endocrine neoplasia type 1 (MEN1) and nonfunctioning pancreatic neuroendocrine tumors (NF-PET). BACKGROUND: Pancreaticoduodenal tumors occur in almost all patients with MEN1 and are a major cause of death. The natural history and clinical outcome are poorly defined, and management is still controversial for small NF-PET. METHODS: Clinical outcome and tumor progression were analyzed in 46 patients with MEN1 with 2 cm or smaller NF-PET who did not have surgery at the time of initial diagnosis. Survival data were analyzed using the Kaplan-Meier method. RESULTS: Forty-six patients with MEN1 were followed prospectively for 10.7 +/- 4.2 (mean +/- standard deviation) years. One patient was lost to follow-up and 1 died from a cause unrelated to MEN1. Twenty-eight patients had stable disease and 16 showed significant progression of pancreaticoduodenal involvement, indicated by increase in size or number of tumors, development of a hypersecretion syndrome, need for surgery (7 patients), and death from metastatic NF-PET (1 patient). The mean event-free survival was 13.9 +/- 1.1 years after NF-PET diagnosis. At last follow-up, none of the living patients who had undergone surgery or follow-up had evidence of metastases on imaging studies. CONCLUSIONS: Our study shows that conservative management for patients with MEN1 with NF-PET of 2 cm or smaller is associated with a low risk of disease-specific mortality. The decision to recommend surgery to prevent tumor spread should be balanced with operative mortality and morbidity, and patients should be informed about the risk-benefit ratio of conservative versus aggressive management when the NF-PET represents an intermediate risk.
PubMed-ID: 28263205
http://dx.doi.org/10.1097/SLA.0000000000002191