



## ESES Review of Recently Published Literature

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

Compilation and design: U. Beutner, [ulrich.beutner@kssg.ch](mailto:ulrich.beutner@kssg.ch)

*Affiliations see next page*

### May - Jun 2017

*Data retrieval from Pubmed: Jan 26, 2018*

### Contents

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

	Publication count:	SR/MA	RCT	CG	Other	Page
Thyroid .....	10	1	1	54	5	
Parathyroids.....	1	1	0	12	30	
Adrenals .....	1	0	0	10	36	
NET .....	3	0	0	13	41	
General .....	0	0	0	0	48	

**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).

## Collectors

**Thomas Clerici, MD**

Department of Surgery, Cantonal Hospital St. Gallen, St. Gallen, Switzerland

**Frédéric Triponez, MD**

**Samira M Sadowski, MD**

Department of Thoracic and Endocrine Surgery, University Hospitals of Geneva, Geneva, Switzerland

**Kerstin Lorenz, MD**

**Malik Elwerr**

**Janine Hein, MD**

Department of General-, Visceral-, and Vascular Surgery, Martin-Luther University of Halle-Wittenberg, Germany

**Liliana Osmak, MD**

Department of Endocrine Surgery, University Hospital Dijon, Dijon, France

**Guzmán Franch-Arcas, MD**

Endocrine Surgery, Department of General and Digestive Tract Surgery, University Hospital Salamanca, Salamanca, Spain

**Cristina Martinez-Santos, MD**

Endocrine Surgery, Hospital Costa del Sol Marbella, Málaga, Spain

## Compilation and Coordination

**Ulrich Beutner, Ph.D**

Department of Surgery, Cantonal Hospital St. Gallen, St. Gallen, Switzerland

[ulrich.beutner@kssg.ch](mailto:ulrich.beutner@kssg.ch)

## Preliminary

Again this ESES collection took longer than it should be, and again it is my blame for not holding the promise to finish the collection in November 2017. Again (for the last time;-) our contributors worked very selective and brought down the article count from 120 to 107. Keep up the good work and I am looking forward to breaking the two-digit barrier of article counts in 2018.

The list of impact factors (IF) on the next page was updated to the current version of 2016. Since I cannot help the impression that a lot of people talk about the Impact Factor but do not know what it actually means, here a quick reminder. To determine the IF for let's say *Ann Surg* in 2016, all reference lists in all covered journals published in 2016 are searched for citations of articles in *Ann Surg* in the two previous years (in our example 2014 and 2015). The total number of these citations is then divided by the number of articles published in 2014 and 2015 in *Ann Surg*. Thus, the IF tells us how often an article in a journal was cited on average 1 and 2 years after publication. Clearly, the IF is a bibliographic parameter, but not an indicator of quality, since even bad or wrong studies have to be cited (who has not written phrases like "in contrast to .." or "opposite to ..." at one time or another to cite work that most likely was wrong or miserably done.) At best the IF might be a surrogate measure for quality of a journal, but clearly not of a single article in a particular journal. Even top journals "earn" their high IF from a small number of articles, the majority is cited much less often than the average (=IF) and some are not at all (<https://quantixed.org/2015/05/05/wrong-number-a-closer-look-at-impact-factors/>). Considering the shortcomings of the IF (and there are more than the one mentioned here) it is amazing how many career decisions nowadays are based on the IF of the journal, scientific work was published in. It seems to me, that most academic leaders requiring the IF for job applications have no idea about the validity and significance of the IF.

Back to the ESES reference list, although belated but wholeheartedly, I wish you all a happy and successful New Year and that the ESES reference list will be helpful for your scientific work.

Yours

Ulrich Beutner, Ph.D.

## Journals covered

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

Journal names are links to the journal's homepage, IF2016: [Impact factor](#) 2016, <sup>†</sup>IF 2015, ---: no IF for 2016

# Thyroid

## Meta-Analyses

### **Neuromonitoring in endoscopic and robotic thyroidectomy.**

*Updates Surg*, 69(2):171-9.

G. Dionigi, H. Y. Kim, C. W. Wu, M. Lavazza, G. Materazzi, C. P. Lombardi, A. Anuwong and R. P. Tufano. Intraoperative neuromonitoring (IONM) has proven effective for intraoperative verification of RLN function in the conventional thyroid surgery. However, no studies have performed a systematic evidence-based assessment of this novel health technology in endoscopic and robotic thyroidectomy. Evidence-based criteria were used in a systematic review of relevant literature for years 2000-2015. Four electronic databases (CENTRAL, MEDLINE, Cochrane and EMBASE) were used to retrieve relevant reports published from January 1, 2000 to September 1, 2016. The search terms included "endoscopic thyroidectomy", "robotic thyroidectomy", "IONM", "continuous IONM (CIONM)", "neural monitoring", "recurrent laryngeal nerve monitoring", and "superior laryngeal monitoring". The following data were retrieved from eligible studies of patients undergoing endoscopic or robotic thyroidectomy: objective of study, design and setting of study, population, intervention examined, quality of data, follow-up and dropout rate, risk of bias, and outcomes assessed. Of 160 studies retrieved, only 9 (5%) studies used IONM. Eight studies reported 522 nerve at risk (NAR) with IONM. Only three were prospective randomized studies. Reports of IONM endoscopic and robotic procedures included their use for re-surgery and use in both benign and malignant cases. None of the IONM endoscopic procedures involved bilateral palsy. Two studies reported the use of a staged strategy. The rates of recurrent laryngeal palsy were 0-3.6% for transient and 0-0.4% for permanent. Only 30% of the studies performed vagus nerve stimulation, and only 25% performed superior laryngeal nerve monitoring. In addition to the use of IONM as an assistive technology for navigating the anatomy in challenging procedures such as endoscopic and robotic thyroidectomy, IONM has potential use as a routine adjunct to the conventional video-assisted nerve identification in thyroidectomy.

PubMed-ID: [28439772](https://pubmed.ncbi.nlm.nih.gov/28439772/)

<http://dx.doi.org/10.1007/s13304-017-0442-z>

### **Prevalence, incidence, and risk factors for shoulder and neck dysfunction after neck dissection: A systematic review.**

*Eur J Surg Oncol*, 43(7):1199-218.

E. M. Gane, Z. A. Michaleff, M. A. Cottrell, S. M. McPhail, A. L. Hatton, B. J. Panizza and S. P. O'Leary.

**INTRODUCTION:** Shoulder pain and dysfunction may occur following neck dissection among people being treated for head and neck cancer. This systematic review aims to examine the prevalence and incidence of shoulder and neck dysfunction after neck dissection and identify risk factors for these post-operative complications. **METHODS:** Electronic databases (Pubmed, CINAHL, EMBASE, Cochrane) were searched for articles including adults undergoing neck dissection for head and neck cancer. Studies that reported prevalence, incidence or risk factors for an outcome of the shoulder or neck were eligible and assessed using the Critical Review Form - Quantitative Studies. **RESULTS:** Seventy-five articles were included in the final review. Prevalence rates for shoulder pain were slightly higher after RND (range, 10-100%) compared with MRND (range, 0-100%) and SND (range, 9-25%). The incidence of reduced shoulder active range of motion depended on surgery type (range, 5-20%). The prevalence of reduced neck active range of motion after neck dissection was 1-13%. Type of neck dissection was a risk factor for shoulder pain, reduced function and health-related quality of life. **CONCLUSIONS:** The prevalence and incidence of shoulder and neck dysfunction after neck dissection varies by type of surgery performed and measure of dysfunction used. Pre-operative education for patients undergoing neck dissection should acknowledge the potential for post-operative shoulder and neck problems to occur and inform patients that accessory nerve preservation lowers, but does not eliminate, the risk of developing musculoskeletal complications.

PubMed-ID: [27956321](https://pubmed.ncbi.nlm.nih.gov/27956321/)

<http://dx.doi.org/10.1016/j.ejso.2016.10.026>

### **The current state of intermittent intraoperative neural monitoring for prevention of recurrent laryngeal nerve injury during thyroidectomy: a PRISMA-compliant systematic review of overlapping meta-analyses.**

*Langenbecks Arch Surg*, 402(4):663-73.

B. M. Henry, M. J. Graves, J. Vikse, B. Sanna, P. A. Pekala, J. A. Walocha, M. Barczynski and K. A. Tomaszewski.

**PURPOSE:** Recurrent laryngeal nerve (RLN) injury is one of the most common and detrimental complications following thyroidectomy. Intermittent intraoperative nerve monitoring (I-IONM) has been proposed to reduce prevalence of RLN injury following thyroidectomy and has gained increasing acceptance in recent years. **METHODS:** A comprehensive database search was performed, and data from eligible meta-analyses meeting the inclusion criteria were extracted. Transient, permanent, and overall RLN injuries were the primary outcome measures. Quality assessment via AMSTAR, heterogeneity appraisal, and selection of best evidence was performed via a Jadad algorithm. **RESULTS:** Eight meta-analyses met the inclusion criteria. Meta-analyses included between 6 and 23 original studies each. Via utilization of the Jadad algorithm, the selection of best evidence resulted in choosing of Pisanu et al. (Surg Res 188:152-161, 2014). Five out of eight meta-analyses demonstrated non-significant ( $p > 0.05$ ) RLN injury reduction with the use of I-IONM versus nerve visualization alone. **CONCLUSIONS:** To date, I-IONM has not achieved a significant level of RLN injury reduction as shown by the meta-analysis conducted by Pisanu et al. (Surg Res 188:152-161, 2014). However, most recent developments of IONM technology including continuous vagal IONM and concept of staged thyroidectomy in case of loss of signal on the first side in order to prevent bilateral RLN injury may provide additional benefits which were out of the scope of this study and need to be assessed in further prospective multicenter trials. PubMed-ID: [28378238](https://pubmed.ncbi.nlm.nih.gov/28378238/)  
<http://dx.doi.org/10.1007/s00423-017-1580-y>

### **Is there a group of patients at greater risk for hematoma following thyroidectomy? A systematic review and meta-analysis.**

*Laryngoscope*, 127(6):1483-90.

A. E. Quimby, S. T. Wells, M. Hearn, H. Javidnia and S. Johnson-Obaseki.

**OBJECTIVE:** The purpose of this study was to perform a systematic review and meta-analysis to determine whether a difference exists in hematoma rates following thyroidectomy for any of the following subgroups of patients: Graves disease, toxic nodular goiter (TNG), and malignancy. **STUDY DESIGN:** Systematic review and meta-analysis. **METHODS:** A systematic literature search was performed for all relevant English and French language studies (1946-2015) using Ovid MEDLINE, EMBASE, and PubMed. Three authors independently extracted data and analyzed articles for quality using the Newcastle-Ottawa Quality Assessment Scale. Our primary outcome of interest was hematoma requiring re-operation. **RESULTS:** A total of 301 studies were screened, with 11 studies meeting the inclusion criteria. The results of our analysis demonstrated that Graves disease is the only indication for thyroidectomy that appears to have an increased risk of postoperative hematoma formation, pooled odds ratio = 1.58 (1.09-2.31);  $P = 0.02$ . Malignancy and TNG did not demonstrate significantly higher rates of postoperative hematoma formation. **CONCLUSION:** This study demonstrates that of patients undergoing thyroidectomy, Graves disease is the only indication in which patients are at increased risk of postoperative hematoma formation. This information may help guide future decisions regarding the implementation of outpatient thyroidectomy. **LEVEL OF EVIDENCE:** NA. *Laryngoscope*, 127:1483-1490, 2017. PubMed-ID: [27481173](https://pubmed.ncbi.nlm.nih.gov/27481173/)  
<http://dx.doi.org/10.1002/lary.26195>

### **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  $\geq 45$  years of age and individuals with aggressive disease. TGDC carcinoma harbors an exceedingly low rate of mortality.



PubMed-ID: [28322121](https://pubmed.ncbi.nlm.nih.gov/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](https://pubmed.ncbi.nlm.nih.gov/28160320/)

<http://dx.doi.org/10.1111/cen.13306>

### **A meta-analysis of intraoperative neuromonitoring of recurrent laryngeal nerve palsy during thyroid reoperations.**

*Clin Endocrinol (Oxf)*, 87(5):572-80.

W. Sun, J. Liu, H. Zhang, P. Zhang, Z. Wang, W. Dong, L. He and T. Zhang.

**BACKGROUND:** The rate of recurrent laryngeal nerve (RLN) palsy, a common complication of thyroid surgery, is especially high in thyroid reoperations. The present meta-analysis assesses whether intraoperative neuromonitoring (IONM) reduces the prevalence of RLN palsy in thyroid reoperations. **DESIGN AND METHODS:** A systematic literature search was conducted in the PubMed, SCIE and Wan Fang databases for studies published up to 31 August 2016. All data were analysed using STATA (version 11) software. Publication bias was assessed using Begg's funnel plot and Egger's test, and sensitivity analysis was performed. **RESULTS:** Nine studies including 2436 at-risk nerves met the inclusion criteria. The results were presented as pooled relative risks (RRs) with 95% confidence intervals (CI). The overall RLN palsy rate was significantly lower in reoperations conducted with IONM than in those conducted without IONM (RR=0.434, 95% CI=0.206-0.916,  $P=.029$ ). High heterogeneity was found ( $I(2)=70.2%$ ,  $P=.001$ ). The rates of transient RLN palsy with and without IONM did not differ significantly (RR=0.607, 95% CI=0.270-1.366,  $P=.227$ ). The heterogeneity was high ( $I(2)=67.4%$ ,  $P=.005$ ). However, IONM was significantly associated with a reduction in permanent RLN palsy (RR=0.426, 95% CI=0.196-0.925,  $P=.031$ ). No significant heterogeneity was found ( $I(2)=13.7%$ ,  $P=.325$ ). Funnel plots for overall and transient RLN palsy showed a possible publication bias. **CONCLUSIONS:** Intraoperative neuromonitoring (IONM) is associated with a reduction in overall and permanent RLN palsy in thyroid reoperations. However, given the limited sample size and heterogeneity in this meta-analysis, further studies are required to confirm our preliminary findings.

PubMed-ID: [28585717](https://pubmed.ncbi.nlm.nih.gov/28585717/)

<http://dx.doi.org/10.1111/cen.13379>

### **Thyroid Hemiagenesis: Incidence, Clinical Significance, and Genetic Background.**

*J Clin Endocrinol Metab*, 102(9):3124-37.

E. Szczepanek-Parulska, A. Zybek-Kocik, L. Wartofsky and M. Ruchala.

**Context:** Thyroid hemiagenesis (THA) constitutes a rare, congenital disorder that is characterized by an absence of one thyroid lobe. Because the pathogenesis and clinical significance of this malformation remain undefined, specific clinical recommendations are lacking, especially for asymptomatic cases. **Evidence Acquisition:** The PubMed database was searched (years 1970 to 2017), and the following terms were used to retrieve the results: "thyroid hemiagenesis," "thyroid hemiaplasia," "one thyroid lobe agenesis," and "one thyroid lobe aplasia." Subsequently, reference sections of the retrieved articles were searched. **Evidence Synthesis:** There is a

noticeable susceptibility of subjects with THA to develop additional thyroid and nonthyroidal pathologies. In pathogenesis of concomitant thyroid pathologies, a chronic elevation in thyroid-stimulating hormone values may play an important role. Thus far, genetic studies failed to find a common genetic background of the anomaly, and the potential underlying cause was identified in a minority of the cases. Conclusions: Patients with THA are prone to develop additional thyroid pathologies and theoretically might benefit from l-thyroxine treatment to lower the thyrotropin levels to those observed in the normal population. However, further research should be done to ascertain whether such intervention early in life would prevent development of associated thyroid conditions. At least, increased vigilance should be maintained to reveal all of the concomitant disorders as soon as possible during follow-up examinations. Application of high-throughput technologies enabling a genome-wide search for novel factors involved in thyroid embryogenesis might be the next step to expand the knowledge on THA pathogenesis.

PubMed-ID: [28666345](https://pubmed.ncbi.nlm.nih.gov/28666345/)

<http://dx.doi.org/10.1210/jc.2017-00784>

### **Prognostic impact of vascular invasion in differentiated thyroid carcinoma: a systematic review and meta-analysis.**

*Eur J Endocrinol*, 177(2):207-16.

H. G. Vuong, T. Kondo, U. N. P. Duong, T. Q. Pham, N. Oishi, K. Mochizuki, T. Nakazawa, L. Hassell and R. Katoh.

**BACKGROUND:** The role of vascular invasion (VI) as a prognostic marker in thyroid cancer is continuously debated among investigators. In this systematic review and meta-analysis, we aimed to investigate the association of VI with tumor recurrence and patient mortality in differentiated thyroid cancers (DTCs). **METHODS:** We searched five electronic databases for cases of DTC matching our criteria. Data of tumor persistence, locoregional recurrence (LRR), distant recurrence (DR) and overall recurrence/persistence (RP) were extracted and pooled into odds ratios (OR) and corresponding 95% confidence intervals (CIs) using random effect model. Pooled hazard ratio (HR) for disease-specific survival (DSS) was calculated using random effect model weighted by inverse variance method. Publication bias was examined by using Egger's test and funnel plot. **RESULTS:** From 1650 studies, we included 26 studies comprising 11 961 DTCs for meta-analyses. In DTC patients, we found significant associations of VI with tumor persistence (OR = 2.75; 95% CI = 1.46-5.18), LRR (OR = 4.44; 95% CI = 2.94-6.71), DR (OR = 5.08; 95% CI = 2.95-8.75), overall RP (OR = 3.53; 95% CI = 2.09-5.96) and worse DSS (HR = 2.47; 95% CI = 1.45-4.21). Our results also demonstrated that the presence of extensive VI is associated with a significantly higher risk for DR in follicular thyroid carcinomas as compared with focal VI. **CONCLUSION:** Our study demonstrated a significant impact of VI on tumor recurrence and patient survival in DTC patients. The presence and extent of VI should be considered an adverse prognostic factor in DTCs.

PubMed-ID: [28566444](https://pubmed.ncbi.nlm.nih.gov/28566444/)

<http://dx.doi.org/10.1530/EJE-17-0260>

### **The Effect of Prophylactic Central Neck Dissection on Locoregional Recurrence in Papillary Thyroid Cancer After Total Thyroidectomy: A Systematic Review and Meta-Analysis : pCND for the Locoregional Recurrence of Papillary Thyroid Cancer.**

*Ann Surg Oncol*, 24(8):2189-98.

W. Zhao, L. You, X. Hou, S. Chen, X. Ren, G. Chen and Y. Zhao.

**BACKGROUND:** The use of prophylactic central neck dissection (pCND) for papillary thyroid cancer (PTC) without clinical evidence of nodal metastasis (cN0) remains controversial. This study was designed to examine whether pCND for PTC affected locoregional recurrence (LRR). **METHODS:** A systematic review was performed to compare the LRR between patients with PTC who underwent total thyroidectomy (TT) and pCND and those who underwent TT alone. The primary outcome was LRR. Other outcomes, including postoperative radioiodine (RAI) ablation and surgically related complications, were evaluated. A meta-analysis was performed using the random-effects model. **RESULTS:** We included 17 studies, which comprised 4437 patients. Patients in the TT+pCND group had a significantly reduced risk of LRR (risk ratio [RR] = 0.66; 95% confidence interval [CI]: 0.49-0.90; P = 0.008). The LRR in the central neck compartment (RR = 0.35; 95% CI 0.18-0.68; P = 0.002) was significantly lower in the TT+pCND group, whereas the LRR in the lateral neck compartment was similar between the two groups. Compared with the TT alone group, patients in the TT+pCND group tended to receive higher RAI (74.6% vs. 59.9%) and experience temporary hypocalcemia (odds ratio [OR] = 2.37; 95% CI 1.89-2.96; P < 0.00001), permanent hypocalcemia (OR = 1.93; 95% CI 1.05-3.57; P = 0.03), and increased overall morbidity (OR = 2.56; 95% CI 1.75-3.74; P < 0.00001). **CONCLUSIONS:** This meta-analysis suggested that although pCND reduced the LRR in PTC-specifically in the central neck compartment-it was accompanied by an increased rate of postoperative hypocalcemia. However, the evidence is limited and randomized, controlled trials



are needed to clarify this role further.

PubMed-ID: [27913945](https://pubmed.ncbi.nlm.nih.gov/27913945/)

<http://dx.doi.org/10.1245/s10434-016-5691-4>

## Randomized controlled trials

### **The Effects of Intravenous Lidocaine Infusions on the Quality of Recovery and Chronic Pain After Robotic Thyroidectomy: A Randomized, Double-Blinded, Controlled Study.**

*World J Surg*, 41(5):1305-12.

K. W. Choi, K. H. Nam, J. R. Lee, W. Y. Chung, S. W. Kang, Y. E. Joe and J. H. Lee.

**BACKGROUND:** The effect of the systemic lidocaine on postoperative recovery has not been definitively investigated despite its analgesic efficacy after surgery. The aim of this randomized, double-blinded, controlled study was to evaluate the effect of intravenously administered lidocaine on the quality of recovery and on acute and chronic postoperative pain after robot-assisted thyroidectomy. **METHODS:** Ninety patients who were undergoing robotic thyroidectomy were randomly assigned to the lidocaine or the control groups. The patients received 2 mg/kg of lidocaine followed by continuous infusions of 3 mg/kg/h of lidocaine (Group L) or the same volume of 0.9% normal saline (Group C) intravenously during anesthesia. The acute pain profiles and the quality of recovery, which was assessed using the quality of recovery-40 questionnaire (QoR-40), were evaluated for 2 days postoperatively. Chronic postsurgical pain (CPSP) and sensory disturbances at the surgical sites were evaluated 3 months after surgery. **RESULTS:** The QoR-40 and pain scores that were assessed during the 2 days that followed surgery were largely comparable between the groups. However, CPSP was more prevalent in the Group C than in the Group L (16/43 vs. 6/41;  $p = 0.025$ ). The tactile sensory score 3 months after the operation was significantly greater in the Group L than in the Group C (7 vs. 5;  $p = 0.001$ ). **CONCLUSION:** Systemic lidocaine administration was associated with reductions in CPSP and sensory impairment after robot-assisted thyroidectomy although it was not able to reduce acute postsurgical pain or improve the quality of recovery. Trial registry number NCT01907997 ( <http://clinicaltrials.gov> ).

PubMed-ID: [27896411](https://pubmed.ncbi.nlm.nih.gov/27896411/)

<http://dx.doi.org/10.1007/s00268-016-3842-1>

## Consensus Statements/Guidelines

### **Indications and extent of central neck dissection for papillary thyroid cancer: An American Head and Neck Society Consensus Statement.**

*Head Neck*, 39(7):1269-79.

N. Agrawal, M. R. Evasovich, E. Kandil, S. I. Noureldine, E. A. Felger, R. P. Tufano, D. H. Kraus, L. A. Orloff, R. Grogan, P. Angelos, B. C. Stack, Jr., B. McIver and G. W. Randolph.

**BACKGROUND:** The primary purposes of this interdisciplinary consensus statement were to review the relevant indications for central neck dissection (CND) in patients with papillary thyroid cancer (PTC) and to outline the appropriate extent and relevant techniques required to accomplish a safe and effective CND. **METHODS:** A writing group convened by the American Head and Neck Society (AHNS) Endocrine Committee was tasked with identifying the important clinical elements to consider when managing the central neck compartment in patients with PTC based on available evidence in the literature, and the group's collective experience. The position statement paper was then submitted to the full Endocrine Committee, Education Committee, and AHNS Council. **RESULTS:** This consensus statement was developed to inform the clinical decision-making process when managing the central neck compartment in patients with PTC from the AHNS. This document is intended to provide clarity through definitions as well as a basic guideline from which to manage the central neck. It is our hope that this improves the quality and reduces variation in management of the central neck, facilitates communication, and furthers research for patients with thyroid cancer. **CONCLUSION:** This represents, in our opinion, contemporary optimal surgical care for this patient population and is endorsed by the American Head and Neck Society. (c) 2017 Wiley Periodicals, Inc. *Head Neck* 39: 1269-1279, 2017.

PubMed-ID: [28449244](https://pubmed.ncbi.nlm.nih.gov/28449244/)

<http://dx.doi.org/10.1002/hed.24715>

## Other Articles

### **Innervation of the human cricopharyngeal muscle by the recurrent laryngeal nerve and external branch of the superior laryngeal nerve.**

*Langenbecks Arch Surg*, 402(4):683-90.

M. Uludag, N. Aygun and A. Isgor.

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

PubMed-ID: [26843022](https://pubmed.ncbi.nlm.nih.gov/26843022/)

<http://dx.doi.org/10.1007/s00423-016-1376-5>

### **Recurrent laryngeal nerve injury with incomplete loss of electromyography signal during monitored thyroidectomy-evaluation and outcome.**

*Langenbecks Arch Surg*, 402(4):691-9.

C. W. Wu, M. Hao, M. Tian, G. Dionigi, R. P. Tufano, H. Y. Kim, K. Y. Jung, X. Liu, H. Sun, I. C. Lu, P. Y. Chang and F. Y. Chiang.

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

PubMed-ID: [26886281](https://pubmed.ncbi.nlm.nih.gov/26886281/)

<http://dx.doi.org/10.1007/s00423-016-1381-8>

### **EMG changes during continuous intraoperative neuromonitoring with sustained recurrent laryngeal nerve traction in a porcine model.**

*Langenbecks Arch Surg*, 402(4):675-81.

K. Brauckhoff, T. Aas, M. Biermann and P. Husby.

**PURPOSE:** Traction is the most common cause of injury to the recurrent laryngeal nerve (RLN) in endocrine neck surgery. The purpose of this study was to evaluate specific alterations to the electromyogram (EMG) and verify safe alarm limits in a porcine model of sustained traction of the RLN using continuous intraoperative neuromonitoring (C-IONM). **METHODS:** Sixteen Norwegian Landrace pigs were anesthetized and intubated with a tracheal tube with a stick-on laryngeal electrode. EMG was recorded at baseline (BL) and during sustained traction applied to each RLN until 70 % amplitude decrease from BL, and during 30-min recovery. **RESULTS:** In

29 nerves at risk (NAR), BL amplitude and latency values were 1098 +/- 418 (586-2255) muV (mean +/- SD (range)) (right vagus) and 845 +/- 289 (522-1634) muV (left vagus), and 4.7 +/- 0.5 (4.1-5.9) ms and 7.9 +/- 0.8 (6.7-9.6) ms, respectively. At 50 % amplitude decrease, latency increased by 14.0 +/- 5.7 % (right side) and 14.5 +/- 9.1 % (left side) compared with BL. Corresponding values for 70 % amplitude depression were 17.9 +/- 6.1 % and 17.3 +/- 12.8 %. Traction time to 50 and 70 % amplitude decrease ranged from 3 to 133 min and 3.9-141 min, respectively. In 16 NAR (55 %), time from 50 to 70 % reduction in amplitude was <=5 min, but in six NAR (21 %) <=1 min. In only 11 (38 %) of 29 nerves, the amplitude recovered to more than 50 % of BL.

CONCLUSIONS: Latency increase may be the first warning of RLN stretch injury. Given the short interval between 50 and 70 % amplitude reduction of the EMG, amplitude reduction by 50 % can be taken as an appropriate alert limit.

PubMed-ID: [27086308](https://pubmed.ncbi.nlm.nih.gov/27086308/)

<http://dx.doi.org/10.1007/s00423-016-1419-y>

### **The learning curve for intraoperative neuromonitoring of the recurrent laryngeal nerve in thyroid surgery.**

*Langenbecks Arch Surg*, 402(4):701-8.

B. Wojtczak, K. Kaliszewski, K. Sutkowski, M. Glod and M. Barczynski.

PURPOSE: Intraoperative neuromonitoring (IONM) of the recurrent laryngeal nerve (RLN) is often used in thyroid surgery. However, this procedure is complex and requires a learning period to master the technique. The aim of the study was to evaluate the learning curve for IONM. METHODS: A 3-year period (2012-2014) of working with IONM (NIM3.0, Medtronic) was prospectively analyzed with a special emphasis on comparing the initial implementation phase in 2012 (101 patients, 190 RLNs at risk) with subsequent years of IONM use in 2013 (70 patients, 124 RLNs at risk) and 2014 (65 patients, 120 RLNs at risk). RESULTS: The rate of successful IONM-assisted RLN identification increased gradually over the 3-year study period (92.11 % in 2012 vs. 95.16 % in 2013 vs. 99.16 % in 2014;  $p = 0.022$ ), with a corresponding decrease in the rate of technical problems (12.87, 4.3, and 4.6 %, respectively;  $p = 0.039$ ). The rate of RLN injuries tended to decrease over time: 3.68, 1.55, and 0.83 %, respectively ( $p = 0.220$ ). Between 2012 and 2014, increases in the sensitivity (71.4 vs. 100 %), specificity (98 vs. 99 %), positive predictive value (62.5 vs. 75 %), negative predictive value (98 vs. 100 %), and overall accuracy of IONM (97.4 vs. 99.6 %) were observed ( $p = 0.049$ ). Increasing experience with IONM resulted in more frequent utilization of total thyroidectomy (92 % in 2012 vs. 100 % in 2013-2014;  $p = 0.004$ ). CONCLUSIONS: There was a sharp decrease in the number of technical problems involving equipment setup from 2012 to 2014.

PubMed-ID: [27178203](https://pubmed.ncbi.nlm.nih.gov/27178203/)

<http://dx.doi.org/10.1007/s00423-016-1438-8>

### **Experience with intraoperative neuromonitoring of the recurrent laryngeal nerve improves surgical skills and outcomes of non-monitored thyroidectomy.**

*Langenbecks Arch Surg*, 402(4):709-17.

B. Wojtczak, K. Sutkowski, K. Kaliszewski, M. Glod and M. Barczynski.

PURPOSE: Intraoperative neuromonitoring (IONM) can serve as a tool to increase skills in recurrent laryngeal nerve (RLN) identification and complete removal of thyroid tissue. The aim of this study was to validate this hypothesis. METHODS: This prospective study involved 632 patients (1161 RLNs at risk) who underwent thyroid surgery in 2011-2014. Although IONM was not used until 2012, this prospective study started on 1 January 2011. The three participating surgeons knew about the study before that date and that the rate of RLN identification would be carefully measured in total and near-total surgery. Solely, visual identification of the RLN was used throughout 2011. IONM was introduced as a training tool in 2012-2014 for the first 3 months of each year. In the remaining months, thyroid operations were performed without IONM. Outcomes of non-monitored thyroid operations were compared before (01-12/2011) vs. after (04-12/2012-2014) 3 months of exposure to IONM yearly (01-03/2012-2014). The rate of RLN identification was assessed in total and near-total thyroidectomies and in totally resected lobes in Dunhill's operation. The prevalence of RLN injury and the utilization of total thyroidectomy were evaluated. RESULTS: In 2011, the rate of successful RLN visual identification in total and near-total thyroidectomies and in totally resected lobes in Dunhill's operation was 45.71 %. After the introduction of IONM in 2012-2014, in the procedures performed without IONM, the rate was 86.66, 90.81, and 91.3 %. The prevalence of RLN injury in 2011 was 6.8 %, while in the years following the introduction of IONM, it was 3.61, 2.65, and 1.45 %. Utilization of total thyroidectomy increased from 47.9 % in 2011 to 100 % in 2014. CONCLUSIONS: Experience with IONM led to an increase in RLN identification ( $p < 0.0001$ ), a decrease of RLN injury ( $p < 0.05$ ), and an increase in the safe utilization of total thyroidectomy ( $p < 0.0001$ ) in non-monitored thyroid operations. IONM is a valuable tool for surgical training.

PubMed-ID: [27209315](https://pubmed.ncbi.nlm.nih.gov/27209315/)  
<http://dx.doi.org/10.1007/s00423-016-1449-5>

### **Comparison of perioperative stress in patients undergoing thyroid surgery with and without neuromonitoring-a pilot study.**

*Langenbecks Arch Surg*, 402(4):719-25.

D. Babinska, M. Barczynski, T. Oseka, M. Sledzinski and A. J. Lachinski.

**PURPOSE:** A comprehensive psychological comparison of preoperative stress in patients scheduled for thyroidectomy with versus without intraoperative neurophysiologic monitoring (IONM) has never been reported. The aim of this study was to assess whether a planned utilization of IONM had any effect on the reduction of stress and anxiety level before and after thyroid surgery. **METHODS:** The outcomes of 32 patients scheduled for thyroidectomy with IONM were compared to the outcomes of a carefully matched control group of 39 patients operated on without IONM. All the patients were tested before the surgery and at 1-7 days postoperatively employing psychological self-report instruments: the Depression Anxiety Stress Scales (DASS), State-Trait Anxiety Inventory (STAI), 12-item General Health Questionnaire (GHQ), Functional Assessment of Cancer Therapy-Head and Neck Scale (FACT H&N), and the visual analog scale (VAS). **RESULTS:** The examined groups were homogenous and carefully matched in terms of mental health (GHQ), the quality of life (FACT H&N), and the intensity of depression level (DASS). The IONM group showed a significantly lower level of "the state anxiety"(STAI) 1 day before the operation ( $p < 0.05$ ), greater trust in the doctor (VAS) ( $p < 0.05$ ), and greater confidence in the treatment method (VAS) as compared to the patients in the control group ( $p < 0.05$ ), while no significant differences were found when the remaining items were compared. **CONCLUSIONS:** The planned use of IONM during thyroidectomy may reduce patient anxiety before surgery. However, further research in this area is necessary to confirm this preliminary finding in a larger population of patients.

PubMed-ID: [27299585](https://pubmed.ncbi.nlm.nih.gov/27299585/)  
<http://dx.doi.org/10.1007/s00423-016-1457-5>

### **Midcervical scar satisfaction in thyroidectomy patients.**

*Laryngoscope*, 127(5):1247-52.

A. R. Best, T. Z. Shipchandler and S. R. Cordes.

**OBJECTIVES/HYPOTHESIS:** Assess long-term patient satisfaction with conventional thyroidectomy scars and the impact of thyroidectomy scars on patient quality of life. **STUDY DESIGN:** Validated survey administration and retrospective review of clinical and demographic data. **METHODS:** Patients who underwent conventional thyroidectomy through years 2000 to 2010 were identified and administered the validated Patient Scar Assessment Questionnaire. Mean satisfaction, appearance and scar-consciousness scores were determined. Thirty-seven patients also measured the length of their current scar. Patient demographic and operative data were collected retrospectively from the medical record. Data were analyzed with one-way analysis of variance and independent samples t testing. **RESULTS:** Sixty of 69 patients perceived the appearance of their scar to be "good" or "excellent." Sixty-three patients (91.3%) were satisfied with all scar outcomes; 67 (97.1%) were satisfied with the overall appearance of their scar. Mean total satisfaction score was 17.3 (<26 indicates a high level of satisfaction). Fifty-six (81.2%) were "not at all" self-conscious of their scar; 65 (94.2%) reported no attempt to hide their scar. Seven patients (10.1%) indicated any likelihood of pursuing scar revision. Females had significantly higher total satisfaction scores, consciousness scores, and satisfaction with appearance scores. The effect of perceived scar length was significant for scar-consciousness, not patient satisfaction. **CONCLUSIONS:** The majority of patients were satisfied with their thyroidectomy scar appearance. Few patients reported a desire to hide the scar or pursue revision. Women were more likely to be dissatisfied than men. Length may play a role in scar consciousness. **LEVEL OF EVIDENCE:** 4 *Laryngoscope*, 127:1247-1252, 2017.

PubMed-ID: [27519726](https://pubmed.ncbi.nlm.nih.gov/27519726/)  
<http://dx.doi.org/10.1002/lary.26177>

### **Safety of LigaSure in recurrent laryngeal nerve dissection-porcine model using continuous monitoring.**

*Laryngoscope*, 127(7):1724-9.

G. Dionigi, F. Y. Chiang, H. Y. Kim, G. W. Randolph, A. Mangano, P. Y. Chang, I. C. Lu, Y. C. Lin, H. C. Chen and C. W. Wu.

**OBJECTIVES/HYPOTHESIS:** This study investigated recurrent laryngeal nerve (RLN) real-time electromyography (EMG) data to define optimal safety parameters of the LigaSure Small Jaw (LSJ) instrument during thyroidectomy. **STUDY DESIGN:** Prospective animal model. **METHODS:** Dynamic EMG tracings were recorded from 32 RLNs (16 piglets) during various applications of LSJ around using continuous electrophysiologic monitoring. At varying distances from the RLN, the LSJ was activated (activation study). The LSJ was also applied to the RLN at timed intervals after activation and after a cooling maneuver through



placement on the sternocleidomastoid muscle (cooling study). RESULTS: In the activation study, there was no adverse EMG event at 2 to 5 mm distance (16 RLNs, 96 tests). In the cooling study, there was no adverse EMG event after 2-second cooling time (16 RLNs, 96 tests) or after the LSJ cooling maneuver on the surrounding muscle before reaching the RLNs (8 RLNs, 24 tests). CONCLUSION: Based on EMG functional assessment, the safe distance for LSJ activation was 2 mm. Further LSJ-RLN contact was safe if the LSJ was cooled for more than 2 seconds or cooled by touch muscle maneuver. The LSJ should be used with these distance and time parameters in mind to avoid RLN injury. LEVEL OF EVIDENCE: N/A. *Laryngoscope*, 127:1724-1729, 2017.

PubMed-ID: [27578605](https://pubmed.ncbi.nlm.nih.gov/27578605/)

<http://dx.doi.org/10.1002/lary.26271>

### **Evaluation of the American college of surgeons thyroid and parathyroid ultrasound course: Results of a web-based survey.**

*Laryngoscope*, 127(8):1950-8.

G. K. Sharma, R. A. Sofferman and W. B. Armstrong.

OBJECTIVES/HYPOTHESIS: The American College of Surgeons Thyroid and Parathyroid Ultrasound Skills-Oriented Course (TPUSC) was designed to teach surgeons how to interpret and perform office-based head and neck ultrasound (HNUS). The objective of this study was to survey attendees of the TPUSC to evaluate the usefulness of the course, to track surgeon performed HNUS practice patterns, and to help identify potential roadblocks to incorporation of HNUS into a surgeon's practice. STUDY DESIGN: Cross-sectional survey. METHODS: A Web-based survey was sent to 952 surgeons who completed the TPUSC between 2010 and 2014. Questions included surgeon specialty, practice type, Likert scale rating of the TPUSC, competency with different HNUS procedures, and current HNUS practice patterns. RESULTS: The response rate was 24%. On a scale from 1 (not useful) to 5 (extremely valuable), the mean course usefulness rating was 4.2. Educational goals were met for 194 (92%) surgeons, and 162 (77%) surgeons reported performing HNUS in their practice. Of 48 surgeons not performing HNUS, 24 (50%) attributed insufficient time in their clinic schedule, and 21 (44%) attributed high equipment costs. CONCLUSIONS: The TPUSC is a valuable educational experience for surgeons seeking to gain proficiency in HNUS. The majority of TPUSC graduates gain competency with at least one type of HNUS procedure following the course. LEVEL OF EVIDENCE: NA *Laryngoscope*, 127:1950-1958, 2017.

PubMed-ID: [27716990](https://pubmed.ncbi.nlm.nih.gov/27716990/)

<http://dx.doi.org/10.1002/lary.26335>

### **Comparison of Empiric Versus Whole-Body/Blood Clearance Dosimetry-Based Approach to Radioactive Iodine Treatment in Patients with Metastases from Differentiated Thyroid Cancer.**

*J Nucl Med*, 58(5):717-22.

D. Deandreis, C. Rubino, H. Tala, S. Leboulloux, M. Terroir, E. Baudin, S. Larson, J. A. Fagin, M. Schlumberger and R. M. Tuttle.

The optimal management of radioactive iodine (RAI) treatment in patients with metastatic thyroid cancer (TC) is still a matter of debate. Methods: We retrospectively analyzed 352 patients with RAI-avid metastatic well-differentiated TC treated with <sup>131</sup>I by an empiric fixed activity of 3.7 GBq at Gustave Roussy (GR, n = 231) or by personalized activity (2.7-18.6 GBq) based on whole-body/-blood clearance (WB/BC) dosimetry at Memorial Sloan Kettering Cancer Center (MSKCC, n = 121). The primary endpoint was to compare overall survival (OS) in the 2 groups of patients by log-rank test. Results: Patients received a median cumulative activity of 14.8 GBq at GR and 24.2 GBq at MSKCC (P < 0.0001). The median follow-up after the diagnosis of metastases was 7.2 y (0.4-31 y). Five-year OS was 86.8% and 78.8% for patients treated at GR and at MSKCC, respectively (P < 0.01). However, there was no statistical difference in OS after correction for sex, age at the diagnosis of distant metastases, metastases site, and metastases extension between the 2 centers (P = 0.16). OS at 5 y was 96% and 96% for patients younger than 40 y with micrometastases, 70% and 65% for patients older than 40 y with macrometastases or multiple metastases, and 92% and 87% for younger patients with macrometastases or older patients with micrometastases treated at GR and MSKCC, respectively (P = not significant). Conclusion: Routine use of WB/BC dosimetry without lesional dosimetry provided no OS advantage when compared with empiric fixed RAI activity in the management of thyroid cancer patients with RAI-avid distant metastases.

PubMed-ID: [27738010](https://pubmed.ncbi.nlm.nih.gov/27738010/)

<http://dx.doi.org/10.2967/jnumed.116.179606>

### **Does resident involvement in thyroid surgery lead to increased postoperative complications?**

*Laryngoscope*, 127(5):1242-6.

R. S. Kshirsagar, Z. Chandy, H. Mahboubi and S. P. Verma.

OBJECTIVES/HYPOTHESIS: To evaluate the impact of resident involvement during thyroid surgery on 30-day

postoperative complications. **STUDY DESIGN:** Retrospective cohort study. **METHODS:** All patients who underwent thyroid surgery in 2011 were identified from the American College of Surgeons National Surgical Quality Improvement Program database. Patient demographics, perioperative details, resident involvement in surgery, and 30-day postoperative complications were extracted. Propensity score analysis was used to match resident and nonresident cases. Univariate and multivariate analysis were performed to determine the relationship between resident involvement in thyroid surgery and postoperative outcomes. **RESULTS:** One thousand seven hundred forty-seven patients with and 1,747 patients without resident involvement were case-matched for patient demographics, perioperative variables, and surgical case type. There was no significant difference ( $P = .19$ ) in 30-day postoperative complication rates of surgeries with and without resident involvement, which were 1.4% and 2%, respectively. Operative time was longer in surgeries with residents than those without residents (119 +/- 67 minutes vs. 102 +/- 55 minutes,  $P < .001$ ). Cases with resident involvement had an unplanned reoperation rate of 0.9%, which was significantly lower than the 2.3% rate of surgeries without residents ( $P = .001$ ). Multivariate analysis revealed no significant association between resident involvement and overall complications (odds ratio = 0.70;  $P = .18$ ). **CONCLUSIONS:** Resident participation in thyroid surgery was not associated with an increased 30-day postoperative complication rate. These findings demonstrate that patient safety is not adversely affected by resident participation in thyroid surgery. **LEVEL OF EVIDENCE:** 2C

Laryngoscope, 127:1242-1246, 2017.

PubMed-ID: [27753090](https://pubmed.ncbi.nlm.nih.gov/27753090/)

<http://dx.doi.org/10.1002/lary.26176>

### **Transoral endoscopic thyroidectomy vestibular approach with intraoperative nerve monitoring.**

*Surg Endosc*, 31(7):3030.

W. B. Inabnet, 3rd, H. Suh and G. Fernandez-Ranvier.

**BACKGROUND:** Transoral endoscopic thyroidectomy by a vestibular approach (TOETVA) is a novel technique for thyroid gland excision. Compared to the transaxillary endoscopic and bilateral axillo-breast approaches, which require substantial dissection to reach the thyroid gland, TOETVA provides the most direct access to the target organ. **METHODS:** The aim of this video is to provide a step-by-step overview of TOETVA and demonstrate how to set up and utilize intraoperative nerve monitoring. **RESULTS:** Three incisions are placed in the vestibular region of the oral cavity just below the lower lip for placement of 2 lateral 5-mm trocars and 1 centrally placed 11-mm trocar. Insufflation to 6 mm Hg is used to maintain the working spacing. Using a 2-handed technique and triangulation, the thyroid gland is mobilized, taking care to identify and preserve the relevant cervical anatomy. **CONCLUSION:** TOETVA is safe and feasible and provides an excellent cosmetic outcome with the most confidentially compared to the other remote access endoscopic approaches.

PubMed-ID: [27834022](https://pubmed.ncbi.nlm.nih.gov/27834022/)

<http://dx.doi.org/10.1007/s00464-016-5322-y>

### **Metastasis to the Thyroid Gland: A Critical Review.**

*Ann Surg Oncol*, 24(6):1533-9.

I. J. Nixon, A. Coca-Pelaz, A. I. Kaleva, A. Triantafyllou, P. Angelos, R. P. Owen, A. Rinaldo, A. R. Shaha, C. E. Silver and A. Ferlito.

**BACKGROUND:** Metastasis to the thyroid gland from nonthyroid sites is an uncommon clinical presentation in surgical practice. The aim of this review was to assess its incidence management and outcomes. **METHODS:** A literature review was performed to identify reports of metastases to the thyroid gland. Both clinical and autopsy series were included. **RESULTS:** Metastases to the gland may be discovered at the time of diagnosis of the primary tumor, after preoperative investigation of a neck mass, or on histologic examination of a thyroidectomy specimen. The most common primary tumors in autopsy studies are from the lung. In clinical series, renal cell carcinoma is most common. For patients with widespread metastases in the setting of an aggressive malignancy, surgery is rarely indicated. However, when patients present with an isolated metastasis diagnosed during follow-up of indolent disease, surgery may achieve control of the central neck and even long-term cure. Other prognosticators include features of the primary tumor, time interval between initial diagnosis and metastasis, and extrathyroid extent of disease. **CONCLUSIONS:** In patients with thyroid metastases, communication among clinicians treating the thyroid and the index primary tumor is essential. The setting is complex, and decisions must be made considering the features of the primary tumor, overall burden of metastases, and comorbidities. Careful balancing of these factors influences individualized approaches.

PubMed-ID: [27873099](https://pubmed.ncbi.nlm.nih.gov/27873099/)

<http://dx.doi.org/10.1245/s10434-016-5683-4>



### **Recombinant Human Thyroid-Stimulating Hormone Versus Thyroid Hormone Withdrawal in (124)I PET/CT-Based Dosimetry for (131)I Therapy of Metastatic Differentiated Thyroid Cancer.**

*J Nucl Med*, 58(7):1146-54.

D. Plyku, R. F. Hobbs, K. Huang, F. Atkins, C. Garcia, G. Sgouros and D. Van Nostrand.

Patients with metastatic differentiated thyroid cancer (DTC) may be prepared using either thyroid-stimulating hormone withdrawal (THW) or recombinant human thyroid-stimulating hormone (rhTSH) injections before (131)I administration for treatment. The objective of this study was to compare the absorbed dose to the critical organs and tumors determined by (124)I PET/CT-based dosimetry for (131)I therapy of metastatic DTC when the same patient was prepared with and imaged after both THW and rhTSH injections. Methods: Four DTC patients at MedStar Washington Hospital Center were first prepared using the rhTSH method and imaged by (124)I PET/CT at 2, 24, 48, 72, and 96 h after administration of approximately 30-63 MBq of (124)I. After 5-8 wk, the same patients were prepared using the THW method and imaged as before. The (124)I PET/CT images acquired as part of a prospective study were used to perform retrospective dosimetric calculations for (131)I therapy for the normal organs with the dosimetry package 3D-RD. The absorbed doses from (131)I for the lungs, liver, heart, kidneys, and bone marrow were obtained for each study (rhTSH and THW). Twenty-two lesions in 3 patients were identified. The contours were drawn on each PET image of each study. Time-integrated activity coefficients were calculated and used as input in OLINDA/EXM sphere dose calculator to obtain the absorbed dose to tumors. Results: The THW-to-rhTSH organ absorbed dose ratio averaged over 5 organs for the first 3 patients was 1.5, 2.5, and 0.64, respectively, and averaged over 3 organs for the fourth patient was 1.1. The absorbed dose per unit administered activity to the bone marrow was 0.13, 0.086, 0.33, and 0.068 mGy/MBq after rhTSH and 0.11, 0.14, 0.22, and 0.080 mGy/MBq after THW for each patient, respectively. With the exception of 3 lesions of 1 patient, the absorbed dose per unit administered activity of (131)I was higher in the THW study than in the rhTSH study. The ratio of the average tumor absorbed dose after stimulation by THW compared with stimulation by rhTSH injections was 3.9, 27, and 1.4 for patient 1, patient 2, and patient 3, respectively. The ratio of mean tumor to bone marrow absorbed dose per unit administered activity of (131)I, after THW and rhTSH, was 232 and 62 (patient 1), 12 and 0.78 (patient 2), and 22 and 11 (patient 3), respectively. Conclusion: The results suggest a high patient variability in the overall absorbed dose to the normal organs per MBq of (131)I administered, between the 2 TSH stimulation methods. The tumor-to-dose-limiting-organ (bone marrow) absorbed dose ratio, that is, the therapeutic index, was higher in the THW-aided than rhTSH-aided administrations. Additional comparison for tumor and normal organ absorbed dose in patients prepared using both methods is needed before definitive conclusions may be drawn regarding rhTSH versus THW patient preparation methods for (131)I therapy of metastatic DTC.

PubMed-ID: [28104741](https://pubmed.ncbi.nlm.nih.gov/28104741/)

<http://dx.doi.org/10.2967/jnumed.116.179366>

### **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.

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  $\geq 1$  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](https://pubmed.ncbi.nlm.nih.gov/28127652/)

<http://dx.doi.org/10.1245/s10434-016-5719-9>

### **Determining Patient Preferences for Indeterminate Thyroid Nodules: Observation, Surgery or Molecular Tests.**

*World J Surg*, 41(6):1513-20.

D. J. Lee, J. J. Xu, D. H. Brown, R. W. Gilbert, P. J. Gullane, J. C. Irish, L. E. Rotstein, D. P. Goldstein and J. R. de Almeida.

**BACKGROUND:** Gene-expression classifiers (GEC) and genetic mutation panels (GMP) have been shown to improve preoperative diagnostic evaluations of indeterminate thyroid nodules. Despite the improvement, uncertainty regarding the proper management exists. Patient preferences may better inform the management of these indeterminate thyroid nodules. **METHODS:** Hypothetical scenarios were administered to two groups of patients: those with previous FNA-confirmed indeterminate thyroid nodules (Group A, n = 50) and those presenting to a general otolaryngology clinic for other reasons (Group B, n = 50). We evaluated patient preferences for surgery, observation and the use of molecular tests while varying the risk of malignancy, cost and diagnostic properties of the tests. **RESULTS:** The mean threshold for choosing surgery over observation was a 38.6% risk of malignancy on FNA. When offered either GEC, GMP or both (with their inherent imperfect diagnostic properties) in addition to the indeterminate FNA, 85.0% of respondents picked at least one of the molecular tests over either observation or surgery if the test(s) were free of charge. However, only 51.7% of respondents chose at least one of the tests when asked to pay the current cost of the test(s) ( $p < 0.001$ ). On multivariable analysis, sex, the presence of an indeterminate FNA diagnosis and income level significantly predicted the desire to proceed with a molecular test above standard management. **CONCLUSION:** Patient preferences for thyroid nodule management are dependent on the risk of malignancy, prognosis of cancer and costs. Patients prefer molecular tests over standard management with indeterminate thyroid nodules, but the costs of the test(s) reduce the desire.

PubMed-ID: [28175931](https://pubmed.ncbi.nlm.nih.gov/28175931/)

<http://dx.doi.org/10.1007/s00268-017-3887-9>

### **Prescribed Activity of (131)I Therapy in Differentiated Thyroid Cancer.**

*J Nucl Med*, 58(5):697-9.

D. Van Nostrand.

PubMed-ID: [28209908](https://pubmed.ncbi.nlm.nih.gov/28209908/)

<http://dx.doi.org/10.2967/jnumed.116.188862>

### **Percutaneous probe stimulation for intraoperative neuromonitoring in total endoscopic thyroidectomy: A preliminary experience.**

*Head Neck*, 39(5):1001-7.

D. Zhang, F. Li, C. W. Wu, X. Liu, J. Xin, F. Y. Chiang and H. Sun.

**BACKGROUND:** The purpose of this study was to investigate the feasibility and value of using intraoperative neuromonitoring (IONM) performed via percutaneous probe stimulation during total endoscopic thyroidectomy. **METHODS:** This study prospectively enrolled a series of 132 consecutive patients with 156 recurrent laryngeal nerves (RLNs) at risk who received total endoscopic thyroidectomy performed via bilateral breast approach using standardized IONM. The stimulation probe was introduced into the working space by percutaneous puncture. During lateral thyroid dissection, the proximal RLN was periodically stimulated to monitor adverse electromyography (EMG) changes. Preoperative and postoperative vocal cord mobility was routinely examined with laryngofiberscopy. **RESULTS:** All IONMs were successfully performed via percutaneous probe stimulation with no morbidity or scarring in the neck. Twelve nerves (7.7%) showed significant changes in EMG (amplitude reduction, 50% to 90% from baseline EMG) during the lateral thyroid dissection. Compression near the inferior thyroid artery (70%) and traction near the Berry's ligament (30%) were the most common causative mechanisms, and modification of the surgical maneuver resulted in partial recovery of the EMG changes (amplitude reduction, 10% to 80% before wound closure). Of the 12 nerves with adverse EMG changes (final amplitude reduction, 65% to 80%), 8 nerves showed temporary (3 months or less) vocal cord palsy. No cases of permanent vocal cord palsy occurred in this series. **CONCLUSION:** Percutaneous probe stimulation is a simple, effective, and safe method of performing IONM in total endoscopic thyroidectomy when the operating space is limited. (c) 2017 Wiley Periodicals, Inc. *Head Neck* 39: 1001-1007, 2017.

PubMed-ID: [28245074](https://pubmed.ncbi.nlm.nih.gov/28245074/)

<http://dx.doi.org/10.1002/hed.24734>

### **Minimal extrathyroidal extension does not affect survival of well-differentiated thyroid cancer.**

*Endocr Relat Cancer*, 24(5):221-6.

Z. Al-Qurayshi, M. A. Shama, G. W. Randolph and E. Kandil.

Differentiated thyroid cancer (DTC) with minimal extrathyroidal extension (MEE) is classified as stage III

regardless of the tumor size. In this study, we aim to examine the effect of MEE on the overall survival and management of this population. A retrospective cohort study was performed, which utilized the National Cancer Database (NCDB), 2004-2012. The study population included patients, aged  $\geq 45$  years, who underwent surgery for DTC (pT3N0M0) with MEE compared to that in patients with pT2N0M0. A total of 9556 patients were included. These were divided into four groups, 4410 patients with pT2N0M0 (Group 1: T  $\leq 4$  cm without MEE), 3274 with pT3N0M0 (Group 2: T  $\leq 4$  cm with MEE), 447 with pT3N0M0 (Group 3: T  $> 4$  cm with MEE) and 1430 patients with pT3N0M0 without MEE (Group 4: T  $> 4$  cm without MEE). Median follow-up time was 46.7 months (interquartile range: 27.8-72.1). Patients in Group 2 (T  $\leq 4$  cm with MEE) had no significant worse survival compared to patients in Group 1 (T  $\leq 4$  cm without MEE) (P = 0.85), whereas Groups 3 and 4 (T  $> 4$  cm), both had significantly lower survival (P < 0.001) with no difference between the two groups. Total thyroidectomy was associated with improved overall survival compared to that in lobectomy in Group 4 (T  $> 4$  cm without MEE). Radioiodine utilization was associated with improved survival only with tumors larger than 4 cm with or without MEE. In DTC patients aged older than 45 years of age with tumor size less than 4 cm, MEE has no survival significance. Tumor size is an independent prognostic marker regardless of MEE status. Our data support re-evaluation of the current staging system.

PubMed-ID: [28249964](https://pubmed.ncbi.nlm.nih.gov/28249964/)

<http://dx.doi.org/10.1530/ERC-16-0509>

### **Clinico-pathological Correlation of Thyroid Nodule Ultrasound and Cytology Using the TIRADS and Bethesda Classifications.**

*World J Surg*, 41(7):1807-11.

R. M. Singaporewalla, J. Hwee, T. U. Lang and V. Desai.

**BACKGROUND:** Clinico-pathological correlation of thyroid nodules is not routinely performed as until recently there was no objective classification system for reporting thyroid nodules on ultrasound. We compared the Thyroid Imaging Reporting and Data System (TIRADS) of classifying thyroid nodules on ultrasound with the findings on fine-needle aspiration cytology (FNAC) reported using the Bethesda System. **METHODS:** A retrospective analysis of 100 consecutive cases over 1 year (Jan-Dec 2015) was performed comparing single-surgeon-performed bedside thyroid nodule ultrasound findings based on the TIRADS classification to the FNAC report based on the Bethesda Classification. TIRADS 1 (normal thyroid gland) and biopsy-proven malignancy referred by other clinicians were excluded. Benign-appearing nodules were reported as TIRADS 2 and 3. Indeterminate or suspected follicular lesions were reported as TIRADS 4, and malignant-appearing nodules were classified as TIRADS 5 during surgeon-performed bedside ultrasound. All the nodules were subjected to ultrasound-guided FNAC, and TIRADS findings were compared to Bethesda FNAC Classification. **RESULTS:** Of the 100 cases, 74 were considered benign or probably benign, 20 were suspicious for malignancy, and 6 were indeterminate on ultrasound. Overall concordance rate with FNAC was 83% with sensitivity and specificity of 70.6 and 90.4%, respectively. The negative predictive value was 93.8%. **CONCLUSION:** It is essential for clinicians performing bedside ultrasound thyroid and guided FNAC to document their sonographic impression of the nodule in an objective fashion using the TIRADS classification and correlate with the gold standard cytology to improve their learning curve and audit their results.

PubMed-ID: [28251273](https://pubmed.ncbi.nlm.nih.gov/28251273/)

<http://dx.doi.org/10.1007/s00268-017-3919-5>

### **Central compartment management in patients with papillary thyroid cancer presenting with metastatic disease to the lateral neck: Anatomic pathways of lymphatic spread.**

*Head Neck*, 39(5):853-9.

I. Likhterov, L. L. Reis and M. L. Urken.

**BACKGROUND:** Papillary thyroid cancer (PTC) occasionally presents with metastases to the lateral neck, without clinically evident disease in the central neck. These cases may ultimately manifest as either skip metastases to the lateral compartment or as occult metastases in the central compartment. **METHODS:** This is a retrospective review of 80 patients with PTC with metastases to the lateral cervical lymph nodes treated from 2006 to 2015. Photographs of the cadaveric dissections were used with permission from the author. Schematic illustrations were created to highlight lymphatic drainage pathways. **RESULTS:** The rate of skip metastasis in this cohort was 5%. Clinical evidence of central neck disease did not predict the pathologic status of the compartment. **CONCLUSION:** PTC rarely spreads to the lateral neck without depositing metastases within the central neck. This finding is supported by the anatomic pathways for lymphatic spread, not previously highlighted in the English literature. (c) 2017 Wiley Periodicals, Inc. *Head Neck* 39: 853-859, 2017.

PubMed-ID: [28252836](https://pubmed.ncbi.nlm.nih.gov/28252836/)

<http://dx.doi.org/10.1002/hed.24568>

### **Impact of resident training on operative time and safety in hemithyroidectomy.**

*Head Neck*, 39(6):1212-7.

C. Folsom, K. Serbousek, W. Lydiatt, K. Rieke, H. Sayles, R. Smith and A. Panwar.

**BACKGROUND:** The purpose of this study was to present our assessment of the impact of resident participation on operative duration and outcomes after hemithyroidectomy, which may identify opportunities for optimization of educational programs, reduction in cost of healthcare delivery, and maximizing patient safety, while continuing to train a competent physician workforce for the future. **METHODS:** The American College of Surgeons' National Surgical Quality Improvement Program (ACS NSQIP) dataset from 2006 to 2012 identified 13,151 adult patients who underwent hemithyroidectomy. Differences in operative duration, postoperative complications, reoperation, and readmission rates were assessed based on stratification by resident participation in surgery. **RESULTS:** Compared with operations performed by attending surgeons alone, resident participation with attending supervision prolonged the operative duration by 10.5% (82.5 minutes vs 91.2 minutes;  $p < .0001$ ). The incidence of readmission and wound complications was higher for patients who underwent surgery with resident participation. **CONCLUSION:** Resident participation in hemithyroidectomy may be associated with increased operative duration, higher incidence of wound complications, and readmission. (c) 2017 Wiley Periodicals, Inc.

*Head Neck* 39: 1212-1217, 2017.

PubMed-ID: [28263429](https://pubmed.ncbi.nlm.nih.gov/28263429/)

<http://dx.doi.org/10.1002/hed.24742>

### **Timing of multikinase inhibitor initiation in differentiated thyroid cancer.**

*Endocr Relat Cancer*, 24(5):237-42.

M. S. Brose, J. Smit, C. C. Lin, F. Pitoia, M. Fellous, Y. DeSanctis, M. Schlumberger, M. Tori and I. Sugitani.

There are limited treatment options for patients with radioactive iodine refractory, progressive differentiated thyroid cancer. Although there is consensus that multikinase inhibitor therapy should be considered in patients with progressive disease with considerable tumor load or symptomatic disease, uncertainty exists on the optimal timing to treat with a multikinase inhibitor, especially for asymptomatic patients. RIFTOS MKI is an international, prospective, open-label, multicenter, noninterventional study with the primary objective to compare the time to symptomatic progression from study entry in asymptomatic patients with radioactive iodine refractory, progressive differentiated thyroid cancer for whom there is a decision to initiate multikinase inhibitors at study entry (cohort 1) with those for whom there is a decision to not initiate multikinase inhibitors at study entry (cohort 2). Secondary endpoints are overall survival and progression-free survival, which will be compared between cohorts 1 and 2. Additional secondary endpoints are postprogression survival from time of symptomatic progression, duration of and response to each systemic treatment regimen and dosing of sorafenib throughout the treatment period. Asymptomatic, multikinase inhibitor-naïve patients aged  $\geq 18$  years with histologically/cytologically documented differentiated thyroid cancer that is radioactive iodine refractory are eligible. Patients may receive any therapy for differentiated thyroid cancer, including sorafenib or other multikinase inhibitors if indicated and decided on by the treating physician. In total, 700 patients are estimated to be enrolled from  $>20$  countries. Final analysis will be performed once the last enrolled patient has been followed up with for 24 months (ClinicalTrials.gov identifier: Nbib2303444).

PubMed-ID: [28270435](https://pubmed.ncbi.nlm.nih.gov/28270435/)

<http://dx.doi.org/10.1530/ERC-17-0016>

### **Mapping the distribution of nodal metastases in papillary thyroid carcinoma: Where exactly are the nodes?**

*Laryngoscope*, 127(8):1959-64.

N. Goyal, M. Pakdaman, D. Kamani, D. Caragacianu, D. Goldenberg and G. W. Randolph.

**OBJECTIVE:** To characterize nodal disease of patients presenting with papillary thyroid carcinoma (PTC) **STUDY DESIGN:** Retrospective chart review. **METHODS:** PTC patients who underwent thyroidectomy and/or neck dissection (revision/primary) from 2004 to 2009 at a tertiary-care hospital were reviewed. Preoperative computed tomography (CT) scan and ultrasonography were utilized to identify macroscopic, clinically apparent nodal metastasis (cN+). Demographic data, type of surgery, nodal disease, and primary tumor information were recorded. **RESULTS:** Of 416 patients reviewed, 35% had cN+ on initial presentation (IP); of these, 88% and 50% had central (CND) and lateral nodal disease (LND), respectively. The presence of ectopic nodal (END) metastases (nodal disease outside typical CND or LND locations) was absent on IP but occurred in 9% of patients with nodal recurrence. END was typically found in the retropharyngeal area but also was noted in the sublingual region, subcutaneous location, axilla, and chest wall. Extrathyroidal extension (ETE) was found in 8.9% without nodal disease, 33.1% with nodal disease, and 57.1% with END ( $P < 0.0001$ ). Primary tumor size greater than 4 cm ( $P = 0.05$ ) was associated with nodal disease. **CONCLUSION:** This report represents a large series describing characteristics of the primary PTC tumor and associated nodal disease not only in the central



and lateral neck but also in the ectopic locations. Our results suggest that a significant proportion of patients will have nodal disease in the central compartment on IP, especially younger patients. ETE and tumor size are associated with macroscopic nodal disease (including END). Nine percent of the patients with nodal recurrence had ectopic nodes occurring in various locations, most commonly in the retropharynx. CT scan can assist with identification and surgical planning of recurrent nodal disease. LEVEL OF EVIDENCE: 4. Laryngoscope, 127:1959-1964, 2017.

PubMed-ID: [28271511](https://pubmed.ncbi.nlm.nih.gov/28271511/)

<http://dx.doi.org/10.1002/lary.26495>

#### **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.

**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](https://pubmed.ncbi.nlm.nih.gov/28273370/)

<http://dx.doi.org/10.1111/cen.13322>

#### **Molecular profiling of thyroid nodule fine-needle aspiration cytology.**

*Nat Rev Endocrinol*, 13(7):415-24.

M. Eszlinger, L. Lau, S. Ghaznavi, C. Symonds, S. P. Chandarana, M. Khalil and R. Paschke.

The differential diagnosis and malignancy risk stratification of thyroid nodules requires multidisciplinary expertise and knowledge of both local ultrasonography practices and the local malignancy rates for a given fine-needle aspiration (FNA) result. Even in such a multidisciplinary setting, FNA cytology has the inherent limitation that indeterminate cytology results cannot distinguish between follicular adenomas, follicular thyroid carcinomas or follicular variant papillary thyroid carcinomas. Accumulating evidence suggests that this limitation can be overcome by using molecular diagnostic approaches. In this Review, we present the advantages and disadvantages of the different molecular diagnostic methodologies, which can be divided into two approaches: those that 'rule out' malignancy (to reduce the overtreatment of benign nodules) and those that 'rule in' malignancy (to optimize surgical planning). We identify microRNA classifiers as potential additional markers for use in a two-step diagnostic approach, consider the potential implications of the reclassification of noninvasive encapsulated follicular variant papillary thyroid carcinomas to noninvasive follicular thyroid neoplasms with papillary-like nuclear features and discuss the cost-effectiveness of molecular testing. Molecular FNA diagnostics is an important complementary addition to FNA cytology that could substantially reduce unnecessary surgery and better define the need for appropriate surgery in patients who have thyroid nodules with indeterminate FNA cytology.

PubMed-ID: [28361927](https://pubmed.ncbi.nlm.nih.gov/28361927/)

<http://dx.doi.org/10.1038/nrendo.2017.24>

#### **Management of unilateral recurrent laryngeal nerve injury after thyroid surgery: A review.**

*Head Neck*, 39(7):1470-8.

J. Lynch and R. Parameswaran.

**BACKGROUND:** Recurrent laryngeal nerve (RLN) damage because of thyroid and parathyroid surgery has been recognized for over a century. Injury rates have been slowly decreasing in this period while effective treatment

strategies have been increasing. METHODS: Recent literature was evaluated on the topics of anatomy, pathophysiology, avoidance, and conservative and surgical treatment of RLN injury. Data for this literature review were identified by PubMed and references from relevant articles using the search terms "thyroid," "laryngeal nerve," and "injury." Only articles published in English between 1990 and 2015 were included. RESULTS: Advances in technique and equipment have made injury less likely. The evidence and role for neuromonitoring is discussed. Treatment strategies may include speech therapy, vocal cord augmentation using injection, laryngeal framework surgery techniques (including laryngoplasty and arytenoid adduction), and reinnervation. CONCLUSION: Injury rates in specialist centers are very low. Good to excellent results may be obtained in most cases.

PubMed-ID: [28370683](https://pubmed.ncbi.nlm.nih.gov/28370683/)

<http://dx.doi.org/10.1002/hed.24772>

### **Preoperative vitamin D level as predictor of post-thyroidectomy hypocalcemia in patients sustaining transient parathyroid injury.**

*Head Neck*, 39(7):1378-81.

D. Danan and D. C. Shonka, Jr.

BACKGROUND: Several studies have sought to identify predictors of postoperative hypocalcemia after total thyroidectomy; however, there have been conflicting results regarding the impact of preoperative vitamin D deficiency. METHODS: The medical records of patients undergoing total thyroidectomy were retrospectively reviewed. The number of parathyroid glands identified or reimplanted at the time of surgery was used as a marker of transient parathyroid gland damage. RESULTS: Sixty-seven patients were included in the study. Vitamin D deficiency was a significant predictor of hypocalcemia in patients in whom  $\geq 3$  parathyroid glands were identified, but not in patients in whom 0-2 parathyroid glands were identified intraoperatively (odds ratio [OR] 5.8;  $P = .036$ ). CONCLUSION: Vitamin D deficiency is a significant predictor of postoperative hypocalcemia in patients in whom  $\geq 3$  parathyroid glands are identified intraoperatively, but not in patients who sustain minimal transient damage to the parathyroid glands.

PubMed-ID: [28370789](https://pubmed.ncbi.nlm.nih.gov/28370789/)

<http://dx.doi.org/10.1002/hed.24775>

### **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.

Objective Thyroidectomy with extensive multicompartiment 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 an effective alternative strategy option to simultaneous bilateral surgery in the management of thyroid cancer with extensive neck metastases.

PubMed-ID: [28374646](https://pubmed.ncbi.nlm.nih.gov/28374646/)

<http://dx.doi.org/10.1177/0194599817697189>

### **Completeness of ultrasound reporting impacts time to biopsy for benign and malignant thyroid nodules.**

*Am J Surg*, 213(5):931-5.

A. Inman, K. Liu, K. Ong, P. Tiwari, P. Vos, A. White and S. M. Wiseman.

BACKGROUND: The objective was to evaluate reporting of guideline-recommended elements for thyroid



ultrasound (US), and to determine whether element reporting was associated with the time to cytological and/or surgical diagnosis. METHODS: US reports of adults who underwent thyroid surgery for benign (n = 106) or malignant (n = 105) thyroid nodules between 2009 and 2014 were retrospectively reviewed for inclusion of 11 elements. RESULTS: On average 5.1 elements of 11 (46.4%) were included in US reports of all nodules. The setting of the US (academic versus community center) also influenced the number of elements reported (6.3 in academic versus 4.9 in community, p < 0.001). A higher number of reported elements were significantly associated with fewer days between US and FNAB, FNAB and OR, and US and OR (p < 0.001, p = 0.007, and p < 0.001, respectively). CONCLUSIONS: Under-reporting of guideline-recommended US elements is associated with delayed cytological diagnosis and surgical treatment of thyroid nodules.

PubMed-ID: [28385381](https://pubmed.ncbi.nlm.nih.gov/28385381/)

<http://dx.doi.org/10.1016/j.amjsurg.2017.03.030>

### **Management of PET diagnosed thyroid incidentalomas in British Columbia Canada: Critical importance of the PET report.**

*Am J Surg*, 213(5):950-7.

J. Wong, K. Liu, C. Siu, S. Jones, M. Sovka, D. Wilson and S. M. Wiseman.

BACKGROUND: PET diagnosed thyroid incidentalomas (TI) should undergo prompt evaluation due to a high risk of underlying malignancy. Our study reviewed physician management of PET diagnosed TIs in British Columbia (BC), Canada. METHODS: All PET reports from BC between 2011 and 2014 were reviewed. Clinical and demographic data was obtained for TI patients through chart review and mail out surveys to physicians. Statistical analysis was performed to identify factors associated with further TI investigation. RESULTS: 4.7% PET scans diagnosed TIs in 5.3% of patients. 9.8% of diffuse and 46.1% of focal TI cases underwent ultrasound +/- biopsy. PET scan report characteristics were significantly associated with further TI investigation (p-value <0.05). CONCLUSIONS: Patients with PET diagnosed TIs are being under-investigated in BC and PET scan report related factors were found to be significantly associated with undergoing further TI workup.

PubMed-ID: [28408111](https://pubmed.ncbi.nlm.nih.gov/28408111/)

<http://dx.doi.org/10.1016/j.amjsurg.2017.03.015>

### **Anatomic Characteristics, Identification, and Protection of the Nonrecurrent Laryngeal Nerve during Thyroidectomy.**

*Otolaryngol Head Neck Surg*, 157(2):210-6.

N. Qiao, L. F. Wu, W. Gao, F. Z. Qu, P. Y. Duan, C. L. Cao, P. Q. Li, B. Sun and G. Wang.

Objective We aimed to investigate the anatomical features and variation pattern of the nonrecurrent laryngeal nerve (NRLN), summarize the methods for identifying the NRLN before and during thyroidectomy, and share experiences regarding preventing and treating its injury. Study Design Retrospective case data analysis. Setting First Affiliated Hospital of Harbin Medical University. Subjects and Methods Between January 2002 and May 2016, 7392 patients underwent thyroidectomy in our hospital. Of them, 28 patients with NRLN were identified, and their clinical data were retrospectively analyzed. Results This study included 7392 patients in which the recurrent laryngeal nerves (RLNs) were routinely identified during surgery. The presence of NRLN was intraoperatively confirmed in 28 patients. All the NRLNs were located on the right side and its overall incidence was 0.37%. Five of the NRLNs were classified as type I, 19 as type IIa, and 4 as type IIb. Of the 28 cases, 4 NRLNs were injured during surgery, in which primary end-to-end anastomosis or local seal with corticosteroid injection was performed as a remedy. In the 4 patients with NRLN injury, 2 presented with postoperative hoarseness that indicated vocal cord paralysis confirmed by laryngoscope; the other 2 patients' voices had no significant changes. Conclusion The NRLN, which is rare in clinical practice and predominantly right-sided, is anatomically more complex and variant at a higher risk of surgical injury. The key factors to accurately identify NRLN and to effectively prevent its injury include careful interpretation of auxiliary examination results before surgery, raising awareness of its presence, meticulous dissection, and routine exposure of the RLN during surgery.

PubMed-ID: [28417660](https://pubmed.ncbi.nlm.nih.gov/28417660/)

<http://dx.doi.org/10.1177/0194599817700583>

### **Thyroid cancer: The thyroid cancer epidemic - overdiagnosis or a real increase?**

*Nat Rev Endocrinol*, 13(6):318-9.

C. La Vecchia and E. Negri.

PubMed-ID: [28450748](https://pubmed.ncbi.nlm.nih.gov/28450748/)

<http://dx.doi.org/10.1038/nrendo.2017.53>

**Facilitating anaplastic thyroid cancer specialized treatment: A model for improving access to multidisciplinary care for patients with anaplastic thyroid cancer.**

*Head Neck*, 39(7):1291-5.

M. E. Cabanillas, M. D. Williams, G. B. Gunn, S. P. Weitzman, L. Burke, N. L. Busaidy, A. K. Ying, Y. H. Yiin, W. N. William, C. Lu and S. Y. Lai.

**BACKGROUND:** Anaplastic thyroid cancer (ATC) is a highly aggressive thyroid cancer. Several treatment trials are available, but the number of eligible patients to participate is very low because of the rarity and aggressiveness of the disease. **METHODS:** Facilitating Anaplastic Thyroid Cancer Specialized Treatment (FAST) is a quality improvement project aimed at decreasing time from referral to disposition (scheduling of first appointment) to our institution. After identifying reasons for delays, we created a new process flow specifically for patients with ATC allowing patients to be scheduled immediately. **RESULTS:** Historical data revealed a mean referral to disposition time for patients with ATC of 8.7 days before our intervention. After the intervention, the mean referral to disposition time was reduced to 0.5 days. Participation in treatment trials for all patients with ATC was 34%. **CONCLUSION:** Since the implementation of FAST, the access time has decreased and the number of successful referrals for ATC has increased significantly.

PubMed-ID: [28452157](https://pubmed.ncbi.nlm.nih.gov/28452157/)

<http://dx.doi.org/10.1002/hed.24784>

**Structural alterations in tumor-draining lymph nodes before papillary thyroid carcinoma metastasis.**

*Head Neck*, 39(8):1639-46.

A. M. Hinson, N. A. Massoll, L. A. Jolly, B. C. Stack, Jr., D. L. Bodenner and A. T. Franco.

**BACKGROUND:** The purpose of this study was to define and characterize the thyroid tumor-draining lymph nodes in genetically engineered mice harboring thyroid-specific expression of oncogenic Braf(V600E) with and without Pten insufficiency. **METHODS:** After intratumoral injection of methylene blue, the lymphatic drainage of the thyroid gland was visualized in real time. The thyroid gland/tumor was resected en bloc with the respiratory system for histological analysis. **RESULTS:** Although mice harboring Braf(V600E) mutations were smaller in body size compared with their wild-type (WT) littermates, the size of their thyroid glands and deep cervical lymph nodes were significantly larger. Additionally, the tumor-draining lymph nodes showed increased and enlarged lymphatic sinuses that were distributed throughout the cortex and medulla. Tumor-reactive lymphadenopathy and histiocytosis, but no frank metastases, were observed in all mice harboring Braf(V600E) mutations.

**CONCLUSIONS:** The tumor-draining lymph nodes undergo significant structural alterations in immunocompetent mice, and this may represent a primer for papillary thyroid carcinoma (PTC) metastasis.

PubMed-ID: [28467685](https://pubmed.ncbi.nlm.nih.gov/28467685/)

<http://dx.doi.org/10.1002/hed.24807>

**Robotic thyroidectomy and parathyroidectomy: An initial experience with retroauricular approach.**

*Head Neck*, 39(8):1568-72.

M. Alshehri, H. E. Mohamed, T. Moulthrop and E. Kandil.

**BACKGROUND:** New approaches for robotic-assisted thyroidectomy were recently described. The purpose of this study was to present the report of our initial experience using a retroauricular approach for thyroid and parathyroid surgeries. **METHODS:** This is a prospective study that was conducted under institutional review board approval and all surgeries were performed by a single surgeon at a North American academic institution. Some patients underwent an additional concomitant neck lift surgery in addition to the thyroid surgery. Some cases were performed without the use of the robot and they have been evaluated compared with the robotic cases. Clinical characteristics, total operative time, blood loss, surgical outcome, and length of hospital stay were evaluated. **RESULTS:** Forty cases representing thirty-eight female patients were included in this study, which includes 37 thyroid lobectomies and 3 parathyroid surgeries. Mean age was 44 +/- 13 years, and mean body mass index (BMI) was 26.9 +/- 5.31. Mean thyroid nodule size was 2.01 +/- 0.94 cm. All cases were completed successfully via a single retroauricular incision. There was no conversion to an open approach. Six of 38 patients underwent additional neck lift surgery with a mean total operative time of 189 +/- 45 minutes. The mean operative time for the remaining 34 patients who underwent retroauricular robotic-assisted hemithyroidectomy without neck lift surgery was 156 +/- 39 minutes. Five patients underwent an endoscopic, retroauricular approach to the thyroid and parathyroid without using the robot. Two of 38 patients developed postoperative hematoma, in whom one of them needed a surgical evacuation. There were no cases of permanent vocal cord paralysis or permanent hypoparathyroidism. However, 2 patients developed transient hoarseness, which resolved 9 weeks and 10 weeks postoperatively, respectively. Mean blood loss was 19.0 +/- 30.93 mL. Twenty-one patients were discharged on the same day of surgery, 17 patients were discharged after an overnight stay, and the remaining 2 patients were discharged after 2 days. **CONCLUSION:** Single-incision retroauricular robotic hemithyroidectomy and parathyroidectomy can be safe and feasible and concomitant neck lift surgery can be

offered in a select group of patients. In addition, the nonrobotic retroauricular approach can be performed safely; however, future studies are warranted to further evaluate the benefits and limitations of this novel robotic retroauricular surgical approach.

PubMed-ID: [28474427](https://pubmed.ncbi.nlm.nih.gov/28474427/)

<http://dx.doi.org/10.1002/hed.24794>

**[Complications after thyroid gland operations in Germany : Further information and routine data analysis].**

*Chirurg*, 88(6):534-5.

M. Maneck, C. Dotzenrath, H. Dralle, C. Fahlenbrach, R. Paschke, T. Steinmuller, E. Tusch, E. Jeschke and C. Gunster.

PubMed-ID: [28477065](https://pubmed.ncbi.nlm.nih.gov/28477065/)

<http://dx.doi.org/10.1007/s00104-017-0439-7>

**Comparison of risk of malignancy in a subgroup with atypia of undetermined significance/follicular lesion of undetermined significance: A meta-analysis.**

*Head Neck*, 39(8):1699-710.

S. H. Ahn, S. D. Kim and W. J. Jeong.

BACKGROUND: As heterogeneous findings are included in the atypia of undetermined significance (AUS)/follicular lesion of undetermined significance (FLUS) category, differing risks of malignancy in subgroups have been reported in several articles. METHODS: We performed a meta-analysis of full-text publications written in English found in the Embase and PubMed databases. RESULTS: The 4-tiered subgroup proportion meta-analysis showed that the 95% confidence interval (95% CI) of the risk of malignancy in the cellular atypia group did not overlap with the other 3 subgroups and demonstrated a significant difference. Two-tiered analysis using the cytologic and architectural atypia groups showed that cytologic atypia group had a 2.64-fold increase in the risk of malignancy compared with the architectural atypia group. CONCLUSION: The cytologic atypia had a significantly higher risk of malignancy than the architectural atypia group, and it should be considered as a separate category.

PubMed-ID: [28493558](https://pubmed.ncbi.nlm.nih.gov/28493558/)

<http://dx.doi.org/10.1002/hed.24768>

**Perioperative practices in thyroid surgery: An international survey.**

*Head Neck*, 39(7):1296-305.

A. Maniakas, A. Christopoulos, E. Bissada, L. Guertin, M. J. Olivier, J. Malaise and T. Ayad.

BACKGROUND: Perioperative practices in thyroid surgery vary from one specialty, institution, or country to the next. We evaluated the preoperative, intraoperative, and postoperative practices of thyroid surgeons focusing on preoperative ultrasound, vocal cord evaluation, wound drains, and hospitalization duration, among others.

METHODS: A survey was sent to 7 different otolaryngology and endocrine/general surgery associations.

RESULTS: There were 965 respondents from 52 countries. Surgeon-performed ultrasound is practiced by more than one third of respondents. Otolaryngologists perform preoperative and postoperative vocal cord evaluation more often than endocrine/general surgeons ( $p < .001$ ). Sixty percent of respondents either never place drains or place drains  $<50\%$  of the time in thyroid lobectomies (43% for total thyroidectomies). Outpatient thyroid surgery is most frequently performed by surgeons in the United States (63%). CONCLUSION: This epidemiologic study is the first global thyroid survey of its kind and clearly demonstrates the variability and evolving trends in thyroid surgery. (c) 2017 Wiley Periodicals, Inc. *Head Neck* 39: 1296-1305, 2017.

PubMed-ID: [28493562](https://pubmed.ncbi.nlm.nih.gov/28493562/)

<http://dx.doi.org/10.1002/hed.24722>

**Disease Progression in Papillary Thyroid Cancer with Biochemical Incomplete Response to Initial Therapy.**

*Ann Surg Oncol*, 24(9):2611-6.

N. K. Zern, R. Clifton-Bligh, A. J. Gill, A. Aniss, S. Sidhu, L. Delbridge, D. Learoyd, B. Robinson and M. Sywak.

BACKGROUND: Dynamic risk stratification is utilized in the follow-up of patients with papillary thyroid carcinoma (PTC). Analysis of outcomes after biochemical incomplete response (BIR) to initial therapy will allow better individualization of care. METHODS: A total of 494 patients with PTC were followed prospectively.

Immunohistochemistry (IHC) for BRAF(V600E) mutation was completed on all surgical specimens. After exclusion of patients with inadequate data, 353 patients were stratified into four categories of response to initial therapy: excellent, biochemical incomplete, structural incomplete, or indeterminate. Patients with BIR, defined as elevated stimulated thyroglobulin  $>2$  microg/L with negative imaging, were analysed for progression of disease.

The primary outcome measure was development of structural recurrence. RESULTS: Forty-nine of 353 (13.9%) patients had BIR. BRAF(V600E) mutation was present in 32 of 49 (65.3%) with BIR. Progression to structural recurrence occurred in 8 of 49 (16.3%) with BIR, all of whom were positive for the BRAF(V600E) mutation ( $p = 0.02$ ). Nine patients (18%) with BIR remitted during follow-up to no evidence of disease (6 had additional RAI therapy). After mean follow-up of 35 months, 12 patients with BIR (24%) remained biochemically abnormal with no structural evidence of disease. CONCLUSIONS: Patients with BIR following initial treatment for PTC have generally favorable outcomes. Positive IHC for BRAF(V600E) identifies patients at risk of structural disease recurrence.

PubMed-ID: [28585075](https://pubmed.ncbi.nlm.nih.gov/28585075/)

<http://dx.doi.org/10.1245/s10434-017-5911-6>

### **Diagnostic Value of Circulating microRNA-95 and -190 in the Differential Diagnosis of Thyroid Nodules: A Validation Study in 1000 Consecutive Patients.**

*Thyroid*, 27(8):1053-7.

T. Pilli, S. Cantara, C. Marzocchi, S. Cardinale, C. Santini, G. Cevenini and F. Pacini.

BACKGROUND: It has recently been demonstrated that the combination of miRNA-190 and -95 (expressed as probability of malignant risk: pmiRNA) in the serum of Caucasian patients with thyroid nodular disease allows the identification of nodules at high risk of malignancy with great accuracy. The present study aimed to validate these results in a larger cohort of patients. MATERIALS AND METHODS: This study prospectively analyzed 1000 patients. Cytological diagnosis was available in 982/1000 (98.2%) and histological diagnosis in 445/1000 (44.5%). The expression levels of circulating miRNA-190 and -95 were determined by real time polymerase chain reaction with the 2(-DeltaDeltaCt) method. The diagnostic performance (sensitivity, specificity, and accuracy) of fine-needle aspiration cytology (FNAC), pmiRNA, and a combination of the two methods was correlated with the cytological and histological diagnoses. RESULTS: The combination of pmiRNA and FNAC significantly increased the sensitivity (96.3%) with respect to each method alone (88.9% for FNAC and 89.6% for pmiRNA) by reducing the rate of false-negative results from 18 for FNAC and 17 for pmiRNA to only five. In patients in whom FNAC was not performed ( $n = 14$ ) or in those with inadequate ( $n = 18$ ) or indeterminate ( $n = 72$ ) lesions submitted to surgery, pmiRNA correctly identified 90.8% of patients with benign disease and 74.3% of patients with cancer. CONCLUSIONS: These results confirm that a combination of serum expression levels of miRNA-95 and -190 is an accurate and noninvasive tool for the differential diagnosis of thyroid nodules in the Italian population.

PubMed-ID: [28605303](https://pubmed.ncbi.nlm.nih.gov/28605303/)

<http://dx.doi.org/10.1089/thy.2017.0035>

### **Aesthetics in Thyroid Surgery: The Patient Perspective.**

*Otolaryngol Head Neck Surg*, 157(3):409-15.

K. Chung, W. S. Duke, S. J. Oh, A. Behr, J. L. Waller, J. Daniel and D. J. Terris.

Objectives To define characteristics that influence patient perceptions of thyroidectomy scar cosmesis. Study Design Prospective cohort study. Setting Tertiary endocrine surgery practice in an academic medical center. Subjects and Methods Institutional review board-approved trial in which 136 subjects were recruited from a population of patients being seen for either thyroid or sinus surgery and evaluated standardized photographs, superimposed with computer-generated thyroidectomy scars of varying lengths (2, 4, and 6 cm) and widths (1 and 2 mm), and graded their perception of the scars using the observer scar assessment scale (OSAS) domains of the patient and observer scar assessment scale. Results There were 69 subjects in the thyroid group and 67 in the nonthyroid group. Controlling for width, longer scars were perceived as worse than shorter scars; controlling for length, thicker scars were perceived as worse than thinner scars ( $P < .01$ ). Beyond 2 cm, thick scars were judged to be worse than thin scars, even when they were shorter. There was no difference in the mean overall OSAS scores between surgery, sex, or age groups. Nonwhites tended to judge scars as being worse than whites did ( $P < .01$ ). Conclusion As expected, patients of all demographics prefer shorter scars compared with longer scars and thinner scars over thick scars. Ethnic differences in scar perception were identified and deserve additional study. Surgeons should endeavor to perform thyroid surgery through the smallest incision that allows the operation to be performed safely to minimize the cosmetic impact of the operation.

PubMed-ID: [28608750](https://pubmed.ncbi.nlm.nih.gov/28608750/)

<http://dx.doi.org/10.1177/0194599817711886>

### **Medullary Thyroid Carcinoma in MEN2A: ATA Moderate- or High-Risk RET Mutations Do Not Predict Disease Aggressiveness.**

*J Clin Endocrinol Metab*, 102(8):2807-13.



R. K. Voss, L. Feng, J. E. Lee, N. D. Perrier, P. H. Graham, S. M. Hyde, F. Nieves-Munoz, M. E. Cabanillas, S. G. Waguespack, G. J. Cote, R. F. Gagel and E. G. Grubbs.

Context: High-risk RET mutations (codon 634) are associated with earlier development of medullary thyroid carcinoma (MTC) and presumed increased aggressiveness compared with moderate-risk RET mutations. Objective: To determine whether high-risk RET mutations are more aggressive. Design: Retrospective cohort study using institutional multiple endocrine neoplasia type 2 registry. Setting: Tertiary cancer care center. Patients: Patients with MTC and moderate- or high-risk germline RET mutation. Intervention: None (observational study). Main Outcome Measures: Proxies for aggressiveness were overall survival (OS) and time to distant metastatic disease (DMD). Results: A total of 127 moderate-risk and 135 high-risk patients were included (n = 262). Median age at diagnosis was 42.3 years (range, 6.4 to 86.4 years; mean, 41.6 years) for moderate-risk mutations and 23.0 years (range, 3.7 to 66.8 years; mean, 25.6 years) for high-risk mutations (P < 0.0001). Moderate-risk patients had more T3/T4 tumors at diagnosis (P = 0.03), but there was no significant difference for N or M stage and no significant difference in OS (P = 0.40). From multivariable analysis for OS, increasing age [hazard ratio (HR), 1.05/y; 95% confidence interval (CI), 1.03 to 1.08], T3/T4 tumor (HR, 2.73; 95% CI, 1.22 to 6.11), and M1 status at diagnosis (HR, 3.93; 95% CI, 1.61 to 9.59) were significantly associated with worse OS but high-risk mutation was not (P = 0.40). No significant difference was observed for development of DMD (P = 0.33). From multivariable analysis for DMD, only N1 status at diagnosis was significant (HR, 2.10; 95% CI, 1.03 to 4.27). Conclusions: Patients with high- and moderate-risk RET mutations had similar OS and development of DMD after MTC diagnosis and therefore similarly aggressive clinical courses. High-risk connotes increased disease aggressiveness; thus, future guidelines should consider RET mutation classification by disease onset (early vs late) rather than by risk (high vs moderate).

PubMed-ID: [28609830](https://pubmed.ncbi.nlm.nih.gov/28609830/)

<http://dx.doi.org/10.1210/jc.2017-00317>

### **Second Primary Cancer in Patients with Differentiated Thyroid Cancer: Does Radioiodine Play a Role?** *Thyroid*, 27(8):1068-76.

M. Silva-Vieira, S. Carrilho Vaz, S. Esteves, T. C. Ferreira, E. Limbert, L. Salgado and V. Leite.

BACKGROUND: Well-differentiated thyroid cancer (WDTC) is the most common endocrine neoplasia, and its incidence is rising. Studies have reported an increased risk of second primary cancer (SPC) in WDTC survivors, but its relationship with radioiodine treatment (RAIT) and other risk factors remains controversial. This study evaluated whether RAIT is an independent risk factor for SPC in WDTC patients. METHODS: This was a retrospective single-center study. A total of 2031 patients with WDTC diagnosed between 1998 and 2009, treated and followed at the authors' tertiary cancer center, were included. RESULTS: The median age of patients was 48 years (range 5-90 years); 83% were women and 77% underwent RAIT. The median follow-up was 8.8 years (range 5.0-17.0 years). A total of 130 SPC were diagnosed: 108/1570 (6.9%) received RAIT (RAIT+) and 22/461 (4.8%) did not (RAIT-). The most common SPC was breast cancer (31%), followed by genitourinary and gastrointestinal cancer (18% each). The 10-year cumulative incidence of SPC was 8.2% in RAIT+ and 4.5% in RAIT-. The absolute risk increase in the RAIT+ group versus the RAIT- group at 10 years of follow-up was 0.039 [confidence interval (CI) 0.011-0.067] per patient-year. The number needed to harm (NNH) was 25.6 [CI 15.0-87.2], indicating that on average during a 10-year follow-up period, there is one additional case of SPC for every 26 patients receiving RAIT. When controlling for age, sex, and familial and personal histories of cancer, there was an 84% increase in the risk of SPC in the RAIT+ group compared to the RAIT- group (p = 0.026; relative risk = 1.84 [CI 1.02-3.31]). There was an association between SPC incidence and total cumulative activity administered, which was statistically significant >200 mCi. The incidence of SPC was higher in both the WDTC and the RAIT+ cohorts compared to the general population (standardized incidence ratios = 1.32 and 1.40, respectively). CONCLUSION: These results indicate that in spite of the low incidence of SPC in WDTC patients, the risk is increased after RAIT, particularly for activities >200 mCi. Thus, considering the excellent survival of patients with WDTC, clinicians need to weigh the risks and benefits of RAIT, especially in patients with low-risk thyroid cancer.

PubMed-ID: [28614983](https://pubmed.ncbi.nlm.nih.gov/28614983/)

<http://dx.doi.org/10.1089/thy.2016.0655>

### **Controversies in the Management of Low-Risk Differentiated Thyroid Cancer.**

*Endocr Rev*, 38(4):351-78.

M. R. Haymart, N. H. Esfandiari, M. T. Stang and J. A. Sosa.

Controversy exists over optimal management of low-risk differentiated thyroid cancer. This controversy occurs in all aspects of management, including surgery, use of radioactive iodine for remnant ablation, thyroid hormone supplementation, and long-term surveillance. Limited and conflicting data, treatment paradigm shifts, and differences in physician perceptions contribute to the controversy. This lack of physician consensus results in

wide variation in patient care, with some patients at risk for over- or undertreatment. To reduce patient harm and unnecessary worry, there is a need to design and implement studies to address current knowledge gaps.

PubMed-ID: [28633444](https://pubmed.ncbi.nlm.nih.gov/28633444/)

<http://dx.doi.org/10.1210/er.2017-00067>

### **Results of Screening in Familial Non-Medullary Thyroid Cancer.**

*Thyroid*, 27(8):1017-24.

J. Klubo-Gwiedzinska, L. Yang, R. Merkel, D. Patel, N. Nilubol, M. J. Merino, M. Skarulis, S. M. Sadowski and E. Kebebew.

**BACKGROUND:** Although a family history of thyroid cancer is one of the main risk factors for thyroid cancer, the benefit of screening individuals with a family history of thyroid cancer is not known. **METHODS:** A prospective cohort study was performed with yearly screening using neck ultrasound and fine-needle aspiration biopsy of thyroid nodule(s) >0.5 cm in at-risk individuals whose relatives were diagnosed with familial non-medullary thyroid cancer (FNMTc). The eligibility criteria were the presence of thyroid cancer in two or more first-degree relatives and being older than seven years of age. Twenty-five kindred were enrolled in the study (12 families with two members affected, and 13 with three or more members affected at enrollment). **RESULTS:** Thyroid cancer was detected by screening in 4.6% (2/43) of at-risk individuals from families with two members affected, and in 22.7% (15/66) of at-risk members from families with three or more patients affected ( $p = 0.01$ ). FNMTc detected by screening was characterized by a smaller tumor size (0.7 +/- 0.5 cm vs. 1.5 +/- 1.1 cm;  $p = 0.006$ ), a lower rate of central neck lymph node metastases (17.6% vs. 51.1%;  $p = 0.02$ ), less extensive surgery (hemithyroidectomy 23.5% vs. 0%;  $p = 0.002$ ), and a lower rate of radioactive iodine therapy (23.5% vs. 79%;  $p < 0.001$ ) compared to those affected at enrollment. **CONCLUSIONS:** Screening of at-risk family members resulted in earlier detection of low-risk FNMTc and was associated with a less aggressive initial treatment. Screening with thyroid ultrasound should be considered in kindred with three or more family members affected by FNMTc. Since active screening might be associated with the risk of overtreatment, it should be implemented with caution, specifically in elderly individuals.

PubMed-ID: [28657510](https://pubmed.ncbi.nlm.nih.gov/28657510/)

<http://dx.doi.org/10.1089/thy.2016.0668>

### **Validation of American Thyroid Association Ultrasound Risk Assessment of Thyroid Nodules Selected for Ultrasound Fine-Needle Aspiration.**

*Thyroid*, 27(8):1077-82.

A. L. Tang, M. Falciglia, H. Yang, J. R. Mark and D. L. Steward.

**OBJECTIVE:** The aim of this study was to validate the American Thyroid Association (ATA) sonographic risk assessment of thyroid nodules. **METHODS:** The ATA sonographic risk assessment was prospectively applied to 206 thyroid nodules selected for ultrasound-guided fine-needle aspiration (US-FNA), and analyzed with The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), as well as surgical pathology for the subset undergoing surgical excision. **RESULTS:** The analysis included 206 thyroid nodules averaging 2.4 cm (range 1-7 cm; standard error of the mean 0.07). Using the ATA US pattern risk assessment, nodules were classified as high (4%), intermediate (31%), low (38%), and very low (26%) risk of malignancy. Nodule size was inversely correlated with sonographic risk assessment, as lower risk nodules were larger on average ( $p < 0.0001$ ). Malignancy rates determined by cytology/surgical pathology were high 100%, intermediate 11%, low 8%, and very low 2%, which were closely aligned with ATA malignancy risk estimates (high 70-90%, intermediate 10-20%, low 5-10%, and very low 3%). ATA US pattern risk assessment also appropriately predicted the proportion of nodules classified as malignant or suspicious for malignancy through TBSRTC classification-high (77%), intermediate (6%), low (1%), and very low 0%-as well as benign TBSRTC classification-high (0%), intermediate (47%), low (61%), and very low (70%) ( $p < 0.0001$ ). Malignancy rates of surgically excised, cytologically indeterminate nodules followed ATA sonographic risk stratification (high 100%, intermediate 21%, low 17%, and very low 12%;  $p = 0.003$ ). **CONCLUSION:** This prospective study supports the new ATA sonographic pattern risk assessment for selection of thyroid nodules for US-FNA based upon TBSRTC and surgical pathology results. In the setting of indeterminate cytopathology, nodules categorized as atypia of undetermined significance/follicular lesion of undetermined significance with ATA high-risk sonographic patterns have a high likelihood of being malignant.

PubMed-ID: [28657511](https://pubmed.ncbi.nlm.nih.gov/28657511/)

<http://dx.doi.org/10.1089/thy.2016.0555>



### **Predictive Factors of Lymph Node Metastasis in Follicular Variant of Papillary Thyroid Carcinoma.**

*Ann Surg Oncol*, 24(9):2617-23.

S. K. Kim, A. Y. Kwon, K. Back, I. Park, N. Hur, J. H. Lee, J. H. Choe, J. H. Kim, Y. L. Oh and J. S. Kim.

**BACKGROUND:** Compared with conventional papillary thyroid carcinoma (PTC), follicular variant of PTC (FV-PTC) shows less aggressive behavior and better prognosis. Nonetheless, regional lymph node (LN) metastasis was found in 22.8% of FV-PTC patients. Because LN metastasis is a proven predictor of recurrence in PTC, it is important to assess LN metastasis in FV-PTC patients. **METHODS:** We retrospectively reviewed 134 FV-PTC patients who underwent thyroidectomy with neck dissection. **RESULTS:** Central LN metastasis (CLNM) and lateral LN metastasis (LLNM) were found in 50 (37.3%) and 16 (11.9%) patients, respectively. In the multivariate analysis for CLNM, male sex (adjusted OR 4.735,  $p = 0.001$ ), nonencapsulated form (adjusted OR 2.863,  $p = 0.022$ ), and tumor size  $>1.0$  cm (adjusted OR 3.157,  $p = 0.008$ ) were independent predictors of high prevalence of CLNM in FV-PTC patients. In the multivariate analysis for LLNM, microscopic extrathyroidal extension (ETE) (adjusted OR 3.939,  $p = 0.041$ ) and CLNM (adjusted OR 13.340,  $p = 0.001$ ) were independent predictors of high prevalence of LLNM in FV-PTC patients. **CONCLUSIONS:** Meticulous perioperative evaluation and prophylactic central neck dissection may be beneficial for FV-PTC patients with male sex, nonencapsulated form, and tumor size  $>1.0$  cm. Moreover, cautious perioperative evaluation of lateral neck LN may be mandatory for FV-PTC patients with microscopic ETE and CLNM.

PubMed-ID: [28685355](https://pubmed.ncbi.nlm.nih.gov/28685355/)

<http://dx.doi.org/10.1245/s10434-017-5912-5>

### **Management of the lateral neck in well differentiated thyroid cancer.**

*Eur J Surg Oncol*,

J. R. Cracchiolo and R. J. Wong.

Lateral neck lymph node metastases in well differentiated thyroid cancer are common, ranging from 30% to 60%, with the majority of these foci identifiable only as microscopic deposits. A skilled ultrasound evaluation of the lymph nodes in the lateral neck is recommended for all patients presenting with newly diagnosed thyroid cancer undergoing surgical management. Ultrasound guided fine needle aspiration biopsy may be used to cytologically confirm suspected lateral neck nodal metastases prior to surgery. For patients with large volume nodal disease, extranodal extension, or multiple nodal metastases, computed tomography (CT) scan of the neck with contrast is an important additional imaging modality to accurately localize disease prior to surgery. Primary surgical management for lateral neck disease typically includes lateral neck dissection in conjunction with total thyroidectomy. Postoperative adjuvant radioactive iodine is typically recommended for patients with clinically evident nodal metastases, or for those with over 5 micrometastatic nodes. In the recurrent or persisting disease setting, complete surgical resection of local and regional disease remains the main treatment approach. However, sub-centimeter nodal disease may take an indolent course, and active surveillance may be a reasonable approach in selected clinical circumstances. Conversely, external beam radiation therapy (EBRT) may be considered for scenarios with unresectable disease, or microscopic residual disease following surgery in a clinically unfavorable setting. Two multi-kinase inhibitors (sorafenib and lenvatinib) are now FDA approved for treatment of RAI refractory thyroid cancer and now play an important role in the management of progressive, metastatic and surgically incurable disease.

PubMed-ID: [28687430](https://pubmed.ncbi.nlm.nih.gov/28687430/)

<http://dx.doi.org/10.1016/j.ejso.2017.06.004>

### **[Definition of R1 resection in thyroid carcinoma].**

*Chirurg*, 88(9):740-7.

S. Synoracki, C. Wittekind, H. Dralle and K. W. Schmid.

**BACKGROUND:** The residual tumor (R) classification describes the tumor status after therapy, which in patients with thyroid carcinomas is predominantly after surgical treatment. The aim of the R classification is to indicate the success of (surgical) therapy, which can influence further therapeutic procedures and allow relevant prognostic statements. **OBJECTIVE:** Definition of R1 resection as well as minimally invasive extrathyroidal growth of thyroid carcinomas as the latter is a common prerequisite for R1 resected thyroid carcinoma.

**RESULTS:** Presentation of the pathological work-up and histopathological assessment. Proposal to supplement and extend the recently introduced 8th edition of the TNM classification in order to systematically classify minimally invasive extrathyroidal carcinomas. **CONCLUSION:** The presented definitions (e.g. R1, minimally invasive extrathyroidal invasion) in combination with the proposed extension of the TNM classification permit the prospective scientific assessment of the biological relevance of these two parameters.

PubMed-ID: [28699034](https://pubmed.ncbi.nlm.nih.gov/28699034/)

<http://dx.doi.org/10.1007/s00104-017-0461-9>

### **Response to therapy of papillary thyroid cancer of known BRAF status.**

*Clin Endocrinol (Oxf)*, 87(6):815-24.

A. Kowalska, A. Walczyk, A. Kowalik, I. Palyga, D. Gasiór-Periczak, T. Trybek, J. Kopczyński, M. Kajor, E. Mikina, M. Szymonek, K. Gadawska-Juszczak, D. Szyska-Skrobot, K. Lizis-Kolus, S. Hurej, M. Chrapek, M. Chlopek and S. Gozdz.

**OBJECTIVE:** A dynamic risk stratification with modified initial estimated risk based on response to therapy and disease course is one of the crucial changes adopted recently by the American Thyroid Association (ATA). This approach focuses on an individualized risk-adapted approach to the management of differentiated thyroid cancer. The BRAF V600E mutation is the most common genetic alteration in papillary thyroid cancer (PTC). However, the prognostic value of this mutation remains unclear. The aim of this study was to examine the relation between the BRAF V600E status in PTC and all ATA response-to-therapy categories, as well as the recurrence and persistence of both biochemical disease and structural disease. **PATIENTS:** Unselected PTC cases with known BRAF status diagnosed from 2000 to 2013 and actively monitored at one institution (n=723) were reviewed retrospectively. The association between the BRAF V600E mutation and clinicopathological characteristics, ATA 2015 response-to-therapy category, recurrence after a period of no evidence of disease (NED) and persistent biochemical or structural disease, was analysed. **RESULTS:** BRAF V600E was found in 65.7% (475/723) of PTC cases. Although BRAF mutation status correlated significantly with certain clinicopathological prognostic factors, there was no correlation with any of the response-to-therapy categories. Recurrences and persistent biochemical or structural disease were not associated with BRAF status.

**CONCLUSIONS:** Our data are consistent with those of other studies reporting a positive relation between BRAF V600E mutation and poor prognostic factors in PTC; however, the BRAF status did not significantly correlate with a response to therapy.

PubMed-ID: [28718951](https://pubmed.ncbi.nlm.nih.gov/28718951/)

<http://dx.doi.org/10.1111/cen.13423>

### **Neck and Upper Limb Dysfunction in Patients following Neck Dissection: Looking beyond the Shoulder.**

*Otolaryngol Head Neck Surg*, 157(4):631-40.

E. M. Gane, S. P. O'Leary, A. L. Hatton, B. J. Panizza and S. M. McPhail.

**Objective** To measure patient-perceived upper limb and neck function following neck dissection and to investigate potential associations between clinical factors, symptoms, and function. **Study Design** Cross-sectional. **Setting** Two tertiary hospitals in Brisbane, Australia. **Subjects and Methods** Inclusion criteria: patients treated with neck dissection (2009-2014). **EXCLUSION CRITERIA:** aged <18 years, accessory nerve or sternocleidomastoid sacrifice, previous neck dissection, preexisting shoulder/neck injury, and inability to provide informed consent (cognition, insufficient English). **Primary outcomes** were self-reported function of the upper limb (Quick Disabilities of the Arm, Shoulder, and Hand) and neck (Neck Disability Index). **Secondary outcomes** included demographics, oncological management, self-efficacy, and pain. Generalized linear models were prepared to examine relationships between explanatory variables and self-reported function. **Results** Eighty-nine participants (male n = 63, 71%; median age, 62 years; median 3 years since surgery) reported mild upper limb and neck dysfunction (median [quartile 1, quartile 3] scores of 11 [3, 32] and 12 [4, 28], respectively). Significant associations were found between worse upper limb function and longer time since surgery (coefficient, 1.76; 95% confidence interval [CI], 0.01-3.51), having disease within the thyroid (17.40; 2.37-32.44), postoperative radiation therapy (vs surgery only) (13.90; 6.67-21.14), and shoulder pain (0.65; 0.44-0.85). Worse neck function was associated with metastatic cervical lymph nodes (coefficient, 6.61; 95% CI, 1.14-12.08), shoulder pain (0.19; 0.04-0.34), neck pain (0.34; 0.21-0.47), and symptoms of neuropathic pain (0.61; 0.25-0.98). **Conclusion** Patients can experience upper limb and neck dysfunction following nerve-preserving neck dissection. The upper quadrant as a whole should be considered when assessing rehabilitation priorities after neck dissection.

PubMed-ID: [28742428](https://pubmed.ncbi.nlm.nih.gov/28742428/)

<http://dx.doi.org/10.1177/0194599817721164>

### **Understanding readmissions following operations of the thyroid and parathyroid glands.**

*Am J Surg*, 214(3):501-8.

K. Collier, J. Sataloff, C. Wirtalla, L. Kuo, G. C. Karakousis and R. R. Kelz.

**BACKGROUND:** In anticipation of bundled-payment models for thyroid and parathyroid disease, a better understanding of resource utilization following surgery is required. We sought to characterize the use of hospital services following such operations using an analysis of readmissions. **METHODS:** Patients age 18+ years who underwent a thyroid or parathyroid operation in CA or NY (2008-2011) were classified by procedure type. Primary outcome was readmission within 90 days. Univariate and multivariable logistic regression were used to determine factors associated with readmission. Subset analysis was performed for thyroid cancer patients. **RESULTS:** Among 59,427 patients, 34.2% had thyroid cancer. Eleven percent (n = 6462) were readmitted within

90 days, with 27% readmitted to a different hospital than the index. 66.2% of thyroid cancer patients were readmitted for a related condition. CONCLUSION: Eleven percent of patients are admitted to the hospital within 90 days of an operation in the thyroid or parathyroid glands. Patient factors and diseases necessitate the use of hospital services. Bundled payments must consider the patients' needs for hospital-based services in calculating costs for surgically treated endocrine disorders.

PubMed-ID: [28818283](#)

<http://dx.doi.org/10.1016/j.amjsurg.2017.01.008>

### **Risk Factors for Lateral Neck Recurrence of N0/N1a Papillary Thyroid Cancer.**

*Ann Surg Oncol*, 24(12):3609-16.

Y. Kim, J. L. Roh, G. Gong, K. J. Cho, S. H. Choi, S. Y. Nam and S. Y. Kim.

BACKGROUND: Current guidelines advocate no prophylactic dissection of the lateral neck compartment for papillary thyroid carcinoma (PTC) without clinical evidence of lateral neck metastasis (cN1b). However, lateral neck recurrence can affect patient treatment outcomes and quality of life. Therefore, this study examined the risk factors for lateral neck recurrence after the definitive treatment of PTC without cN1b. METHODS: The study enrolled 1928 consecutive patients who underwent total thyroidectomy between 2006 and 2012 for PTC without cN1b. Logistic regression analysis was used to identify the relationship of clinicopathologic factors with lateral neck recurrence. Uni- and multivariate Cox-proportional hazards regression analyses were used to identify factors predictive of lateral neck recurrence-free survival (LRFS). RESULTS: During a median follow-up period of 94 months (range, 24-133 months), lateral neck recurrence occurred in 47 patients (2.4%). Binary logistic regression showed that tumor size (>2 cm), multifocality, clinical central neck metastasis (cN1a), number of positive lymph nodes (LNs, >5), and LN ratio (>0.5) were significantly associated with lateral neck recurrence ( $P < 0.05$ ). Multivariate analyses showed that multifocality (hazards ratio [HR], 2.338; 95% confidence interval [CI], 1.126-4.858;  $P = 0.023$ ), cN1a (HR, 5.301; 95% CI, 2.416-11.630;  $P < 0.001$ ), LN ratio (HR, 2.628; 95% CI, 1.228-5.626;  $P = 0.013$ ), extranodal extension (HR, 2.570; 95% CI, 1.063-6.213;  $P = 0.036$ ), and MACIS (distant metastasis, patient age, completeness of resection, local invasion and tumour size) score (HR, 2.513; 95% CI, 1.211-5.216;  $P = 0.013$ ) were independent factors for LRFS. CONCLUSIONS: Lateral neck recurrence after thyroidectomy is predicted by the clinicopathologic factors of multifocality, cN1a, LN ratio, extranodal extension, and MACIS score in N0/N1a PTC patients.

PubMed-ID: [28822118](#)

<http://dx.doi.org/10.1245/s10434-017-6057-2>

# Parathyroids

## Meta-Analyses

### **Focused Versus Bilateral Parathyroid Exploration for Primary Hyperparathyroidism: A Systematic Review and Meta-analysis.**

*Ann Surg Oncol*, 24(7):1924-34.

M. Jinih, E. O'Connell, D. P. O'Leary, A. Liew and H. P. Redmond.

**BACKGROUND:** Focused exploration (FE) and bilateral parathyroid exploration (BE) are the standard surgical options for patients with primary hyperparathyroidism. However, the relative risk of recurrence, persistence, overall failure, reoperation, and any complications associated with either surgical approach is unclear. This study compared the outcomes and complication rates after FE and BE for patients with primary hyperparathyroidism. **METHODS:** PubMed and Embase were searched for studies comparing these outcomes between FE and BE. A meta-analysis was performed using RevMan 5.3 software. Published data were pooled using the DerSimonian random-effect model, and results were presented as odds ratio (OR) or mean difference with 95% confidence interval (CI). **RESULTS:** A total of 12,743 patients from 19 studies were included in this meta-analysis. In comparison with BE, the FE arm had comparable rates of recurrence (OR 1.08; 95% CI 0.59-2.00;  $p = 0.80$ ;  $n = 9$  studies), persistence (OR 0.89; 95% CI 0.58-1.35;  $p = 0.58$ ;  $n = 13$ ), overall failure (OR 0.88; 95% CI 0.58-1.34;  $p = 0.56$ ;  $n = 13$ ), and reoperation (OR 1.05; 95% CI 0.25-4.32;  $p = 0.95$ ,  $n = 4$ ). The operative time was significantly shorter (mean difference = -39.86; 95% CI -53.05 to -26.84;  $p < 0.01$ ,  $n = 9$ ), with a lower overall complication rate in the FE arm (OR 0.35; 95% CI 0.15-0.84;  $p = 0.02$ ;  $n = 12$ ). The latter was attributed predominantly to a lower risk of transient hypocalcemia (OR 0.36; 95% CI 0.14-0.90;  $p = 0.03$ ;  $n = 9$ ). There was a significant heterogeneity among these studies for all outcomes except for disease recurrence.

**CONCLUSIONS:** Compared with BE, FE has similar recurrence, persistence, and reoperation rates but significantly lower overall complication rates and shorter operative time.

PubMed-ID: [27896505](https://pubmed.ncbi.nlm.nih.gov/27896505/)

<http://dx.doi.org/10.1245/s10434-016-5694-1>

## Randomized controlled trials

### **Primary hyperparathyroidism, hypercalciuria, and bone recovery after parathyroidectomy.**

*Surgery*, 162(2):429-36.

I. L. Nilsson, S. Norenstedt, J. Zedenius, Y. Pernow and R. Branstrom.

**BACKGROUND:** In primary hyperparathyroidism, successful parathyroidectomy leads to improved bone mineral density in the majority of cases. Our aim was to further explore the relationship between hypercalciuria, kidney function, and bone recovery after parathyroidectomy. **METHODS:** Bone mineral density, estimated glomerular filtration rate, and 24-hour urinary calcium were analyzed before and one year after parathyroidectomy in a cohort of 150 primary hyperparathyroidism patients (119 women; median age 60 [range 30-80] years) taking part in a clinical trial. The patients were randomized to 1-year daily treatment with either cholecalciferol 1,600 IU and calcium carbonate 1,000 mg or calcium carbonate alone. **RESULTS:** Baseline 24-hour urinary calcium correlated directly with s-calcium, parathyroid hormone, 25-OH-D, the bone markers beta C-terminal telopeptide of type 1 collagen and procollagen type 1 amino-terminal propeptide, and estimated glomerular filtration rate ( $r = 0.19-0.30$ ;  $P < .05$ ) and inversely with age ( $r = -0.25$ ;  $P = .004$ ); 24-hour urinary calcium decreased and bone mineral density in lumbar spine and hip increased similarly in the 2 groups. Baseline 24-hour urinary calcium in the highest quartile ( $>10$  mmol/d) was associated with greater increases in all locations. In a multivariable model adjusting for age, sex, smoking, diabetes, body mass index, estimated glomerular filtration rate, baseline bone mineral density, and vitamin D group, the increase in total hip bone mineral density remained independently associated with baseline 24-hour urinary calcium in the highest quartile ( $>10$  mmol/d) and with plasma parathyroid hormone. Patients with persistent increases in 24-hour urinary calcium at follow-up (14%) had similar bone mineral density improvement. **CONCLUSION:** Overall, 24-hour urinary calcium  $> 10$  mmol/d was an independent determinant of improvement in bone mineral density and should be taken into account when considering parathyroidectomy.

PubMed-ID: [28522130](https://pubmed.ncbi.nlm.nih.gov/28522130/)

<http://dx.doi.org/10.1016/j.surg.2017.02.017>

## Consensus Statements/Guidelines

- None -

## Other Articles

### **Four-dimensional computed tomography scan utility in parathyroidectomy for primary hyperparathyroidism with low baseline intact parathyroid hormone.**

*Laryngoscope*, 127(6):1476-82.

A. Rameau, S. Eng, J. Vu, R. Saket, P. Jun and M. Friduss.

**OBJECTIVES/HYPOTHESIS:** The prevalence of multiglandular disease (MGD) of the parathyroid has been reported to be higher in patients with primary hyperparathyroidism and low baseline intact parathyroid hormone (PTH) levels (<100 pg/mL). Low baseline PTH is associated with lower localization rate and positive predictive value with both preoperative sestamibi and ultrasound. This study sought to evaluate our experience with four-dimensional computed tomography (4D-CT) for the localization of abnormal parathyroid glands, including MGD, in patients with low baseline intact PTH (LbPTH). **STUDY DESIGN:** A single institution case series. **METHODS:** A case series of patients with primary hyperparathyroidism with low baseline PTH or an inconclusive sestamibi, who underwent surgery with a single surgeon from April 2012 to June 2015 following 4D-CT to help with abnormal gland localization. **RESULTS:** We identified 14 patients who underwent a 4D-CT in the setting of primary hyperparathyroidism and LbPTH. A sestamibi scan had been ordered in 71% and was inconclusive in all cases. No ultrasound was performed. In all patients, 4D-CT was 84.6% sensitive in localizing abnormal glands, yielding a positive predictive value of 91.7%. Overall, 42.9% of patients had evidence of MGD, and 4D-CT detected 83.3% of MGD cases. A focused unilateral exploration was performed in 28.6% of cases, and a four-gland exploration was performed in all remaining patients. **CONCLUSIONS:** In patients with hypercalcemia and LbPTH, with higher likelihood of MGD and of inconclusive results on sestamibi, 4D-CT may be a superior modality for localizing smaller adenoma or multiple hypercellular glands. This may allow for improved interpretation of intraoperative PTH results, and in a minority of cases, a focused parathyroid exploration. **LEVEL OF EVIDENCE:** 4 *Laryngoscope*, 127:1476-1482, 2017.

PubMed-ID: [27515539](https://pubmed.ncbi.nlm.nih.gov/27515539/)

<http://dx.doi.org/10.1002/lary.26201>

### **Persistently elevated parathyroid hormone after successful parathyroid surgery.**

*Laryngoscope*, 127(7):1720-3.

W. S. Duke, A. S. Kim, J. L. Waller and D. J. Terris.

**OBJECTIVES/HYPOTHESIS:** Explore potential causes of persistently elevated parathyroid hormone levels after curative parathyroidectomy in patients with primary hyperparathyroidism due to single gland disease. **STUDY DESIGN:** Case series with planned data collection. **METHODS:** An analysis was undertaken of 314 patients with primary hyperparathyroidism undergoing parathyroid surgery in a tertiary academic practice between January 2009 and April 2013. There were 187 patients with single-gland disease; 68 failed to meet inclusion criteria, resulting in a study population of 119 patients. Preoperative parathyroid hormone, calcium, ionized calcium, 25-OH-vitamin D, creatinine, and glomerular filtration rate values were determined, along with postoperative calcium, ionized calcium, and parathyroid hormone levels. Patients were divided into two groups based on their postoperative parathyroid hormone values: elevated parathyroid hormone and normal parathyroid hormone. **RESULTS:** Thirty (25.2%) patients achieved postoperative normocalcemia but had elevated parathyroid hormone levels. This group had significantly higher preoperative levels of parathyroid hormone ( $P = .002$ ) and creatinine ( $P = .007$ ), and a lower glomerular filtration rate ( $P = .002$ ) than patients with normal postoperative parathyroid hormone levels. The preoperative 25-OH-vitamin D level was not significantly associated with an elevated parathyroid hormone (odds ratio [OR]: 1.56). Preoperative impaired renal function, specifically an abnormal glomerular filtration rate (OR: 12.8), was significantly associated with an elevated parathyroid hormone. **CONCLUSIONS:** Parathyroid hormone remains elevated in 25% of patients who are cured (eucalceic) after surgery for primary hyperparathyroidism. This phenomenon was associated with higher preoperative parathyroid hormone levels and impaired renal function rather than low 25-OH-vitamin D levels. **LEVEL OF EVIDENCE:** 4. *Laryngoscope*, 127:1720-1723, 2017.



### **Ethnic and economic disparities effect on management of hyperparathyroidism.**

*Am J Surg*, 213(6):1134-42.

Z. Al-Qurayshi, A. Hauch, S. Srivastav and E. Kandil.

**BACKGROUND:** Successful parathyroidectomy requires advanced surgeon experience. We aim to examine population characteristics at risk of being managed by low-volume surgeons. **METHODS:** A cross-sectional study was performed utilizing the Nationwide Inpatient Sample database, 2004 to 2009. The study population included adult inpatients who underwent parathyroidectomy for primary hyperparathyroidism. **RESULTS:** A total of 3,503 discharge records were included. Men, Hispanics, and those with Medicaid/Medicare health coverage were more likely to be managed by low-volume surgeons ( $P < .05$  each). Low-volume surgeons were more likely to operate in rural (odds ratio [OR], 3.99; 95% confidence interval [CI], 1.95 to 8.16;  $P < .001$ ) or nonteaching hospitals (OR, 2.15; 95% CI, 1.42 to 3.27;  $P < .001$ ). Southern region of the United States had a high prevalence of low-volume surgeons compared with other regions (Southern: 51.3%, Northeast: 24.3%, Midwest: 25.6%, and West: 27.6%,  $P < .001$ ). Operations by the low-volume surgeons associated with a higher risk of postoperative complications (OR, 1.81; 95% CI, 1.11 to 2.97) and a hospital stay more than 2 days (OR, 7.12; 95% CI, 3.75 to 13.45;  $P < .001$ ). **CONCLUSIONS:** Certain populations are at risk of management by low-volume surgeons based on their demographic and economic characteristics.

PubMed-ID: [27771035](https://pubmed.ncbi.nlm.nih.gov/27771035/)

<http://dx.doi.org/10.1016/j.amjsurg.2016.07.008>

### **Predictors of operative failure in parathyroidectomy for primary hyperparathyroidism.**

*Am J Surg*, 214(3):509-14.

D. C. Cron, S. R. Kapeles, E. A. Andraska, S. T. Kwon, P. S. Kirk, B. L. McNeish, C. S. Lee and D. T. Hughes.

**INTRODUCTION:** Many adjuncts guide surgical decision making in parathyroidectomy, yet their independent associations with outcome are poorly characterized. We examined a broad range of perioperative factors and used multivariate techniques to identify independent predictors of operative failure (persistent disease) after parathyroidectomy. **METHODS:** This was a retrospective review of 2239 patients with primary hyperparathyroidism who underwent parathyroidectomy at a single-center from 1999 to 2014. We used multivariate logistic regress to measure associations between multiple perioperative factors and an operative failure (persistent hypercalcemia). **RESULTS:** Operative failure was identified in 67 patients (3.0%). The following variables were independently associated with operative failure on multivariate analysis: IOPTH criteria met (protective, OR = 0.22,  $P < 0.001$ ), preoperative calcium (risk factor, OR = 2.27 per unit increase,  $P < 0.001$ ), weight of excised gland(s) (protective, OR = 0.70 per two-fold increase,  $P = 0.003$ ), and preoperative PTH (protective, OR = 0.55 per two-fold increase,  $P = 0.008$ ). **CONCLUSION:** In addition to the well-established IOPTH criteria, we suggest that consideration of the above independent perioperative risk factors may further inform surgical decision-making in parathyroidectomy.

PubMed-ID: [28108069](https://pubmed.ncbi.nlm.nih.gov/28108069/)

<http://dx.doi.org/10.1016/j.amjsurg.2017.01.012>

### **Is Unilateral Neck Surgery Feasible in Patients with Sporadic Primary Hyperparathyroidism and Double Negative Localisation?**

*World J Surg*, 41(6):1494-9.

D. M. Scott-Coombes, J. Rees, G. Jones and M. J. Stechman.

**INTRODUCTION:** Ultrasound and Tc99mMIBI scans are used to localise parathyroid tumours in sporadic primary hyperparathyroidism (pHPT). Intra-operative PTH (ioPTH) assay facilitates unilateral neck exploration (UNE). When both ultrasound and MIBI are negative, it is our policy to explore the left side of the neck and only proceed to bilateral neck exploration (BNE) when either a tumour is not found or when ioPTH does not fall to >50% of the highest pre-excision value. The aim of this study was to investigate the outcome of our approach to 'double negative' patients. **METHODS:** A retrospective analysis of patients undergoing primary parathyroidectomy for pHPT. Data were obtained from a prospective surgical database and the hospital electronic patient record. **RESULTS:** Between January 2004 and November 2014, 746 patients underwent a parathyroidectomy for pHPT. Those who did not have both pre-operative scans, ioPTH or a minimum of 6-month follow-up were excluded. Of 552 patients, 111 (20%) had double negative scans (group A), and in 441, either one or both scans were positive (group B). Median age was 61.5 years (range 10-88). Pre-operative PTH level was significantly lower in group A: 11.8 pmol/l (range 3.1-38.8) versus 14.9 pmol/l (range 2.8-101.6;  $P < 0.01$ ). Median tumour weight was significantly lower in group A: 280 mg (range 50-3710) versus 573 mg (range 10-12,000;  $P < 0.01$ ). Overall rate of multiple gland disease (MGD) was 11%; 24% in group A and 7% in group B ( $P$



< 0.01). Overall rate of UNE in Group A was 28% and converse to the rate in Group B (76%; P < 0.01). Sensitivity and specificity of ioPTH to detect MGD were 98 and 98% in Group A versus 98 and 100% in Group B. First-time cure rate was 92.7% in group A and 96.8% in group B (P < 0.05). CONCLUSION: A double negative scan is associated with small tumours and higher rates of MGD. Despite these challenges, surgery is successful in this group of patients reinforcing the message that negative localisation is not a contraindication for parathyroidectomy. We demonstrated that it is feasible to offer unilateral neck surgery to 28% of patients with double negative scans. A randomised trial is needed to compare BNE with ioPTH/UNE in this select population.

PubMed-ID: [28116482](https://pubmed.ncbi.nlm.nih.gov/28116482/)

<http://dx.doi.org/10.1007/s00268-017-3891-0>

### **Intraoperative Identification of the Parathyroid Gland with a Fluorescence Detection System.**

*World J Surg*, 41(6):1506-12.

Y. Shinden, A. Nakajo, H. Arima, K. Tanoue, M. Hirata, Y. Kijima, K. Maemura and S. Natsugoe.

BACKGROUND: Intraoperative identification of the difficult-to-spot parathyroid gland is critical during surgery for thyroid and parathyroid disease. Recently, intrinsic fluorescence of the parathyroid gland was identified, and a new method was developed for intraoperative detection of the parathyroid with an original fluorescent detection apparatus. Here, we describe a method for intraoperative detection of the parathyroid using a ready-made photodynamic eye (PDE) system without any fluorescent dye or contrast agents. METHODS: Seventeen patients who underwent surgical treatment for thyroid or parathyroid disease at Kagoshima University Hospital were enrolled in this study. Intrinsic fluorescence of various tissues was detected with the PDE system. Intraoperative in vivo and ex vivo intrinsic fluorescence of the parathyroid, thyroid, lymph nodes and fat tissues was measured and analyzed. RESULTS: The parathyroid gland had a significantly higher fluorescence intensity than the other tissues, including the thyroid glands, lymph nodes and fat tissues, and we could identify them during surgery using the fluorescence-guided method. Our method could be applicable for two intraoperative clinical procedures: ex vivo tissue identification of parathyroid tissue and in vivo identification of the location of the parathyroid gland, including ectopic glands. CONCLUSION: The PDE system may be an easy and highly feasible method to identify the parathyroid gland during surgery.

PubMed-ID: [28168320](https://pubmed.ncbi.nlm.nih.gov/28168320/)

<http://dx.doi.org/10.1007/s00268-017-3903-0>

### **Intraoperative PTH May Not Be Necessary in the Management of Primary Hyperparathyroidism Even with Only One Positive or Only Indeterminate Preoperative Localization Studies.**

*World J Surg*, 41(6):1500-5.

A. Najafian, S. Kahan, M. T. Olson, R. P. Tufano and M. A. Zeiger.

BACKGROUND: Intraoperative PTH (IOPTH) monitoring has been widely used to confirm the removal of the culprit lesion during operation. However, the true benefit of IOPTH in patients with preoperatively well-localized single adenoma has been questioned. The aim of this study was to examine how or if IOPTH changes the surgical management and outcomes in patients with only one positive or only indeterminate localization studies.

METHODS: This is a retrospective review of data from a parathyroid surgery database and patient records from July 2004 to June 2014, including patients with primary hyperparathyroidism with a planned MIP by two experienced endocrine surgeons after  $\geq 1$  positive/indeterminate preoperative localization study by ultrasound and/or sestamibi. RESULTS: A total of 482 patients with positive (342: 259 only 1, 83 with  $\geq 2$ ) or indeterminate (140: 105 only 1, 35 with  $\geq 2$ ) preoperative imaging studies were included. IOPTH changed the management in only 16 (3%) patients, with an additional lesion found in 12 of them. Surgical cure was achieved in 471 (98%) of patients (98% in the positive vs. 97% in the indeterminate group, p 0.58). With or without IOPTH, the cure rate would not have been significantly different in patients with only 1 positive preoperative imaging (96 vs. 98%, p 0.12). Similar results were seen in those with  $\geq 2$  indeterminate (100% cure rate with or without IOPTH).

CONCLUSION: Our study suggests that MIP may be safely and successfully performed without IOPTH for patients with  $\geq 1$  positive or  $\geq 2$  indeterminate preoperative imaging studies. This study is retrospective within inherent biases, and future prospective study is warranted.

PubMed-ID: [28224198](https://pubmed.ncbi.nlm.nih.gov/28224198/)

<http://dx.doi.org/10.1007/s00268-017-3871-4>

### **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.

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](https://pubmed.ncbi.nlm.nih.gov/28324108/)

<http://dx.doi.org/10.1210/jc.2016-3712>

### **Superior parathyroid gland approach to the recurrent laryngeal nerve.**

*Head Neck*, 39(7):1287-90.

E. Elsheikh.

BACKGROUND: The superior parathyroid gland is known to be almost constant in its location under the false thyroid capsule. Could it be a landmark to point to the site of incision of the false thyroid capsule and find the plane of the recurrent laryngeal nerve (RLN) during thyroidectomy? METHODS: The study included 48 patients with benign goiter scheduled for hemithyroidectomy or total thyroidectomy; there were 16 cases of solitary thyroid nodules, 27 cases of multinodular goiter, and 5 cases of toxic goiter. RESULTS: This study included 80 lobectomies. All patients showed no evidence of postoperative RLN palsy, bleeding, or hypoparathyroidism. The superior parathyroid gland was consistently found within the false capsule in all cases, whereas the inferior parathyroid was found within the same layer in 64 sides (80%). CONCLUSION: The described approach can accurately guide dissection between true and false capsules of the thyroid to reach and preserve both the RLN and the superior parathyroid gland. (c) 2017 Wiley Periodicals, Inc. *Head Neck* 39: 1287-1290, 2017.

PubMed-ID: [28493593](https://pubmed.ncbi.nlm.nih.gov/28493593/)

<http://dx.doi.org/10.1002/hed.24690>

### **Parathyroid Hormone Levels Predict Long-Term Outcome After Operative Management of Parathyroid Cancer.**

*Horm Metab Res*, 49(7):485-92.

A. Machens, K. Lorenz and H. Dralle.

The role of parathyroid hormone (PTH) serum levels for prediction of outcome is ill defined for parathyroid cancer, which is a very rare disease. This investigation of 17 consecutive patients with parathyroid cancer, (re-)operated on at a tertiary referral center between 1994 and July 2016, with a mean follow-up of 179.6 months (15 years) aimed to clarify the suitability of PTH serum levels for prediction of clinical outcome after comprehensive operative management of parathyroid cancer. Cancer-specific mortality occurred significantly more often with the performance of sternotomy before or at first operation at this institution (80 vs. 0%; p=0.002); mean PTH serum levels before first operation (1 105 vs. 357 pg/ml; p=0.008; r=0.77) and at most recent follow-up (3 167 vs. 101 pg/ml; p=0.019; r=0.60); and normalization of PTH serum levels at most recent follow-up (0 vs. 64%; p=0.034). For cancer-specific survival, receiver-operating characteristics analysis identified as optimum cut-off point an initial PTH serum level of 700 pg/ml. For local recurrence, no significant associations were found. Kaplan-Meier analysis confirmed that the patients with initial PTH serum levels >700 pg/ml (plog-rank=0.011) and sternotomy (plog-rank<0.001), but not node or lung metastases, had worse cancer-specific survival. Parathyroid cancer is much more an endocrine disease with oncological features than an oncological disease with endocrine features. Operative intervention(s) should be comprehensive and directed at clearing all metabolically active parathyroid tumor deposits early. If surgical cure cannot be reached, it is pivotal to achieve metabolic control, obviating the need for, or facilitating, medical therapy of hypercalcemia, and preserve renal function.

PubMed-ID: [28525934](https://pubmed.ncbi.nlm.nih.gov/28525934/)

<http://dx.doi.org/10.1055/s-0043-109562>

**Percentage arterial enhancement: An objective index for accurate identification of parathyroid adenoma/hyperplasia in primary hyperparathyroidism.**

*Clin Endocrinol (Oxf)*, 87(6):791-8.

M. Goroshi, A. R. Lila, S. S. Jadhav, S. Sonawane, P. Hira, S. Goroshi, M. N. Garle, A. Dalvi, P. Sathe, T. R. Bandgar and N. S. Shah.

**BACKGROUND:** Radiation exposure to neck by four-dimensional computerized tomography (4DCT) is relatively high and limits its use as a first-line investigation in evaluation of primary hyperparathyroidism (PHPT). Radiation exposure can be reduced by restricting the number of CT phases. Our aim was to study the performance of 4DCT in cohort of surgery-naïve PHPT patients, and to evaluate percentage enhancement as an objective radiological index to discriminate parathyroid lesions (adenoma/hyperplasia) from thyroid tissue and lymph nodes. **MATERIALS AND METHOD:** Retrospective study of 49 PHPT patients {(44 single-gland diseases (SGD) and five multiple-gland disease (MGD)} who underwent 4DCT (unenhanced, early arterial, early venous and delayed venous phase) pre-operatively. Two radiologists who were blinded to surgical location of parathyroid lesions examined the scans. Attenuation values were recorded for parathyroid lesions (n=50), thyroid gland (n=50) and lymph nodes (n=12) in different phases. Percentage enhancement for different phases was calculated as "(HU in a specific enhanced phase-HU in unenhanced phase)/HU in unenhanced phase" x100. **RESULTS:** Inter-rater reliability between the two radiologists was 0.83 (Cohen's kappa). In SGD, sensitivity and PPV were 93.18% and 98.8% for lateralization, and 89.77% and 95.18% for quadrant localization, respectively. In MGD, 4DCT showed 50% sensitivity and 100% PPV. Percentage arterial enhancement showed highest area under curve (AUC=0.992) for differentiation of parathyroid lesions from thyroid tissue and lymph nodes. A cut-off value of 128.9% showed 95.8% sensitivity and 100% specificity for the identification of parathyroid lesions. **CONCLUSIONS:** We propose that percentage arterial enhancement can be used as an objective radiological index for accurate identification of parathyroid adenoma/hyperplasia.

PubMed-ID: [28656592](https://pubmed.ncbi.nlm.nih.gov/28656592/)

<http://dx.doi.org/10.1111/cen.13406>

**Surgery for Primary Hyperparathyroidism: Adherence to Consensus Guidelines in an Academic Health System.**

*Ann Surg*,

E. J. Kuo, M. A. Al-Alusi, L. Du, A. Shieh, M. J. Livhits, A. M. Leung and M. W. Yeh.

**OBJECTIVE:** To determine the extent to which consensus guidelines for surgery in patients with primary hyperparathyroidism (PHPT) are followed within an academic health system. **BACKGROUND:** Previous studies have shown that adherence to consensus guidelines in community practice is low. **METHODS:** Adults with biochemically confirmed PHPT who received primary care within an academic health system were identified from 2005 to 2015. Multivariable logistic regression was used to analyze predictors of parathyroidectomy (PTx). **RESULTS:** In 617 patients, the overall PTx rate was 30.8%. When individual consensus criteria were examined, age <50 (P<0.01), serum calcium >11.3 mg/dL (P < 0.01), and hypercalciuria (P = 0.02) were associated with PTx; while nephrolithiasis (P = 0.07) and osteoporosis (P = 0.34) did not affect the PTx rate. The PTx rate increased with the number of consensus criteria satisfied (1 criterion, 33%; 2 criteria, 45%; 3 or more criteria, 82%, P < 0.01). Independent predictors of PTx included male sex [odds ratio (OR) 1.7, 95% confidence interval (CI) 1.1-2.8], increasing serum parathyroid hormone (OR 1.1 per 10 pg/dL 95% CI 1.05-1.13), and endocrinologist evaluation (OR 1.6, 95% CI 1.1-2.4); while Black race (OR 0.4, 95% CI 0.2-0.8), lack of 24-hour urine calcium measurement (OR 0.5, 95% CI 0.3-0.8), Charlson Comorbidity Index  $\geq$  2 (OR 0.6, 95% CI 0.4-0.9), and age  $\geq$ 80 years (OR 0.2, 95% CI 0.1-0.4) predicted against PTx. **CONCLUSION:** Within an academic health system, consensus guidelines do appear to influence the decision for surgery in patients with PHPT. However, the level of compliance is generally low, and similar to that observed in community practice.

PubMed-ID: [28806302](https://pubmed.ncbi.nlm.nih.gov/28806302/)

<http://dx.doi.org/10.1097/SLA.0000000000002474>

# Adrenals

## Meta-Analyses

### **Outcomes of patients with metastatic pheochromocytoma and paraganglioma: A systematic review and meta-analysis.**

*Clin Endocrinol (Oxf)*, 87(5):440-50.

O. Hamidi, W. F. Young, Jr., L. Gruber, J. Smestad, Q. Yan, O. J. Ponce, L. Prokop, M. H. Murad and I. Bancos. OBJECTIVE: The outcomes of patients with metastatic pheochromocytoma (PHEO) and paraganglioma (PGL) are unclear. We performed a systematic review and meta-analysis of baseline characteristics and mortality rates of patients with metastatic PHEO and PGL (PPGL). DESIGN: Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, Scopus, Web of Science, and references of key articles were searched from inception to 2016. PATIENTS: Studies comprised  $\geq 20$  patients with metastatic PPGL and reported baseline characteristics and follow-up data. MEASUREMENTS: Reviewers extracted standardized data and assessed risk of bias using a modified Newcastle-Ottawa tool. Random-effects meta-analysis was used to pool event rates across studies. RESULTS: Twenty retrospective noncomparative studies reported on 1338 patients with metastatic PHEO (685/1296, 52.9%) and PGL (611/1296, 47.1%), diagnosed at a mean age of 43.9  $\pm$  5.2 years. Mean follow-up was 6.3  $\pm$  3.2 years. Of 532 patients with reported data, 40.4% had synchronous metastases. Five-year (7 studies, n = 738) and 10-year (2 studies, n = 55) mortality rates for patients with metastatic PPGL were 37% (95% CI, 24%-51%) and 29% (95% CI, 17%-42%), respectively. Higher mortality was associated with male sex (RR 1.50; 95% CI, 1.11-2.02) and synchronous metastases (RR 2.43; 95% CI, 1.01-5.85). CONCLUSIONS: Available low-quality evidence from heterogeneous studies suggests low mortality rates of patients with metastatic PPGL. Male sex and synchronous metastases correlated with increased mortality. The outcomes of patients with metastatic PPGL have been inadequately assessed, indicating the need for carefully planned prospective studies.

PubMed-ID: [28746746](https://pubmed.ncbi.nlm.nih.gov/28746746/)

<http://dx.doi.org/10.1111/cen.13434>

## Randomized controlled trials

- None -

## Consensus Statements/Guidelines

- None -

## Other Articles

### **Evaluating the learning curve for retroperitoneoscopic adrenalectomy in a high-volume center for laparoscopic adrenal surgery.**

*Surg Endosc*, 31(7):2771-5.

A. van Uitert, F. C. H. d'Ancona, J. Deinum, H. Timmers and J. F. Langenhuisen.

BACKGROUND: Laparoscopic adrenalectomy is an effective method for benign adrenal tumor removal. In the literature, both lateral transperitoneal (TLA) and posterior retroperitoneoscopic (RPA) approaches are described. Since 2007, the number of patients increased significantly in our center. Therefore, RPA was introduced in 2011 because of its potential advantages in operating and recovery times. The learning curve of RPA is now evaluated. METHODS: All data of patients undergoing laparoscopic adrenalectomy from 2007 until 2014 were prospectively collected. Patients were eligible for RPA with a tumor  $< 7$  cm, with BMI  $< 35$  kg/m<sup>2</sup>, and with low suspicion of malignancy. The learning curve of RPA was measured by operating time. Furthermore, blood loss, preoperative complications and hospital stay were analyzed. Descriptive statistics were performed using SPSS



20.0. RESULTS: In the study period, 290 patients underwent surgery, of whom 113 underwent RPA. After starting with RPA, operating times decreased significantly (median 100 min in the first 20 patients to 60 min after 40 patients,  $p < 0.05$ ). There was a significant difference in operating times (median 108 vs. 62 min,  $p < 0.05$ ) and hospital stay (median 4 vs. 3 days,  $p < 0.05$ ) in unilateral surgery in favor of RPA, compared to TLA. Also in bilateral surgery, operating times were significantly shorter (median 236 vs. 117 min,  $p < 0.05$ ). In both groups, few major complications occurred. CONCLUSION: After the introduction of RPA, a short learning curve was seen for a single surgeon with extensive experience in laparoscopic adrenal surgery. Compared to TLA, RPA has significant advantages in operating times and hospital stay. Therefore, RPA may be the preferred approach for patients with BMI  $< 35$  kg/m<sup>2</sup> and small benign adrenal tumors ( $< 7$  cm).

PubMed-ID: [27752814](https://pubmed.ncbi.nlm.nih.gov/27752814/)

<http://dx.doi.org/10.1007/s00464-016-5284-0>

### **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.

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](https://pubmed.ncbi.nlm.nih.gov/28058556/)

<http://dx.doi.org/10.1245/s10434-016-5739-5>

### **Implications of SDHB genetic testing in patients with sporadic pheochromocytoma.**

*Langenbecks Arch Surg*, 402(5):787-98.

A. Maignan, C. Guerin, V. Julliard, N. C. Paladino, E. Kim, P. Roche, F. Castinetti, W. Essamet, J. Mancini, A. Imperiale, R. Clifton-Bligh, P. Romanet, A. Barlier, K. Pacak, F. Sebag and D. Taieb.

PURPOSE: Succinate dehydrogenase B (SDHB) associated pheochromocytomas (PHEOs) are associated with a higher risk of tumor aggressiveness and malignancy. The aim of the present study was to evaluate (1) the frequency of germline SDHB mutations in apparently sporadic patients with PHEO who undergo preoperative genetic testing and (2) the ability to predict pathogenic mutations. METHODS: From 2012 to 2016, 82 patients underwent a PHEO surgical resection. Sixteen were operated in the context of hereditary PHEO and were excluded from analysis. Among the 66 remaining cases, 48 were preoperatively screened for an SDHB mutation.

In addition to imaging studies with specific radiopharmaceuticals ((<sup>123</sup>I)-MIBG or (<sup>18</sup>F)-FDOPA) for exclusion of multifocality/metastases, 36 patients underwent (<sup>18</sup>F)-FDG PET/CT. RESULTS: From the 48 genetically screened patients, genetic testing found a germline SDHB variant in two (4.2%) cases: a variant of unknown significance, exon 1, c.14T>G (p.Val5Gly), and a most likely pathogenic mutation, exon 5, c.440A>G (p.Tyr147Cys), according to in silico analysis. Structural and functional analyses of the protein predicted that p.Tyr147Cys mutant was pathogenic. Both tumors exhibited moderate (<sup>18</sup>F)-FDG PET uptake with similar uptake patterns to non-SDHB mutated PHEOs. The two patients underwent total laparoscopic adrenalectomies. Of the remaining patients, 44 underwent a laparoscopic adrenalectomy, and two had an open approach.

Pathological analysis of the tumors from patients bearing two germline SDHB variants revealed a typical PHEO (PASS 0 and 2). Ex-vivo analyses (metabolomics, SDHB immunohistochemistry, loss of heterozygosity analysis) allowed a reclassification of the two SDHB variants as probably non-pathogenic variants. CONCLUSIONS: This study illustrates that SDHx mutational analysis can be misleading, even if structural and functional analyses are done. Surgeons should be aware of the difficulty of classifying new SDHB variants prior to implementing SDHB mutation status into a tailored surgical management strategy of a patient.



PubMed-ID: [28229225](https://pubmed.ncbi.nlm.nih.gov/28229225/)  
<http://dx.doi.org/10.1007/s00423-017-1564-y>

### **Adrenal Vein Catecholamine Levels and Ratios: Reference Intervals Derived from Patients with Primary Aldosteronism.**

*Horm Metab Res*, 49(6):418-23.

C. W. C. Sze, S. M. O'Toole, R. K. Tirador, S. A. Akker, M. Matson, L. Perry, M. R. Druce, T. Dekkers, J. Deinum, J. W. M. Lenders, G. Eisenhofer and W. M. Drake.

Phaeochromocytoma localisation is generally reliably achieved with modern imaging techniques, particularly in sporadic cases. On occasion, however, there can be diagnostic doubt due to the presence of bilateral adrenal abnormalities, particularly in patients with mutations in genes predisposing them to the development of multiple phaeochromocytomas. In such cases, surgical intervention is ideally limited to large or functional lesions due to the long-term consequences associated with hypoadrenalism. Adrenal venous sampling (AVS) for catecholamines has been used in this situation to guide surgery, although there are few data available to support diagnostic thresholds. Retrospective analyses of AVS results from 2 centres were carried out. A total of 172 patients (88 men, 84 women) underwent AVS under cosyntropin stimulation for the diagnosis of established primary aldosteronism (PA) with measurement of adrenal and peripheral venous cortisol, aldosterone and catecholamines. Six patients (3 men, 3 women) with phaeochromocytoma underwent AVS for diagnostic purposes with subsequent histological confirmation. Reference intervals for the adrenal venous norepinephrine to epinephrine ratio were created from the PA group. Using the 97.5th centile (1.21 on the left, 1.04 on the right), the false negative rate in the phaeochromocytoma group was 0%. In conclusion, this study describes the largest dataset of adrenal venous catecholamine measurements and provides reference intervals in patients without phaeochromocytoma. This strengthens the certainty with which conclusions related to adrenal venous sampling for catecholamines can be drawn, acknowledging the procedure is not part of the routine diagnostic workup and is an adjunct for use only in difficult clinical cases.

PubMed-ID: [28445897](https://pubmed.ncbi.nlm.nih.gov/28445897/)  
<http://dx.doi.org/10.1055/s-0042-124419>

### **PRKAR1A mutation causing pituitary-dependent Cushing disease in a patient with Carney complex.**

*Eur J Endocrinol*, 177(2):K7-K12.

F. W. Kiefer, Y. Winhofer, D. Iacovazzo, M. Korbonits, S. Wolfsberger, E. Knosp, F. Trautinger, R. Hoftberger, M. Krebs, A. Luger and A. Gessl.

CONTEXT: Carney complex (CNC) is an autosomal dominant condition caused, in most cases, by an inactivating mutation of the PRKAR1A gene, which encodes for the type 1 alpha regulatory subunit of protein kinase A. CNC is characterized by the occurrence of endocrine overactivity, myxomas and typical skin manifestations. Cushing syndrome due to primary pigmented nodular adrenocortical disease (PPNAD) is the most frequent endocrine disease observed in CNC. CASE DESCRIPTION: Here, we describe the first case of a patient with CNC and adrenocorticotrophic hormone (ACTH)-dependent Cushing disease due to a pituitary corticotroph adenoma. Loss-of-heterozygosity analysis of the pituitary tumour revealed loss of the wild-type copy of PRKAR1A, suggesting a role of this gene in the pituitary adenoma development. CONCLUSION: PRKAR1A loss-of-function mutations can rarely lead to ACTH-secreting pituitary adenomas in CNC patients. Pituitary-dependent disease should be considered in the differential diagnosis of Cushing syndrome in CNC patients.

PubMed-ID: [28522647](https://pubmed.ncbi.nlm.nih.gov/28522647/)  
<http://dx.doi.org/10.1530/EJE-17-0227>

### **Cortisol-related metabolic alterations assessed by mass spectrometry assay in patients with Cushing's syndrome.**

*Eur J Endocrinol*, 177(2):227-37.

G. Di Dalmazi, M. Quinkler, T. Deutschbein, C. Prehn, N. Rayes, M. Kroiss, C. M. Berr, G. Stalla, M. Fassnacht, J. Adamski, M. Reincke and F. Beuschlein.

OBJECTIVE: Endogenous hypercortisolism is a chronic condition associated with severe metabolic disturbances and cardiovascular sequela. The aim of this study was to characterize metabolic alterations in patients with different degrees of hypercortisolism by mass-spectrometry-based targeted plasma metabolomic profiling and correlate the metabolomic profile with clinical and hormonal data. DESIGN: Cross-sectional study. METHODS: Subjects (n = 149) were classified according to clinical and hormonal characteristics: Cushing's syndrome (n = 46), adrenocortical adenomas with autonomous cortisol secretion (n = 31) or without hypercortisolism (n = 27). Subjects with suspicion of hypercortisolism, but normal hormonal/imaging testing, served as controls (n = 42). Clinical and hormonal data were retrieved for all patients and targeted metabolomic profiling was performed. RESULTS: Patients with hypercortisolism showed lower levels of short-/medium-chain acylcarnitines and

branched-chain and aromatic amino acids, but higher polyamines levels, in comparison to controls. These alterations were confirmed after excluding diabetic patients. Regression models showed significant correlation between cortisol after dexamethasone suppression test (DST) and 31 metabolites, independently of confounding/contributing factors. Among those, histidine and spermidine were also significantly associated with catabolic signs and symptoms of hypercortisolism. According to a discriminant analysis, the panel of metabolites was able to correctly classify subjects into the main diagnostic categories and to distinguish between subjects with/without altered post-DST cortisol and with/without diabetes in >80% of the cases. **CONCLUSIONS:** Metabolomic profiling revealed alterations of intermediate metabolism independently associated with the severity of hypercortisolism, consistent with disturbed protein synthesis/catabolism and incomplete beta-oxidation, providing evidence for the occurrence of metabolic inflexibility in hypercortisolism.

PubMed-ID: [28566446](https://pubmed.ncbi.nlm.nih.gov/28566446/)

<http://dx.doi.org/10.1530/EJE-17-0109>

### **Phaeochromocytoma in multiple endocrine neoplasia type 2: RET codon-specific penetrance and changes in management during the last four decades.**

*Clin Endocrinol (Oxf)*, 87(4):320-6.

L. Mucha, G. Leidig-Bruckner, K. Frank-Raue, T. Bruckner, M. Kroiss and F. Raue.

**OBJECTIVES:** We describe phaeochromocytoma (phaeo) penetrance in multiple endocrine neoplasia type 2 (MEN2) according to RET protooncogene-specific mutations and report changes in phaeo diagnosis and management from 1968 to 2015. **DESIGN:** This retrospective chart review included 309 MEN2 patients from one specialized ambulatory care centre. Phaeo patients were categorized by diagnosis date: early, 1968-1996, n=40, and recent, 1997-2015, n=45. **RESULTS:** Phaeochromocytoma was diagnosed in 85/309 patients with RET mutations in the following exons (phaeos/all carriers, %): exon 11 (56/120, 46.6%); exon 16 (7/17, 41.2%), exon 10 (14/47, 29.8%), and exon 13-15 (2/116, 1.7%). Age at phaeo diagnosis differed according to affected exon: 21.9+/-1.5 years, exon 16; 34.1+/-11.6 years, exon 11; and 41.8+/-8.8 years, exon 10. Age-related phaeo penetrance differed among five amino acid substitutions at codon 634 and was highest for Cys634Arg and Cys634Tyr. Age at diagnosis was 34.4+/-11.6 years in the early and recent groups. Phaeochromocytoma and medullary thyroid carcinoma (MTC) were diagnosed synchronously in 21/40 (early) vs 8/45 (recent) and metachronously in 19/40 vs 37/45 cases. Diagnostic methods significantly changed from clinical (22/40 vs 4/45) to biochemical and/or imaging based (14/40 vs 35/45). Phaeochromocytoma diameter at diagnosis was 4.6 vs 2.6 cm. **CONCLUSION:** Phaeochromocytoma penetrance and age of diagnosis are highly correlated with MTC aggressiveness based on RET mutation status, with higher penetrance and younger age of diagnosis associated with more aggressive MTC. Penetrance steadily increases with age. At-risk patients require lifelong follow-up.

PubMed-ID: [28605116](https://pubmed.ncbi.nlm.nih.gov/28605116/)

<http://dx.doi.org/10.1111/cen.13386>

### **Malignant Pheochromocytoma and Paraganglioma: 272 Patients Over 55 Years.**

*J Clin Endocrinol Metab*, 102(9):3296-305.

O. Hamidi, W. F. Young, Jr., N. M. Iniguez-Ariza, N. E. Kittah, L. Gruber, C. Bancos, S. Tamhane and I. Bancos.

**Context:** Malignant pheochromocytoma (PHEO) and paraganglioma (PGL) are rare and knowledge of the natural history is limited. **Objective:** We aimed to describe baseline characteristics and outcomes of patients with malignant PHEO and PGL (PPGL) and to identify predictors of shorter survival. **Design:** Retrospective review of patients with malignant PPGL evaluated from 1960 to 2016. **Setting:** Referral center. **Patients:** The group comprised 272 patients. **Main Outcome Measures:** Baseline description, survival outcomes, and predictors of shorter survival were evaluated in patients with rapidly progressive (n = 29) and indolent disease (n = 188). **Results:** Malignant PPGL was diagnosed at a median age of 39 years (range, 7 to 83 years), with synchronous metastases in 96 (35%) patients. In 176 (65%) patients, metastases developed at a median of 5.5 years (range, 0.3 to 53.4 years) from the initial diagnosis. Median follow-up was 8.2 years (range, 0.01 to 54.1 years). Median overall and disease-specific survivals were 24.6 and 33.7 years, respectively. Shorter survival correlated with male sex (P = 0.014), older age at the time of primary tumor (P = 0.0011), synchronous metastases (P < 0.0001), larger primary tumor size (P = 0.0039), elevated dopamine (P = 0.0195), and not undergoing primary tumor resection (P < 0.0001). There was no difference in the type of primary tumor or presence of SDHB mutation. **Conclusions:** The clinical course of patients with malignant PPGL is remarkably variable. Rapid disease progression is associated with male sex, older age at diagnosis, synchronous metastases, larger tumor size, elevated dopamine, and not undergoing resection of primary tumor. An individualized approach to patients with metastatic PPGL is warranted.

PubMed-ID: [28605453](https://pubmed.ncbi.nlm.nih.gov/28605453/)

<http://dx.doi.org/10.1210/jc.2017-00992>

**The penetrance of MEN2 pheochromocytoma is not only determined by RET mutations.**

*Endocr Relat Cancer*, 24(8):L63-L7.

F. Castinetti, A. L. Maia, M. Peczkowska, M. Barontini, K. Hasse-Lazar, T. P. Links, R. A. Toledo, S. Dvorakova, C. Mian, M. J. Bugalho, S. Zovato, M. Alevizaki, A. Kvachenyuk, B. Bausch, P. Loli, S. R. Bergmann, A. Patocs, M. Pfeifer, J. B. Costa, E. von Dobschuetz, C. Letizia, G. Valk, M. Barczynski, M. Czetwertynska, J. T. M. Plukker, P. Sartorato, T. Zelinka, P. Vleck, S. Yaremchuk, G. Weryha, L. Canu, N. Wohllk, F. Sebag, M. K. Walz, C. Eng and H. P. H. Neumann.

PubMed-ID: [28649091](https://pubmed.ncbi.nlm.nih.gov/28649091/)

<http://dx.doi.org/10.1530/ERC-17-0189>

**Diagnosis and Differential Diagnosis of Cushing's Syndrome.**

*N Engl J Med*, 377(2):e3.

R. L. Goodman.

PubMed-ID: [28704027](https://pubmed.ncbi.nlm.nih.gov/28704027/)

<http://dx.doi.org/10.1056/NEJMc1705984>

# NET

## Meta-Analyses

### **The Impact of Somatostatin Receptor-Directed PET/CT on the Management of Patients with Neuroendocrine Tumor: A Systematic Review and Meta-Analysis.**

*J Nucl Med*, 58(5):756-61.

M. Barrio, J. Czernin, S. Fanti, V. Ambrosini, I. Binse, L. Du, M. Eiber, K. Herrmann and W. P. Fendler. Somatostatin receptor (SSTR) imaging is widely used for guiding the management of neuroendocrine tumor (NET) patients. (68)Ga-DOTATATE approval by the U.S. Food and Drug Administration has triggered widespread clinical interest in SSTR PET/CT throughout the United States. Here, we performed a systematic review and meta-analysis to evaluate the impact of SSTR PET/CT on the management of patients with NETs. Methods: A comprehensive literature search was performed using The National Center for Biotechnology Information PubMed online database, applying the following key words: "management" AND "PET" AND "neuroendocrine". Fourteen of 190 studies were deemed suitable based on the following inclusion criteria: original research, cohort study, number of patients 10 or more, and reported change in management after SSTR PET/CT. Change in management across studies was determined by a random-effects model. Results: A total of 1,561 patients were included. Overall, change in management occurred in 44% (range, 16%-71%) of NET patients after SSTR PET/CT. In 4 of 14 studies, SSTR PET/CT was performed after an (111)In-Octreotide scan. In this subgroup, additional information by SSTR PET/CT led to a change in management in 39% (range, 16%-71%) of patients. Seven of 14 studies differentiated between inter- and intramodality changes, with most changes being intermodality (77%; intramodality, 23%). Conclusion: The management was changed in more than one third of patients undergoing SSTR PET/CT even when performed after an (111)In-Octreotide scan. Intermodality changes were 3 times more likely than intramodality changes, underlining the clinical impact of SSTR PET/CT.

PubMed-ID: [28082438](https://pubmed.ncbi.nlm.nih.gov/28082438/)

<http://dx.doi.org/10.2967/jnumed.116.185587>

### **Role of palliative resection of the primary tumour in advanced pancreatic and small intestinal neuroendocrine tumours: A systematic review and meta-analysis.**

*Eur J Surg Oncol*, 43(10):1808-15.

L. M. Almond, J. Hodson, S. J. Ford, D. Gourevitch, K. J. Roberts, T. Shah, J. Isaac and A. Desai. PURPOSE: This study aimed to evaluate the impact on overall survival following palliative surgery to remove the primary lesion in unresectable metastatic small intestinal (SI-NET) and pancreatic neuroendocrine tumours (P-NET). METHODS: A systematic review of the literature and meta-analysis was performed. MEDLINE and Embase databases were searched to identify articles comparing patients undergoing palliative primary tumour resection without metastatectomy vs. no resection. Relevant articles were identified in accordance with PRISMA guidelines. The primary outcome was overall survival. Included studies were evaluated for heterogeneity and publication bias. RESULTS: 13 studies met the inclusion criteria, of which 6 presented data suitable for meta-analysis. No randomised controlled trials were identified. Analysis of pooled multivariate hazard ratios demonstrated significantly longer overall survival in patients undergoing resection of both P-NETs (HR 0.43; 95% CI: 0.34-0.57,  $p < 0.001$ ) and SI-NETs (HR 0.47; 95% CI: 0.35-0.55,  $p = 0.007$ ). The increase in median survival in patients treated surgically relative to non-surgically ranged from 14 to 46 months in P-NET, and 22-112 months in SI-NET. The number needed to treat in order that one additional patient was alive at five years, ranged from 3.0 to 4.2, and 1.7 to 7.7 respectively. CONCLUSIONS: Meta-analysis demonstrates that palliative resection of primary SI-NETs and P-NETs in the setting of unresectable metastatic disease can increase survival. Although these results should be interpreted with caution due to potential selection and publication bias, the data supports consideration of surgery, particularly in patients with low tumour burdens and good functional status.

PubMed-ID: [28583792](https://pubmed.ncbi.nlm.nih.gov/28583792/)

<http://dx.doi.org/10.1016/j.ejso.2017.05.016>

### **Sporadic Small ( $\leq 20$ mm) Nonfunctioning Pancreatic Neuroendocrine Neoplasm: is the Risk of Malignancy Negligible When Adopting a More Conservative Strategy? A Systematic Review and Meta-analysis.**

*Ann Surg Oncol*, 24(9):2603-10.

C. Ricci, R. Casadei, G. Taffurelli, C. A. Pacilio, D. Campana, V. Ambrosini, S. Donatella and F. Minni.

**BACKGROUND:** The management of small ( $\leq 20$  mm), nonfunctioning pancreatic neuroendocrine neoplasms (pNENs) remains under debate. The European Neuroendocrine Tumor Society guidelines advocate the possibility of a conservative approach. **METHODS:** A systematic literature search was conducted to identify all studies comparing the risk of malignancy in small pNENs with respect to large ones ( $>20$  mm). Malignancy was defined based on the presence of nodal metastases. Distant metastases, tumor grading (G2-3), vascular microscopic invasion, stage III-IV, and overall and disease-free survival also were evaluated. The data were reported in two ways: using the risk difference (RD) and the likelihood of being helped or harmed (LHH). **RESULTS:** The search identified only 6 eligible studies with an overall population of 1697 resected pNENs: 382 (22.5%) small and 1315 (77.5%) large. The RD of lymph nodal metastases was -0.26 (95% confidence interval (CI): -0.31 to -0.22;  $P < 0.001$ ). The LHH was 0.34, suggesting that the risk of leaving a malignancy during follow-up due to the adoption of a conservative strategy was three times higher than the benefits. The risk difference of distant metastases, G3 lesions, G2-G3 lesions, stage III/IV, microscopic vascular invasion, death, and recurrence of the disease were lower in small NF-PNETs than large ones. The related LHH values suggested that a watch-and-wait policy never provided a benefit. **CONCLUSIONS:** Even if the malignancy rate in sporadic, small pancreatic neuroendocrine neoplasms was lower than in large ones, this difference did not justify a watch-and-wait policy.

PubMed-ID: [28681158](https://pubmed.ncbi.nlm.nih.gov/28681158/)

<http://dx.doi.org/10.1245/s10434-017-5946-8>

## Randomized controlled trials

- None -

## Consensus Statements/Guidelines

- None -

## Other Articles

### **Shape and Enhancement Characteristics of Pancreatic Neuroendocrine Tumor on Preoperative Contrast-enhanced Computed Tomography May be Prognostic Indicators.**

*Ann Surg Oncol*, 24(5):1399-405.

H. Okabe, D. Hashimoto, A. Chikamoto, M. Yoshida, K. Taki, K. Arima, K. Imai, Y. Tamura, O. Ikeda, T. Ishiko, H. Uchiyama, T. Ikegami, N. Harimoto, S. Itoh, Y. I. Yamashita, T. Yoshizumi, T. Beppu, Y. Yamashita, H. Baba and Y. Maehara.

**BACKGROUND:** Prognostic indicators of the malignant potential of pancreatic neuroendocrine tumors (PNET) are limited. We assessed tumor shape and enhancement pattern on contrast-enhanced computed tomography as predictors of malignant potential. **METHODS:** Sixty cases of PNET patients undergoing curative surgery from 2001 to 2014 were enrolled onto our retrospective study. Preoperative enhanced CTs were assessed, and criteria defined for regularly shaped and enhancing tumors (group 1), and irregularly shaped and/or enhancing tumors (group 2). The relation of tumor shape and enhancement pattern to outcome was assessed. **RESULTS:** Interobserver agreement was substantial ( $\kappa = 0.74$ ). Group 2 ( $n = 24$ ) was significantly correlated with synchronous liver metastasis (23 vs. 0 %), lymph node metastasis (36 vs. 3 %), pathologic capsular invasion (68 vs. 8 %), larger tumor size (30 vs. 12 mm), tumor, node, metastasis classification system (TNM) stage III/IV disease (46 vs. 3 %), and histologic grade 2/3 (41 vs. 0 %). Multivariate analysis revealed that tumor grade 2/3 and group 2 criteria correlated with tumor relapse (hazard ratio 6.5 and 13.6,  $P = 0.0071$  and 0.039, respectively), and that only group 2 criteria were independently correlated with poor overall survival (hazard ratio 5.56e + 9,  $P = 0.0041$ ). **CONCLUSIONS:** Irregular tumor shape/enhancement on preoperative computed tomography is a negative prognostic factor after curative surgery for PNET.

PubMed-ID: [27896509](https://pubmed.ncbi.nlm.nih.gov/27896509/)

<http://dx.doi.org/10.1245/s10434-016-5630-4>



### **Limited Value of Ga-68-DOTATOC-PET-CT in Routine Screening of Patients with Multiple Endocrine Neoplasia Type 1.**

*World J Surg*, 41(6):1521-7.

M. B. Albers, D. Librizzi, C. L. Lopez, J. Manoharan, J. C. Apitzsch, E. P. Slater, C. Bollmann, P. H. Kann and D. K. Bartsch.

**BACKGROUND:** Routine screening is recommended for patients with multiple endocrine neoplasia type 1 (MEN1) to enable early detection and treatment of associated neuroendocrine neoplasms (NEN). Gallium(68)-DOTATOC-Positron emission tomography combined with computed tomography (Ga-68-DOTATOC-PET-CT) is a very sensitive and specific imaging technique for the detection of sporadic neuroendocrine tumors. The present study evaluated the value of Ga-68-DOTATOC-PET-CT in routine screening of patients with MEN1. **METHODS:** Between January 2014 and March 2016, all MEN1 patients underwent Ga-68-DOTATOC-PET-CT in addition to conventional imaging (computed tomography of the thorax, magnetic resonance imaging of the abdomen and pituitary, endoscopic ultrasonography). The diagnostic yield of conventional imaging and Ga-68-DOTATOC-PET-CT was prospectively documented and compared, and treatment changes caused by the addition of Ga-68-DOTATOC-PET-CT were recorded. **RESULTS:** Conventional imaging detected 145 NENs, mainly pancreaticoduodenal NENs (n = 117, 81%), in 31 of 33 MEN1 patients. Ga-68-DOTATOC-PET-CT detected 55 NENs in 23 of the 33 patients (p = 0.0001). Ninety (62%) NENs detected by conventional imaging were missed by DOTATOC-PET-CT. The majority of missed lesions were pNEN (n = 68; 74%). The sensitivity of Ga-68-DOTATOC-PET-CT for NENs <5, 5-9, 10-19 and ≥20 mm was 0, 29, 81 and 100%, respectively. However, Ga-68-DOTATOC-PET-CT detected more liver and lymph node metastases in patients with known metastatic disease, which did not lead to a change of patients' management. In one patient (3%), Ga-68-DOTATOC-PET-CT was the only imaging modality that detected a small intestine NEN and led to potentially curative surgery. **CONCLUSION:** Ga-68-DOTATOC-PET-CT cannot be recommended for routine screening of MEN1 patients. It might provide important additional information in patients with suspected or known metastatic disease.

PubMed-ID: [28138732](https://pubmed.ncbi.nlm.nih.gov/28138732/)

<http://dx.doi.org/10.1007/s00268-017-3907-9>

### **Localization of Unknown Primary Site with (68)Ga-DOTATOC PET/CT in Patients with Metastatic Neuroendocrine Tumor.**

*J Nucl Med*, 58(7):1054-7.

Y. Menda, T. M. O'Doriso, J. R. Howe, M. Schultz, J. S. Dillon, D. Dick, G. L. Watkins, T. Ginader, D. L. Bushnell, J. J. Sunderland, G. K. D. Zamba, M. Graham and M. S. O'Doriso.

Localization of the site of the unknown primary tumor is critical for surgical treatment of patients presenting with neuroendocrine tumor (NET) with metastases. **Methods:** Forty patients with metastatic NET and unknown primary site underwent (68)Ga-DOTATOC PET/CT in a single-site prospective study. The (68)Ga-DOTATOC PET/CT was considered true-positive if the positive primary site was confirmed by histology or follow-up imaging. The scan was considered false-positive if no primary lesion was found corresponding to the (68)Ga-DOTATOC-positive site. All negative scans for primary tumor were considered false-negative. A scan was classified unconfirmed if (68)Ga-DOTATOC PET/CT suggested a primary, however, no histology was obtained and imaging follow-up was not confirmatory. **Results:** The true-positive, false-positive, false-negative, and unconfirmed rates for unknown primary tumor were 38%, 7%, 50%, and 5%, respectively. **Conclusion:** (68)Ga-DOTATOC PET/CT is an effective modality in the localization of unknown primary in patients with metastatic NET.

PubMed-ID: [28153957](https://pubmed.ncbi.nlm.nih.gov/28153957/)

<http://dx.doi.org/10.2967/jnumed.116.180984>

### **PET Imaging for Endocrine Malignancies: From Woe to Go.**

*J Nucl Med*, 58(6):878-80.

D. Taieb, R. J. Hicks and K. Pacak.

PubMed-ID: [28232613](https://pubmed.ncbi.nlm.nih.gov/28232613/)

<http://dx.doi.org/10.2967/jnumed.117.189688>

### **Management of Neuroendocrine Tumor Liver Metastases: Long-Term Outcomes and Prognostic Factors from a Large Prospective Database.**

*Ann Surg Oncol*, 24(8):2319-25.

M. Fairweather, R. Swanson, J. Wang, L. K. Brais, T. Dutton, M. H. Kulke and T. E. Clancy.

**BACKGROUND:** Liver-directed therapies have been used to treat neuroendocrine liver metastases (NELM) for both symptomatic improvement and tumor growth control. We reviewed our experience with NELM to investigate

the outcomes of available treatment modalities and to identify prognostic factors for survival. **METHODS:** We identified all patients with NELM, who were managed at our institution, from a prospectively collected institutional database. Overall survival (OS) was determined for each treatment modality. **RESULTS:** Between 2003 and 2010, we identified 939 patients with neuroendocrine tumors, of whom 649 patients had NELM. The primary tumor site was the small intestine in 245 patients (38%) and pancreas in 194 patients (30%). With a median follow-up of 44 months, the median, 5 and 10 year OS for each treatment group was as follows: hepatic resection (n = 58, 9%), 160 months, 90%, 70%; radiofrequency ablation (n = 28, 4%), 123 months, 84%, 55%; chemoembolization (n = 130, 20%), 66 months, 55%, 28%; systemic therapy (n = 316, 49%), 70 months, 58%, 31%; and observation (n = 117, 18%), 38 months, 38%, 20%. Age [hazard ratio (HR) 1.0, p < 0.001], small bowel primary site (HR 0.5, p < 0.001), hepatic resection (HR 0.3, p = 0.001), well-differentiated tumors (HR 0.3, p < 0.001), alkaline phosphatase within normal limit (WNL) (HR 0.4, p < 0.001), and chromogranin A WNL (HR 0.5, p < 0.001) were significant independent prognosticators for OS. **CONCLUSIONS:** This series represents one of the largest single-institution studies of NELM reported. We found that hepatic resection was associated with highly favorable OS. Our observations support hepatic resection in appropriately selected patients.

PubMed-ID: [28303430](https://pubmed.ncbi.nlm.nih.gov/28303430/)

<http://dx.doi.org/10.1245/s10434-017-5839-x>

### **Is Routine Screening of Young Asymptomatic MEN1 Patients Necessary?**

*World J Surg*, 41(8):2026-32.

J. Manoharan, F. Raue, C. L. Lopez, M. B. Albers, C. Bollmann, V. Fendrich, E. P. Slater and D. K. Bartsch.

**BACKGROUND:** Recent clinical practice guidelines recommend that routine screening of MEN1 mutation carriers should start at the age of 5 years. The occurrence of clinically relevant MEN1 organ manifestations in children (<=18 years) was evaluated. **METHODS:** Two prospective collected databases of MEN1 patients (n = 166) who underwent annual screening were retrospectively analyzed for organ manifestations in MEN1 patients <=18 years. The follow-up was based on the most recent screening examination until December 2015. **RESULTS:** Twenty [11 females, 9 males, (12%)] of 166 MEN1 patients were diagnosed with at least one organ manifestation at age <=18 years. The most frequent manifestation was mild asymptomatic pHPT (n = 9, 45%, age range 8-18 years). Eight (40%) young patients had pNENs (three non-functioning pNENs, five insulinomas, age range 9-18 years). All five insulinomas were diagnosed based on hypoglycemic symptoms. The other organ manifestations were asymptomatic pituitary adenomas in six patients (30%, age range 15-18 years) and a bronchial carcinoid in one 15-year-old patient. Only six (30%) patients <=18 years had clinically relevant organ manifestations. **CONCLUSION:** Symptomatic or severe manifestations in MEN1 patients rarely occur below the age of 16 years. With regard to psychological burden and cost-effectiveness, routine screening of asymptomatic MEN1 patients should be postponed at least until the age of 16 years.

PubMed-ID: [28321559](https://pubmed.ncbi.nlm.nih.gov/28321559/)

<http://dx.doi.org/10.1007/s00268-017-3992-9>

### **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.

**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.

PubMed-ID: [28323985](https://pubmed.ncbi.nlm.nih.gov/28323985/)  
<http://dx.doi.org/10.1210/jc.2016-3865>

### **Functional Imaging in the Follow-Up of Enteropancreatic Neuroendocrine Tumors: Clinical Usefulness and Indications.**

*J Clin Endocrinol Metab*, 102(5):1486-94.

E. Merola, M. E. Pavel, F. Panzuto, G. Capurso, N. Cicchese, A. Rinke, T. M. Gress, E. Iannicelli, D. Prosperi, P. Pizzichini, V. Prasad, P. Kump, R. Lipp, S. Partelli, M. Falconi, B. Wiedenmann and G. Delle Fave.

Context: Functional imaging tests (FITs) detecting somatostatin receptor expression [i.e., somatostatin receptor scintigraphy, 68Ga-DOTA positron emission tomography/computed tomography (CT)] have a pivotal role in the diagnosis of neuroendocrine tumors (NETs), although their indication during follow-up still needs to be clarified. Objective: Investigate the role of FITs after diagnosis of metastatic enteropancreatic NETs, identifying patients who might benefit from these exams. Design: Multicenter retrospective analysis of metastatic enteropancreatic NETs. Setting: Analysis of imaging tests performed between January 1995 and December 2015 in Rome, Berlin, Milan, Marburg, or Graz. Subjects: One hundred forty-three patients with metastatic pancreatic NETs and small intestine NETs, at least 2-year follow-up, and positive FITs. Interventions: Patients had received CT every 6 months (unless clinical conditions and tumor behavior required shorter intervals) and FIT every 12 months. Main Outcome Measures: Clinical usefulness of FITs, defined as changes in patient management (indication to biopsy, medical therapy, surgery, or further imaging tests) due only to FITs. Results: FITs affected management in 73.4% of patients, mostly when G2 vs G1 [odds ratio (OR), 2.40; 95% confidence interval (CI), 1.09 to 5.27;  $P = 0.03$ ]. Changes were observed in a 12-month time frame especially with pancreatic NETs vs small intestine NETs (OR, 2.89; 95% CI, 1.09 - 7.67;  $P = 0.03$ ) or metastases since diagnosis vs developed during follow-up (OR, 4.00; 95% CI, 1.43 to 11.17;  $P < 0.01$ ). Conclusions: FITs used in addition to CT in the follow-up of stage IV enteropancreatic NETs improve patient management (especially for G2 tumors). Follow-up program should be tailored according to tumor features.

PubMed-ID: [28324047](https://pubmed.ncbi.nlm.nih.gov/28324047/)  
<http://dx.doi.org/10.1210/jc.2016-3732>

### **Thymic Neuroendocrine Neoplasms: Biological Behaviour and Therapy.**

*Neuroendocrinology*, 105(2):105-14.

R. Jia, P. Sulentic, J. M. Xu and A. B. Grossman.

Thymic neuroendocrine neoplasms are rare tumours, but their management can often be highly problematic. While previously assumed to be essentially variants of bronchopulmonary (lung) carcinoids, they are generally more aggressive and more difficult to treat. Some 25% are associated with multiple endocrine neoplasia-1, while a higher proportion are associated with the ectopic ACTH syndrome, and occasionally both. We discuss the classification of these tumours, their biology as far as is known, and their clinical, biochemical and imaging features. We also review possible management options and suggest stratagems to optimise their treatment, which even today is far from optimal.

PubMed-ID: [28355610](https://pubmed.ncbi.nlm.nih.gov/28355610/)  
<http://dx.doi.org/10.1159/000472255>

### **Surgical approaches in hereditary endocrine tumors.**

*Updates Surg*, 69(2):181-91.

M. Iacobone, M. Citton, G. Viel, D. Schiavone and F. Torresan.

Endocrine tumors of thyroid, adrenal and parathyroid glands may be due to germline and inheritable mutations in 5-30% of patients. Medullary Thyroid Carcinoma, Pheochromocytoma, Paraganglioma, and Familial Primary Hyperparathyroidism are the most frequent entity. Hereditary endocrine tumors usually have a suggestive familial history; they occur earlier than sporadic variants, are multifocal, and have increased recurrence rates. They may be present as isolated variant or associated to other neoplasms in a syndromic setting. Genetic diagnosis should be preferably available before surgery because specific and targeted operative management are needed to achieve the best chance of cure. This review was aimed to discuss the surgical approaches for some of the most frequent hereditary endocrine tumors of thyroid, adrenal and parathyroid glands, focusing on medullary thyroid carcinoma, Pheochromocytoma, Paraganglioma and hereditary primary hyperparathyroidism (pHPT). Hereditary Medullary Thyroid Carcinoma is caused by RET mutations, and may be associated to Pheochromocytomas in MEN 2 setting. Total thyroidectomy and at least central neck nodal dissection is required. The availability of genetic screening allows prophylactic or early surgery in asymptomatic patients, with subsequent definitive cure. Hereditary Pheochromocytomas may be present in several syndromes (MEN 2, VHL, NF1, Paraganglioma/Pheochromocytoma syndrome); it may involve both adrenals; in these cases, a cortical sparing adrenalectomy should be performed to avoid permanent hypocorticosurrealism. Hereditary Primary

Hyperparathyroidism may frequently occur associated to MEN 1, MEN 2A, MEN 4, Hyperparathyroidism-Jaw Tumor Syndrome; it may involve all the parathyroid glands, requiring subtotal parathyroidectomy or total parathyroidectomy plus autotransplantation. In some cases, a selective parathyroidectomy might be performed. PubMed-ID: [28455835](https://pubmed.ncbi.nlm.nih.gov/28455835/)  
<http://dx.doi.org/10.1007/s13304-017-0451-y>

### **Increased Grade in Neuroendocrine Tumor Metastases Negatively Impacts Survival.**

*Ann Surg Oncol*, 24(8):2206-12.

K. J. Keck, A. Choi, J. E. Maxwell, G. Li, T. M. O'Dorisio, P. Breheny, A. M. Bellizzi and J. R. Howe. BACKGROUND: Tumor grade is an important predictor of survival in gastroenteropancreatic (GEP) neuroendocrine tumors (NETs), as determined by Ki-67 expression and mitotic rate. NETs generally grow indolently, but some cells may acquire traits facilitating metastasis. It is unclear how frequently metastases differ in grade from their primary tumors, and whether increasing grade in metastases affects prognosis. METHODS: Ki-67 immunohistochemistry was performed on resected GEPNET specimens and cases with results for both primary tumors and concurrent metastases were identified. Grade was determined using a modified World Health Organization classification (Ki-67: G1 = 0-2%; G2 > 2-20%; G3 > 20%). RESULTS: Ki-67 was performed on both the primary tumor and metastases in 103 patients. Tumor grade was higher in metastases from 25 (24%) patients, 24 increased from G1 to G2, and 1 increased from G2 to G3; 68 (66%) patients had no change in grade (42 G1 and 26 G2), and 10 (10%) decreased from G2 to G1. No clinicopathologic factors were predictive of higher grade in metastases. The 5-year progression-free survival (PFS) was 55% for patients with stable grade versus 8% of patients with increased grade, while 5-year overall survival (OS) was 92 and 54%, respectively. The 5-year OS of patients who had stable grade with G1 and G2 primaries was 92 and 64%, respectively. CONCLUSIONS: Nearly one-third of patients had metastases with a different grade than their primary, and, when grade increased, both PFS and OS significantly decreased. Determining the grade in both the primary tumor and a metastasis is important for estimating prognosis and to help inform decisions regarding additional therapies.

PubMed-ID: [28560597](https://pubmed.ncbi.nlm.nih.gov/28560597/)

<http://dx.doi.org/10.1245/s10434-017-5899-y>

### **Novel Somatic RET Mutation Questioning the Causality of the RET I852M Germline Sequence Variant in Multiple Endocrine Neoplasia 2A.**

*Thyroid*, 27(8):1103-4.

J. S. Mathiesen, T. van Overeem Hansen, A. K. Rasmussen, T. D. Hjortshoj, K. Kiss, S. R. Larsen, L. N. Krogh, A. L. Frederiksen, A. P. Hermann and C. Godballe.

PubMed-ID: [28578594](https://pubmed.ncbi.nlm.nih.gov/28578594/)

<http://dx.doi.org/10.1089/thy.2017.0131>

### **Risk Factors and Mitigation Strategies for Pancreatic Fistula After Distal Pancreatectomy: Analysis of 2026 Resections From the International, Multi-institutional Distal Pancreatectomy Study Group.**

*Ann Surg*,

B. L. Ecker, M. T. McMillan, V. Allegrini, C. Bassi, J. D. Beane, R. M. Beckman, S. W. Behrman, E. J. Dickson, M. P. Callery, J. D. Christein, J. A. Drebin, R. H. Hollis, M. G. House, N. B. Jamieson, A. A. Javed, T. S. Kent, M. D. Kluger, S. J. Kowalsky, L. Maggino, G. Malleo, V. Valero, 3rd, L. K. P. Velu, A. A. Watkins, C. L. Wolfgang, A. H. Zureikat and C. M. Vollmer, Jr.

OBJECTIVE: To identify a clinical fistula risk score following distal pancreatectomy. BACKGROUND: Clinically relevant pancreatic fistula (CR-POPF) following distal pancreatectomy (DP) is a dominant contributor to procedural morbidity, yet risk factors attributable to CR-POPF and effective practices to reduce its occurrence remain elusive. METHODS: This multinational, retrospective study of 2026 DPs involved 52 surgeons at 10 institutions (2001-2016). CR-POPFs were defined by 2016 International Study Group criteria, and risk models generated using stepwise logistic regression analysis were evaluated by c-statistic. Mitigation strategies were assessed by regression modeling while controlling for identified risk factors and treating institution. RESULTS: CR-POPF occurred following 306 (15.1%) DPs. Risk factors independently associated with CR-POPF included: age (<60 yrs: OR 1.42, 95% CI 1.05-1.82), obesity (OR 1.54, 95% CI 1.19-2.12), hypoalbuminemia (OR 1.63, 95% CI 1.06-2.51), the absence of epidural anesthesia (OR 1.59, 95% CI 1.17-2.16), neuroendocrine or nonmalignant pathology (OR 1.56, 95% CI 1.18-2.06), concomitant splenectomy (OR 1.99, 95% CI 1.25-3.17), and vascular resection (OR 2.29, 95% CI 1.25-3.17). After adjusting for inherent risk between cases by multivariable regression, the following were not independently associated with CR-POPF: method of transection, suture ligation of the pancreatic duct, staple size, the use of staple line reinforcement, tissue patches, biologic sealants, or prophylactic octreotide. Intraoperative drainage was associated with a greater fistula rate (OR 2.09,

95% CI 1.51-3.78) but reduced fistula severity ( $P < 0.001$ ). CONCLUSIONS: From this large analysis of pancreatic fistula following DP, CR-POPF occurrence cannot be reliably predicted. Opportunities for developing a risk score model are limited for performing risk-adjusted analyses of mitigation strategies and surgeon performance.

PubMed-ID: [28857813](#)

<http://dx.doi.org/10.1097/SLA.0000000000002491>



## **General**

### Meta-Analyses

- None -

### Randomized controlled trials

- None -

### Consensus Statements/Guidelines

- None -

### Other Articles

- None -