



## ESES Review of Recently Published Literature

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**SR:** systematic review, **MA:** meta-analysis, **RCT:** randomized controlled trial,  
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## Journals covered

Journal	IF2012	Journal	IF2012
<a href="#">Acta Cytol</a>	0.69	<a href="#">J Bone Miner Res</a>	6.128
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<a href="#">J Bone Miner Metab</a>	2.219	<a href="#">World J Surg</a>	2.228

Journal names are links to the journal's homepage!, IF2012: [Impact factor](#) 2012

# Thyroid

## Meta-Analyses

### **Thyroglobulin in Lymph Node Fine-Needle Aspiration Washout: a Systematic Review and Meta-Analysis of Diagnostic Accuracy.**

*J Clin Endocrinol Metab*, 99(6):1970-82.

Grani G, Fumarola A. 2014.

CONTEXT: The thyroglobulin measurement in the needle washout after fine-needle aspiration (FNA) has been reported to increase the sensitivity of FNA in identifying lymph node (LN) metastases from differentiated thyroid cancer (DTC). OBJECTIVE: The aim of the study was to estimate the diagnostic accuracy of this technique. DATA SOURCES: To identify eligible studies, we searched electronic databases for original articles in English from 1975 through 2013. STUDY SELECTION: Studies that enrolled participants with suspicious neck LNs during thyroid nodule workup or thyroid cancer follow-up were included. DATA EXTRACTION: Working independently, authors used a standard form to extract data. For quality assessment, QUADAS2 guidelines were applied. DATA SYNTHESIS: Including all the selected studies (24 studies, 2865 LNs) in the pooled analysis, overall sensitivity was 95.0% (95% confidence interval [CI], 93.7-96.0%), specificity was 94.5% (95% CI, 93.2-95.7%), and diagnostic odds ratio (DOR) was 338.91 (95% CI, 164.82-696.88) with significant heterogeneity (inconsistency [I(2)] = 65.7%; heterogeneity,  $P < .001$ ). Stratifying different populations and including only patients with thyroid gland (410 LNs), pooled sensitivity was 86.2% (95% CI, 80.9-90.5%), specificity was 90.2% (85.1-94.0%), and DOR was 56.621 (22.535-142.26; I(2) = 37.3%; heterogeneity,  $P = .121$ ). Including only patients after thyroidectomy (1007 LNs), pooled sensitivity was 96.9% (95% CI, 94.9-98.2%), specificity was 94.1% (91.7-96.0%), and DOR was 407.65 (198.67-836.46; I(2) = 0.0%; heterogeneity,  $P = .673$ ). CONCLUSIONS: Thyroglobulin measurement in washout from LN FNA has high accuracy in early detection of nodal metastases from DTC. The technique is simple, but a better standardization of criteria for patient selection, analytical methods, and cutoff levels is required.

PubMed-ID: [24617715](https://pubmed.ncbi.nlm.nih.gov/24617715/)

<http://dx.doi.org/10.1210/jc.2014-1098>

### **The Proportion of Malignancy in Incidental Thyroid Lesions on 18-FDG PET Study: A Systematic Review and Meta-Analysis.**

*Otolaryngol Head Neck Surg*, 151(2):190-200.

Nayan S, Ramakrishna J, Gupta MK. 2014.

OBJECTIVE: To evaluate through a systematic review and meta-analysis the malignancy rates of thyroid incidentalomas identified in adults by 18-fluorodeoxyglucose positron emission tomography, computed tomography (18-FDG PET-CT) imaging studies. DATA SOURCES: The literature search was conducted using OVID Medline, EMBASE, the Cochrane Library, Google Scholar, Pubmed, and reference list review (inception to April 2013) by 2 independent review authors. REVIEW METHODS: Studies with adults undergoing 18-FDG PET scan identifying a thyroid incidentaloma with definitive histological or cytological results reported were included. RESULTS: Thirty-one studies with a total of 197,296 PET studies and 3659 focal thyroid incidentalomas were identified with 1341 having definitive cytopathology or histopathology. The pooled proportion of malignancy was calculated as 19.8% (95% confidence interval [CI], 15.3%-24.7%) with 15.4% (95% CI, 11.4%-20.0%) of the total cases being papillary thyroid cancer. Distant metastases represented 1.1% (95% CI, 0.6%-1.8%) of the total cases. CONCLUSIONS: Our systematic review and meta-analysis suggests that the incidence of malignancy is high in thyroid incidentalomas identified through 18-FDG PET imaging studies. Thyroid incidentalomas identified through 18-FDG PET require thorough investigation.

PubMed-ID: [24759908](https://pubmed.ncbi.nlm.nih.gov/24759908/)

<http://dx.doi.org/10.1177/0194599814530861>

### **Differences in the Recurrence and Mortality Outcomes Rates of Incidental and Nonincidental Papillary Thyroid Microcarcinoma: a Systematic Review and Meta-Analysis of 21 329 Person-Years of Follow-Up.**

*J Clin Endocrinol Metab*, 99(8):2834-43.

Mehanna H, Al-Maqbili T, Carter B, Martin E, Campain N, Watkinson J, McCabe C, Boelaert K, Franklyn JA. 2014.

CONTEXT: There is controversy as to whether papillary thyroid microcarcinoma (PTMC) represents more than one disease entity with different outcomes, requiring different treatment. OBJECTIVES: To compare characteristics, outcomes, and factors associated with prognosis of incidental and nonincidental PTMC.

**SETTING AND DESIGN:** Two reviewers performed searches of online databases (1966-2012), reference lists, and conference abstract books. Longitudinal studies of subjects >16 years old receiving any treatments for papillary thyroid cancer  $\leq 10$  mm in size were included. Two reviewers independently screened abstracts and articles, extracted data, and assessed quality of studies using National Institute of Clinical Excellence and PRISMA criteria. **RESULTS:** Of 1102 abstracts identified, 262 studies were reviewed and 17 studies included, comprising 3523 subjects, with mean follow-up of 70 months and total follow-up of 21 329 person-years. This included 854 subjects with incidental PTMC (follow-up, 4800 person-years; mean tumor size, 4.6 mm [range 3.3-6.7 mm]) and 2669 nonincidental PTMC cases (follow-up, 16 529 person-years; mean tumor size, 6.9 mm [range 5.6-8.0 mm]). The recurrence rate in the incidental group (0.5%; 95% confidence interval [CI], 0-1%,  $P < .001$ ) was significantly lower than that in the nonincidental group PTMC (7.9%; 95% CI, 5-11%), with an OR of recurrence of 14.7 (95% CI, 5.6-54.8,  $P < .001$ ) for nonincidental PTMC, compared with incidental PTMC. Lymph nodes were involved in 80% (126/157) of recurrences. On meta-regression, age, sex, size, tumor multifocality, lymph node involvement, and treatment modality were not significantly associated with recurrence. **CONCLUSIONS:** Our meta-analysis strongly suggests the existence of at least two distinct entities of PTMC. Incidental PTMC has different clinical characteristics and a much lower recurrence rate than nonincidental PTMC, suggesting that management protocols should be re-considered. Additional studies with standardized data collection are required to explore potential differences between subgroups of nonincidental PTMC. PubMed-ID: [24828487](https://pubmed.ncbi.nlm.nih.gov/24828487/)  
<http://dx.doi.org/10.1210/jc.2013-2118>

## Randomized controlled trials

### **Radioiodine Ablation of Postsurgical Thyroid Remnants After Treatment With Recombinant Human TSH (RhTSH) in Patients With Moderate-to-Severe Graves' Orbitopathy (GO): a Prospective, Randomized, Single-Blind Clinical Trial.**

*J Clin Endocrinol Metab*, 99(5):1783-9.

Moleti M, Violi MA, Montanini D, Trombetta C, Di BB, Sturniolo G, Presti S, Alibrandi A, Campenni A, Baldari S, Trimarchi F, Vermiglio F. 2014.

**CONTEXT:** Recent evidence suggests thyroidectomy (Tx) followed by radioiodine remnant ablation to be beneficial to Graves' orbitopathy (GO) patients. **OBJECTIVE:** The aim of the study was to evaluate the effect of (131)I thyroid ablation after recombinant human TSH stimulation in patients with moderate-to-severe GO. **DESIGN, PATIENTS, AND INTERVENTIONS:** The study was prospective, randomized, and single-blind, and it included 40 consecutive patients with moderate-to-severe GO randomized into: 1) a Tx-radioactive iodine (RAI) group (20 subjects who underwent total-Tx and (131)I ablation after recombinant human TSH stimulation); and 2) a Tx group (20 subjects who underwent total-Tx alone). **OUTCOME MEASURES:** The overall GO outcome 12 months after Tx/radioiodine ablation was the main measure. **RESULTS:** GO evaluation at the end of iv glucocorticoids showed eye disease to be improved in 65% of the Tx-RAI group and 60% of the Tx group patients. At 6 and 12 months, no further changes in the GO outcome could be observed in the Tx-RAI group. Conversely, five patients from the Tx group exhibited a deterioration in GO. At 12 months, GO was found to be improved in 70% of the Tx-RAI and 20% of the Tx group patients, the latter being found to be stable (55%) or worse (25%) than at baseline evaluation. At 12 months, GO was found to be inactive in a significantly higher percentage of patients in the Tx-RAI than in the Tx group (75 vs 30%;  $P < .01$ ). **CONCLUSIONS:** Postoperative radioiodine ablation proved more effective than Tx alone in inducing earlier and steadier GO improvement in patients with moderate-to-severe GO treated with iv glucocorticoids over a 24-month follow-up period.

PubMed-ID: [24432992](https://pubmed.ncbi.nlm.nih.gov/24432992/)

<http://dx.doi.org/10.1210/jc.2013-3093>

### **A Prospective, Randomized Trial of Intravenous Glucocorticoids Therapy With Different Protocols for Patients With Graves' Ophthalmopathy.**

*J Clin Endocrinol Metab*, 99(6):1999-2007.

Zhu W, Ye L, Shen L, Jiao Q, Huang F, Han R, Zhang X, Wang S, Wang W, Ning G. 2014.

**BACKGROUND:** For patients with active moderate-to-severe Graves' ophthalmopathy (GO), a course of 4.5 g iv glucocorticoids (GCs) is the recommended therapy. The weekly protocol is preferred because of the potential safety concerns with the daily protocol. However, evidence for the superiority of different administration protocols is lacking. **METHODS:** We conducted a prospective, randomized trial to compare the efficacy and safety of two protocols of iv 4.5 g methylprednisolone in a total of 80 patients in our institute. The patients were randomized to receive iv methylprednisolone weekly or daily. The response rate (a composite response endpoint including lid

width, soft tissue involvement, proptosis, intraocular pressure, Clinical Activity Score [CAS], diplopia, and visual acuity) was evaluated as the primary outcome, and adverse effects were recorded at each visit. GO-associated serum cytokines were measured. RESULTS: We found a significantly greater response rate for the weekly protocol vs the daily protocol at the 12th week (76.92 vs 41.03%;  $P = .0025$ ) and a similar response rate at the fourth week. Seven patients on the daily protocol worsened when tapering iv methylprednisolone to oral prednisone in the fourth week. Patients in both groups showed significant CAS response, and at the 12th week, patients on the weekly protocol showed a nonsignificant trend toward greater CAS response. Weekly protocol showed significant prolonged retreatment-free survival. Severe side effects were only observed in two cases, both of which were on the daily protocol. Furthermore, we observed sustained decreased levels of serum CXCL10 in the 12th week compared to the baseline level ( $P = .0009$ ) in the patients on the weekly protocol. CONCLUSIONS: The weekly protocol of iv methylprednisolone therapy is more efficient and safer than the daily protocol for patients with active moderate-to-severe GO.

PubMed-ID: [24606088](https://pubmed.ncbi.nlm.nih.gov/24606088/)

<http://dx.doi.org/10.1210/jc.2013-3919>

### **Cosmetic Result and Overall Satisfaction After Minimally Invasive Video-Assisted Thyroidectomy (MIVAT) Versus Robot-Assisted Transaxillary Thyroidectomy (RATT): a Prospective Randomized Study.**

*World J Surg*, 38(6):1282-8.

Materazzi G, Fregoli L, Manzini G, Baggiani A, Miccoli M, Miccoli P. 2014.

BACKGROUND: No studies have compared robot-assisted transaxillary thyroidectomy (RATT) and minimally invasive video-assisted thyroidectomy (MIVAT) regarding cosmetic outcome and satisfaction. METHODS: Patients matching the inclusion criteria (benign nodule less than 4 cm and thyroid volume less than 30 mL) were randomly allotted to undergo MIVAT (group A) or RATT (group B). Cosmetic result, overall satisfaction, operative time, and complications were evaluated. RESULTS: A total of 62 patients underwent hemithyroidectomy (30 in group A and 32 in group B). All patients were women, with the exception of one man in each group. The mean patient age was 36.9 years (group A) and 32.5 years (group B). Total operative time (intubation-extubation) was shorter in group A (71.6 min) than in group B (120.4 min). Complications included one transient laryngeal nerve injury in each group and one subcutaneous hematoma in group B. Postoperative hospital stay was longer in group B (1.85 days) than in group A (1.15 days). On the PASQ questionnaire, "scar appearance" and "satisfaction with appearance" scores were better in group A than in group B. In the Short Form (SF-36) 36-Item Health Survey Questionnaire, domains of "social activity" and "general health" were better in group B than in group A, whereas "bodily pain" scored higher in group B than in group A. CONCLUSIONS: RATT seems not to supersede MIVAT in terms of satisfaction when comparing two groups of patients undergoing thyroidectomy for benign disease.

PubMed-ID: [24615602](https://pubmed.ncbi.nlm.nih.gov/24615602/)

<http://dx.doi.org/10.1007/s00268-014-2483-5>

### **A Prospective, Randomized Study Between the Small Jaw(R) and the Harmonic Focus(R) in Open Thyroidectomy.**

*Otolaryngol Head Neck Surg*, 150(6):943-8.

Hwang SO, Jung JH, Park HY, Kim WW. 2014.

OBJECTIVES: LigaSure Small Jaw(R) (LSJ) was recently developed and applied to thyroid surgery along with Harmonic Focus(R) (HF). We compared the 2 devices in open total thyroidectomy for papillary thyroid carcinoma (PTC). STUDY DESIGN: A prospective, randomized study. SETTING: Tertiary care center. METHODS: This prospective, randomized study included 126 patients enrolled between December 2011 and June 2012. The numbers of patients in the LSJ group and the HF group were 64 and 62, respectively. Operative times, drain output, parathyroid status, complications, laboratory data, hospital stay, and analgesia requirements were analyzed. RESULTS: Operation time, parathyroid status, postoperative complications including hypocalcemia, oral calcium supplement, calcium, parathyroid hormone, usage count of painkiller, and hospital stay were not different among the 2 groups. Ionized calcium on postoperative days 1, 2, and 10 was higher in the LSJ group ( $P = .04$ ,  $P = .04$ ,  $P = .01$ ), and drain output was lower in the LSJ group (106.8 vs 123.6 mL,  $P = .01$ ). CONCLUSIONS: Open thyroidectomy for PTC using the HF or the LSJ was safe and effective and was not associated with any increase in complications. Surgical outcomes and operative morbidity were equivalent between the 2 groups.

PubMed-ID: [24671461](https://pubmed.ncbi.nlm.nih.gov/24671461/)

<http://dx.doi.org/10.1177/0194599814527730>

### **Sorafenib in Radioactive Iodine-Refractory, Locally Advanced or Metastatic Differentiated Thyroid Cancer: a Randomised, Double-Blind, Phase 3 Trial.**

*Lancet*, 384(9940):319-28.

Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, de la Fouchardiere C, Pacini F, Paschke R, Shong YK, Sherman SI, Smit JW, Chung J, Kappeler C, Pena C, Molnar I, Schlumberger MJ. 2014.

**BACKGROUND:** Patients with radioactive iodine ((131)I)-refractory locally advanced or metastatic differentiated thyroid cancer have a poor prognosis because of the absence of effective treatment options. In this study, we assessed the efficacy and safety of orally administered sorafenib in the treatment of patients with this type of cancer. **METHODS:** In this multicentre, randomised, double-blind, placebo-controlled, phase 3 trial (DECISION), we investigated sorafenib (400 mg orally twice daily) in patients with radioactive iodine-refractory locally advanced or metastatic differentiated thyroid cancer that had progressed within the past 14 months. Adult patients ( $\geq 18$  years of age) with this type of cancer were enrolled from 77 centres in 18 countries. To be eligible for inclusion, participants had to have at least one measurable lesion by CT or MRI according to Response Evaluation Criteria In Solid Tumors (RECIST); Eastern Cooperative Oncology Group performance status 0-2; adequate bone marrow, liver, and renal function; and serum thyroid-stimulating hormone concentration lower than 0.5 mIU/L. An interactive voice response system was used to randomly allocate participants in a 1:1 ratio to either sorafenib or matching placebo. Patients, investigators, and the study sponsor were masked to treatment assignment. The primary endpoint was progression-free survival, assessed every 8 weeks by central independent review. Analysis was by intention to treat. Patients in the placebo group could cross over to open-label sorafenib upon disease progression. Archival tumour tissue was examined for BRAF and RAS mutations, and serum thyroglobulin was measured at baseline and at each visit. This study is registered with ClinicalTrials.gov, number NCT00984282, and with the EU Clinical Trials Register, number EudraCT 2009-012007-25. **FINDINGS:** Patients were randomly allocated on a 1:1 basis to sorafenib or placebo. The intention-to-treat population comprised 417 patients (207 in the sorafenib group and 210 in the placebo group) and the safety population was 416 patients (207 in the sorafenib group and 209 in the placebo group). Median progression-free survival was significantly longer in the sorafenib group (10.8 months) than in the placebo group (5.8 months; hazard ratio [HR] 0.59, 95% CI 0.45-0.76;  $p < 0.0001$ ). Progression-free survival improved in all prespecified clinical and genetic biomarker subgroups, irrespective of mutation status. Adverse events occurred in 204 of 207 (98.6%) patients receiving sorafenib during the double-blind period and in 183 of 209 (87.6%) patients receiving placebo. Most adverse events were grade 1 or 2. The most frequent treatment-emergent adverse events in the sorafenib group were hand-foot skin reaction (76.3%), diarrhoea (68.6%), alopecia (67.1%), and rash or desquamation (50.2%). **INTERPRETATION:** Sorafenib significantly improved progression-free survival compared with placebo in patients with progressive radioactive iodine-refractory differentiated thyroid cancer. Adverse events were consistent with the known safety profile of sorafenib. These results suggest that sorafenib is a new treatment option for patients with progressive radioactive iodine-refractory differentiated thyroid cancer. **FUNDING:** Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals (an Amgen subsidiary).

PubMed-ID: [24768112](https://pubmed.ncbi.nlm.nih.gov/24768112/)

[http://dx.doi.org/10.1016/S0140-6736\(14\)60421-9](http://dx.doi.org/10.1016/S0140-6736(14)60421-9)

### **The Rate of Operative Success Achieved With Radioguided Occult Lesion Localization and Intraoperative Ultrasonography in Patients With Recurrent Papillary Thyroid Cancer.**

*Surgery*,

Giles YS, Sarici IS, Tunca F, Sormaz IC, Salmaslioglu A, Adalet I, Ozgur I, Tezelman S, Terzioglu T. 2014.

**BACKGROUND:** To investigate the rate of operative success in excision of nonpalpable lymph nodes with metastatic disease achieved with radioguided occult lesion localization (ROLL) and intraoperative ultrasonography (IOUS) in patients with papillary thyroid cancer (PTC). **METHODS:** Twenty consecutive PTC patients with nonpalpable lymph nodes with metastatic disease localized in previously operated fields were randomized to receive ROLL ( $n = 11$ ) or IOUS ( $n = 9$ ). Nodes were excised along with adjacent soft tissue to accomplish a compartment-oriented dissection. The duration of operation, rate of postoperative complications, pre- and postoperative serum thyroglobulin (Tg) levels, and the findings of postoperative neck ultrasonography and postablation scan were recorded in all patients. Measures of operative success included a postoperative Tg level  $< 50\%$  of preoperative Tg level and no abnormal lesions on postoperative imaging. **RESULTS:** Histopathologic examination confirmed the excision of all preoperatively identified metastatic nodes. Additional nodes also were excised (2.3  $\pm$  3.3 per specimen in the ROLL group and 1.6  $\pm$  1.8 per specimen in the IOUS group), 23% of which were metastatic. No postoperative complications occurred in either group. The duration of operation was similar in the 2 groups ( $P = .4$ ). Postoperative imaging confirmed the clearance of suspicious nodes in all patients. The rate of operative success in ROLL and IOUS group were 100% and 89%, respectively. **CONCLUSION:** In patients with recurrent PTC, a high rate of operative success in excision of nonpalpable

metastatic lymph nodes was achieved by both ROLL and IOUS. We recommend compartment-oriented dissection; this approach may maximize the removal of metastatic nodes not identified by preoperative imaging. PubMed-ID: [24953276](https://pubmed.ncbi.nlm.nih.gov/24953276/)  
<http://dx.doi.org/10.1016/j.surg.2014.04.012>

## Consensus Statements/Guidelines

### **Thyroglobulin Measurement Using Highly Sensitive Assays in Patients With Differentiated Thyroid Cancer: a Clinical Position Paper.**

*Eur J Endocrinol*, 171(2):R33-R46.

Giovanella L, Clark PM, Chiovato L, Duntas L, Elisei R, Feldt-Rasmussen U, Leenhardt L, Luster M, Schalin-Jantti C, Schott M, Seregini E, Rimmelme H, Smit J, Verburg FA. 2014.

Differentiated thyroid cancer (DTC) is the most common endocrine cancer and its incidence has increased in recent decades. Initial treatment usually consists of total thyroidectomy followed by ablation of thyroid remnants by iodine-131. As thyroid cells are assumed to be the only source of thyroglobulin (Tg) in the human body, circulating Tg serves as a biochemical marker of persistent or recurrent disease in DTC follow-up. Currently, standard follow-up for DTC comprises Tg measurement and neck ultrasound combined, when indicated, with an additional radioiodine scan. Measurement of Tg after stimulation by endogenous or exogenous TSH is recommended by current clinical guidelines to detect occult disease with a maximum sensitivity due to the suboptimal sensitivity of older Tg assays. However, the development of new highly sensitive Tg assays with improved analytical sensitivity and precision at low concentrations now allows detection of very low Tg concentrations reflecting minimal amounts of thyroid tissue without the need for TSH stimulation. Use of these highly sensitive Tg assays has not yet been incorporated into clinical guidelines but they will, we believe, be used by physicians caring for patients with DTC. The aim of this clinical position paper is, therefore, to offer advice on the various aspects and implications of using these highly sensitive Tg assays in the clinical care of patients with DTC.

PubMed-ID: [24743400](https://pubmed.ncbi.nlm.nih.gov/24743400/)

<http://dx.doi.org/10.1530/EJE-14-0148>

### **Revisiting the Guidelines Issued by the Japanese Society of Thyroid Surgeons and Japan Association of Endocrine Surgeons: a Gradual Move Towards Consensus Between Japanese and Western Practice in the Management of Thyroid Carcinoma.**

*World J Surg*, 38(8):2002-10.

Takami H, Ito Y, Okamoto T, Onoda N, Noguchi H, Yoshida A. 2014.

**BACKGROUND:** In 2010, the Japanese Society of Thyroid Surgeons (JSTS) and Japanese Association of Endocrine Surgeons (JAES) established new guidelines entitled "Treatment of Thyroid Tumors." Since then, several new studies, including those that address the treatment of differentiated thyroid carcinoma (DTC) have been published, and the DTC treatment policy not only of Japanese physicians but those in Western countries has continued to evolve. **METHODS:** We selected six clinical questions regarding the treatment of DTC and revisited them based on newly published data from Western countries and Japan. **RESULTS:** More data have accumulated about treatment of low-risk papillary microcarcinoma. It has become clear that conservative treatment (observation) of low-risk papillary microcarcinoma in elderly patients is an acceptable alternative to immediate surgery. Total thyroidectomy versus hemithyroidectomy for low-risk papillary thyroid carcinoma (PTC) has become an important issue, and some publications after 2010 indicated that hemithyroidectomy is adequate for these low-risk patients. Unfortunately, no published manuscripts on prophylactic central node dissection offered good evidence regarding its indications or included a large number of patients. Also, it was not evident that prophylactic lateral node dissection improves cause-specific survival, although it might reduce lymph node recurrence especially in PTC patients with large tumors, distant metastases, or clinical central node metastases. Although completion total thyroidectomy was not recommended for minimally invasive follicular thyroid carcinoma in our guidelines, it may be better to perform it in elderly patients and those with a large tumor or extensive vascular invasion. Radioactive iodine (RAI) ablation after total thyroidectomy is still performed almost routinely in many Western institutions, although recent studies showed that ablation is not beneficial in low-risk patients. In Japan, because of legal restrictions, most patients did not undergo RAI ablation, and their prognoses are excellent. **CONCLUSIONS:** Recently, policy for treating DTCs has changed not only in Western countries but also in Japan, resulting in a gradual move toward consensus between Western practice and ours. We will continue to present the best treatments for patients with thyroid carcinoma each time we revise our guidelines.

## Other Articles

### **The Impact of Iodinated Contrast Agent Administered During Preoperative Computed Tomography Scan on Body Iodine Pool in Patients With Differentiated Thyroid Cancer Preparing for Radioactive Iodine Treatment.**

*Thyroid*, 24(5):872-7.

Sohn SY, Choi JH, Kim NK, Joung JY, Cho YY, Park SM, Kim TH, Jin SM, Bae JC, Lee SY, Chung JH, Kim SW. 2014.

**BACKGROUND:** Iodine in iodinated contrast agents (ICAs) interferes with radioactive iodine treatment (RAIT) and diagnostic scans in patients with differentiated thyroid carcinoma (DTC) because it can compete with  $^{131}\text{I}$ . Published guidelines recommend delaying RAIT for three to four months in patients who have been exposed to ICA. Spot urinary iodine concentration is a useful marker to reflect the body iodine pool. We investigated the impact of ICAs administered at preoperative computed tomography (CT) scan on the body iodine pool to determine the proper time interval between preoperative CT and RAIT in DTC patients. **METHODS:** We performed a retrospective review of 1023 patients with DTC who underwent a preoperative CT scan with ICA, total thyroidectomy, and one week of low-iodine diet in preparation for RAIT. Urine iodine excretion (UIE) was measured in spot urine by inductively coupled plasma mass spectrometry and reported both in simple concentration ( $\mu\text{g/L}$ ) and divided by gram creatinine ( $\mu\text{g/gCr}$ ). Patients were divided into five groups by time interval in days between preoperative CT scan and spot urine iodine measurement (A, 31-60 [ $n=29$ ]; B, 61-90 [ $n=155$ ]; C, 91-120 [ $n=546$ ]; D, 121-150 [ $n=226$ ]; E, 151-180 [ $n=67$ ]). **RESULTS:** The median (interquartile range) of UIE ( $\mu\text{g/gCr}$ ) in each group was 44.4 (27.7-73.2) in group A, 33.3 (22.8-64.7) in group B, 32.7 (20.8-63.0) in group C, 32.0 (20.6-67.0) in group D, and 30.4 (19.6-70.8) in group E. There was no significant difference between group A and the remaining groups ( $p>0.05$ ). Also, the proportion of patients who achieved the appropriate UIE for RAIT according to our hospital's cutoff ( $\leq 66.2 \mu\text{g/gCr}$ ) was not different between groups (A, 72.4%; B, 76.1%; C, 77.5%; D, 74.8%; E, 74.6%) ( $p=0.78$ ). **CONCLUSION:** This study shows that a UIE of one month after preoperative CT scan with ICA was not higher than that of six months after CT scan in patients who underwent total thyroidectomy for DTC. Thus, current guidelines that recommend delay of RAIT for three to four months after CT scan with ICA should be revisited and future studies to clarify the appropriate time interval between CT scan with ICA and RAIT are warranted.

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<http://dx.doi.org/10.1089/thy.2013.0238>

### **Effects of Low-Dose and High-Dose Postoperative Radioiodine Therapy on the Clinical Outcome in Patients With Small Differentiated Thyroid Cancer Having Microscopic Extrathyroidal Extension.**

*Thyroid*, 24(5):820-5.

Han JM, Kim WG, Kim TY, Jeon MJ, Ryu JS, Song DE, Hong SJ, Shong YK, Kim WB. 2014.

**BACKGROUND:** It is unclear whether differentiated thyroid cancer (DTC) patients classified as intermediate risk based on the presence of microscopic extrathyroidal extension (ETE) should be treated with low or high doses of radioiodine (RAI) after surgery. We evaluated success rates and long-term clinical outcomes of patients with DTC of small tumor size, microscopic ETE, and no cervical lymph node (LN) metastasis treated either with a low (1.1 GBq) or high RAI dose (5.5 GBq). **METHODS:** This is a retrospective analysis of a historical cohort from 2000 to 2010 in a tertiary referral hospital. A total of 176 patients with small ( $\leq 2 \text{ cm}$ ) DTC, microscopic ETE, and no cervical LN metastasis were included. Ninety-six patients were treated with 1.1 GBq (LO group) and 80 patients with 5.5 GBq (HI group). Successful RAI therapy was defined as (i) negative stimulated thyroglobulin (Tg) in the absence of Tg antibodies, and (ii) absence of remnant thyroid tissue and of abnormal cervical LNs on ultrasonography. Clinical recurrence was defined as the reappearance of disease after ablation, which was confirmed by cytologically or pathologically proven malignant tissue or of distant metastatic lesions. **RESULTS:** There was no significant difference in the rate of successful RAI therapy between the LO and HI groups ( $p=0.75$ ). In a subgroup analysis based on tumor size, success rates were not different between the LO group (34/35, 97%) and the HI group (50/56, 89%) in patients with a tumor size of 1-2 cm ( $p=0.24$ ). In patients with smaller tumor size ( $\leq 1 \text{ cm}$ ), there was no significant difference in success rates between the LO (59/61, 97%) and HI groups (22/24, 92%;  $p=0.30$ ). No patient had clinical recurrences in either group during the median 7.2 years of follow-up. **CONCLUSIONS:** Low-dose RAI therapy is sufficient to treat DTC patients classified as intermediate risk just by the presence of microscopic ETE.

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<http://dx.doi.org/10.1089/thy.2013.0362>

### **Malignancy Rate in Thyroid Nodules Classified As Bethesda Category III (AUS/FLUS).**

*Thyroid*, 24(5):832-9.

Ho AS, Sarti EE, Jain KS, Wang H, Nixon IJ, Shaha AR, Shah JP, Kraus DH, Ghossein R, Fish SA, Wong RJ, Lin O, Morris LG. 2014.

**BACKGROUND:** The Bethesda System for Reporting Thyroid Cytopathology is the standard for interpreting fine needle aspiration (FNA) specimens. The "atypia of undetermined significance/follicular lesion of undetermined significance" (AUS/FLUS) category, known as Bethesda Category III, has been ascribed a malignancy risk of 5-15%, but the probability of malignancy in AUS/FLUS specimens remains unclear. Our objective was to determine the risk of malignancy in thyroid FNAs categorized as AUS/FLUS at a comprehensive cancer center. **METHODS:** The management of 541 AUS/FLUS thyroid nodule patients treated at Memorial Sloan-Kettering Cancer Center between 2008 and 2011 was analyzed. Clinical and radiologic features were examined as predictors for surgery. Target AUS/FLUS nodules were correlated with surgical pathology. **RESULTS:** Of patients with an FNA initially categorized as AUS/FLUS, 64.7% (350/541) underwent immediate surgery, 17.7% (96/541) had repeat FNA, and 17.6% (95/541) were observed. Repeat FNA cytology was unsatisfactory in 5.2% (5/96), benign in 42.7% (41/96), AUS/FLUS in 38.5% (37/96), suspicious for follicular neoplasm in 5.2% (5/96), suspicious for malignancy in 4.2% (4/96), and malignant in 4.2% (4/96). Of nodules with two consecutive AUS/FLUS diagnoses that were resected, 26.3% (5/19) were malignant. Among all index AUS/FLUS nodules (triaged to surgery, repeat FNA, or observation), malignancy was confirmed on surgical pathology in 26.6% [CI 22.4-31.3]. Among AUS/FLUS nodules triaged to surgery, the malignancy rate was 37.8% [CI 33.1-42.8]. Incidental cancers were found in 22.3% of patients. On univariate logistic regression analysis, factors associated with triage to surgery were younger patient age ( $p < 0.0001$ ), increasing nodule size ( $p < 0.0001$ ), and nodule hypervascularity ( $p = 0.032$ ). **CONCLUSIONS:** In patients presenting to a comprehensive cancer center, malignancy rates in nodules with AUS/FLUS cytology are higher than previously estimated, with 26.6-37.8% of AUS/FLUS nodules harboring cancer. These data imply that Bethesda Category III nodules in some practice settings may have a higher risk of malignancy than traditionally believed, and that guidelines recommending repeat FNA or observation merit reconsideration.

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<http://dx.doi.org/10.1089/thy.2013.0317>

### **Papillary Thyroid Carcinoma Located in the Isthmus or Upper Third Is Associated With Delphian Lymph Node Metastasis.**

*World J Surg*, 38(6):1306-11.

Chai YJ, Kim SJ, Choi JY, Koo dH, Lee KE, Youn YK. 2014.

**BACKGROUND:** Delphian lymph node (DLN) metastasis is a recognized indicator of further lymph node involvement in papillary thyroid carcinoma (PTC). The aim of this study was to evaluate the clinicopathological significance of and risk factors for DLN metastasis. **METHODS:** The medical records of 1,436 patients who underwent primary thyroidectomy for classical PTC with a tumor size of 2 cm or less were reviewed. Of these, 370 patients from whom the DLN was harvested were enrolled. Metastasis in DLN was present in 46 patients and absent in 324 patients. Clinicopathological features were compared according to DLN metastasis. **RESULTS:** In univariate analysis, DLN metastasis was associated with suspected lymph node metastasis on preoperative ultrasonography, tumor location in the isthmus or upper third of the thyroid, larger tumor size, extrathyroid extension, lymphovascular invasion, and further lymph node metastasis. Multivariable analysis revealed that DLN metastasis was associated with tumor location in the isthmus or upper third of the thyroid (odds ratio [OR] = 2.420; 95 % confidence interval [CI] 1.193-4.910) and further lymph node metastasis (OR = 4.746; 95 % CI 2.065-10.908). **CONCLUSIONS:** DLN metastasis in PTC is associated with tumor location in the isthmus or upper third of the thyroid and unfavorable clinicopathological characteristics. Careful consideration and patient management are warranted when preoperative ultrasonography indicates that the tumor is located in the isthmus or upper third of the thyroid.

PubMed-ID: [24366273](https://pubmed.ncbi.nlm.nih.gov/24366273/)  
<http://dx.doi.org/10.1007/s00268-013-2406-x>

### **A Novel Method for the Management of Post-Thyroidectomy or Parathyroidectomy Hematoma: a Single-Institution Experience After Over 4,000 Central Neck Operations.**

*World J Surg*, 38(6):1262-7.

Dixon JL, Snyder SK, Lairmore TC, Jupiter D, Govednik C, Hendricks JC. 2014.

**BACKGROUND:** Cervical hematoma is a rare but serious complication of thyroid and parathyroid surgery that

has historically required inpatient monitoring. With improved surgical technique and experience, operations are being performed increasingly as outpatient procedures. Therefore, a safe and systematic approach to cervical exploration of a postoperative hematoma needs to be defined. METHODS: From 1996 to 2013, a retrospective review was performed of 4,140 thyroid and parathyroid operations. Surgical outcomes data were recorded, specifically including the occurrence of a cervical hematoma, time interval to presentation, and methods of management. RESULTS: A total of 18 patients (0.43 %) developed a postoperative cervical hematoma that required surgical intervention. The occurrence of hematoma was 0.66 % (n = 11) for bilateral thyroid procedures, 0.21 % (n = 3) for unilateral thyroid procedures, and 0.13 % (n = 1) for parathyroid procedures. There were 3 (1.69 %) patients who had combined unilateral thyroid and parathyroid procedures and developed hematomas. Emergent bedside decompression was required for only two patients, both of whom suffered respiratory arrest in the postoperative anesthesia recovery unit. The remaining 16 patients were explored in the operating room, utilizing initial local anesthesia in the semi-upright position in 11 patients (69 %). CONCLUSIONS: From our experience, hematomas that caused significant airway compromise leading to respiratory arrest occurred in the postoperative anesthesia recovery room, and hematoma presentation after this time did not require emergent bedside decompression. Hematoma, when it occurs, can otherwise be managed safely in the operating room after inpatient or outpatient procedures using initial local anesthesia with the patient in the semi-upright position for hematoma evacuation.

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<http://dx.doi.org/10.1007/s00268-013-2425-7>

#### **Update: the Status of Clinical Trials With Kinase Inhibitors in Thyroid Cancer.**

*J Clin Endocrinol Metab*, 99(5):1543-55.

Wells SA, Jr., Santoro M. 2014.

CONTEXT: Thyroid cancer is usually cured by timely thyroidectomy; however, the treatment of patients with advanced disease is challenging because their tumors are mostly unresponsive to conventional therapies. Recently, the malignancy has attracted much interest for two reasons: the dramatic increase in its incidence over the last three decades, and the discovery of the genetic mutations or chromosomal rearrangements causing most histological types of thyroid cancer. OBJECTIVE: This update reviews the molecular genetics of thyroid cancer and the clinical trials evaluating kinase inhibitors (KIs) in patients with locally advanced or metastatic disease. The update also reviews studies in other malignancies, which have identified mechanisms of efficacy, and also resistance, to specific KIs. This information has been critical both to the development of effective second-generation drugs and to the design of combinatorial therapeutic regimens. Finally, the update addresses the major challenges facing clinicians who seek to develop more effective therapy for patients with thyroid cancer. RESULTS: PubMed was searched from January 2000 to November 2013 using the following terms: thyroid cancer, treatment of thyroid cancer, clinical trials in thyroid cancer, small molecule therapeutics, kinase inhibitors, and next generation sequencing. CONCLUSIONS: A new era in cancer therapy has emerged based on the introduction of KIs for the treatment of patients with liquid and solid organ malignancies. Patients with thyroid cancer have benefited from this advance and will continue to do so with the development of drugs having greater specificity and with the implementation of clinical trials of combined therapeutics to overcome drug resistance.

PubMed-ID: [24423326](https://pubmed.ncbi.nlm.nih.gov/24423326/)

<http://dx.doi.org/10.1210/jc.2013-2622>

#### **TERT Promoter Mutations Are a Major Indicator of Poor Outcome in Differentiated Thyroid Carcinomas.**

*J Clin Endocrinol Metab*, 99(5):E754-E765.

Melo M, da Rocha AG, Vinagre J, Batista R, Peixoto J, Tavares C, Celestino R, Almeida A, Salgado C, Eloy C, Castro P, Prazeres H, Lima J, Amaro T, Lobo C, Martins MJ, Moura M, Cavaco B, Leite V, Cameselle-Teijeiro JM, Carrilho F, Carvalheiro M, Maximo V, Sobrinho-Simoes M, Soares P. 2014.

CONTEXT: Telomerase promoter mutations (TERT) were recently described in follicular cell-derived thyroid carcinomas (FCDC) and seem to be more prevalent in aggressive cancers. OBJECTIVES: We aimed to evaluate the frequency of TERT promoter mutations in thyroid lesions and to investigate the prognostic significance of such mutations in a large cohort of patients with differentiated thyroid carcinomas (DTCs). DESIGN: This was a retrospective observational study. SETTING AND PATIENTS: We studied 647 tumors and tumor-like lesions. A total of 469 patients with FCDC treated and followed in five university hospitals were included. Mean follow-up (+/-SD) was 7.8 +/- 5.8 years. MAIN OUTCOME MEASURES: Predictive value of TERT promoter mutations for distant metastasization, disease persistence at the end of follow-up, and disease-specific mortality. RESULTS: TERT promoter mutations were found in 7.5% of papillary carcinomas (PTCs), 17.1% of follicular carcinomas, 29.0% of poorly differentiated carcinomas, and 33.3% of anaplastic thyroid carcinomas. Patients with TERT-mutated tumors were older (P < .001) and had larger tumors (P = .002). In

DTCs, TERT promoter mutations were significantly associated with distant metastases ( $P < .001$ ) and higher stage ( $P < .001$ ). Patients with DTC harboring TERT promoter mutations were submitted to more radioiodine treatments ( $P = .009$ ) with higher cumulative dose ( $P = .004$ ) and to more treatment modalities ( $P = .001$ ). At the end of follow-up, patients with TERT-mutated DTCs were more prone to have persistent disease ( $P = .001$ ). TERT promoter mutations were significantly associated with disease-specific mortality [in the whole FCDTC ( $P < .001$ )] in DTCs ( $P < .001$ ), PTCs ( $P = .001$ ), and follicular carcinomas ( $P < .001$ ). After adjusting for age at diagnosis and gender, the hazard ratio was 10.35 (95% confidence interval 2.01-53.24;  $P = .005$ ) in DTC and 23.81 (95% confidence interval 1.36-415.76;  $P = .03$ ) in PTCs. CONCLUSIONS: TERT promoter mutations are an indicator of clinically aggressive tumors, being correlated with worse outcome and disease-specific mortality in DTC. TERT promoter mutations have an independent prognostic value in DTC and, notably, in PTC.

PubMed-ID: [24476079](https://pubmed.ncbi.nlm.nih.gov/24476079/)

<http://dx.doi.org/10.1210/jc.2013-3734>

### **Barriers to Same-Day Discharge of Patients Undergoing Total and Completion Thyroidectomy.**

*Otolaryngol Head Neck Surg*, 150(5):770-4.

Rutledge J, Siegel E, Belcher R, Bodenner D, Stack BC, Jr. 2014.

OBJECTIVE: Describe barriers to same-day surgery for patients undergoing total and completion thyroidectomy. STUDY DESIGN: Case series with chart review. SETTING: Academic health sciences center. SUBJECTS AND METHODS: The subjects were patients who underwent total thyroidectomy or completion thyroidectomy and remained in hospital overnight or longer. A review was performed on patients who were operated on by a single surgeon from July 2005 through June 2013. RESULTS: Two hundred and sixty-eight cases were planned for same-day surgery. One hundred patients were not discharged on the same day (37%). Patients observed overnight or admitted to hospital had significantly lower postoperative calcium levels, 8.4 mg/dL ( $P < .0001$ ), and lower intraoperative parathyroid hormone (PTH), mean 6.0 pg/mL ( $P < .0001$ ). Those significantly more likely to require overnight observation were male patients ( $P = .0117$ ), black patients ( $P = .0045$ ), those with completion thyroidectomy ( $P = .0039$ ), and those with a complication of surgery ( $P = .003$ ). CONCLUSION: Intraoperative PTH less than 10 pg/mL was the most frequent factor (25.7%) precluding same-day discharge, followed by admission for social/financial/transportation reasons (22.6%), large dead space from goiter (15.5%), multiple comorbidities (13.4%), multiple surgical reasons (5.2%), airway observation (5.2%), pain management (3.1%), and intractable nausea due to general anesthetic (2.1%). Hypocalcemia and postoperative bleeding still remain obstacles to outpatient thyroid surgery; however, the use of rapid PTH testing, modern hemostatic techniques, appropriate calcium prophylaxis, and experienced clinical decision making can effectively stratify which patients require overnight observation.

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<http://dx.doi.org/10.1177/0194599814521568>

### **Costs of Outpatient Thyroid Surgery From the University HealthSystem Consortium (UHC) Database.**

*Otolaryngol Head Neck Surg*, 150(5):762-9.

Marino M, Spencer H, Hohmann S, Bodenner D, Stack BC, Jr. 2014.

OBJECTIVE: To compare the cost of same-day vs 23-hour observation outpatient thyroidectomy at US academic medical centers. STUDY DESIGN: Cross-sectional analysis of a national database. SETTING: The University HealthSystem Consortium (UHC) data collected from discharge summaries. SUBJECTS AND METHODS: Discharge data were collected from the first quarter of 2009 through the second quarter of 2013. The UHC database, compiled from more than 200 affiliated hospitals, was searched based on diagnosis codes for outpatient thyroid procedures. Cost data, calculated based on reported charges, were collected in addition to demographics. Comparisons were made between same-day vs 23-hour observation based on cost. Additional stratification was performed based on the extent of thyroidectomy. RESULTS: During the study period, 49,936 outpatient thyroidectomies were performed. Overnight observation (63%) was more common than same-day discharge (37%). The overall mean cost of outpatient thyroidectomy was \$5617, with a mean cost of same-day surgery of \$4642 compared with \$6101 for overnight observation ( $P < .0001$ ). When stratifying by extent of thyroidectomy, the cost of same-day surgery was consistently lower than that for overnight observation. CONCLUSION: Outpatient thyroidectomy is commonly performed in the United States. It is most commonly performed on a 23-hour overnight observation basis. Overnight stay and complications were chief among other factors associated with higher cost, independent of the type of thyroid procedure performed. In appropriately selected patients, same-day thyroidectomy is a safe and cost-effective alternative to overnight observation or inpatient thyroid procedures.

PubMed-ID: [24496743](https://pubmed.ncbi.nlm.nih.gov/24496743/)

<http://dx.doi.org/10.1177/0194599814521583>

### **Long-Term Sensory Disturbance and Discomfort After Robotic Thyroidectomy.**

*World J Surg*, 38(7):1743-8.

Song CM, Ji YB, Bang HS, Park CW, Kim H, Tae K. 2014.

**BACKGROUND:** The aim of this study was to compare short-term and long-term sensory disturbance and discomfort after robotic thyroidectomy versus conventional open thyroidectomy. **METHODS:** We compared 118 patients who underwent robotic thyroidectomy by a gasless unilateral axillobreast (GUAB) or axillary (GUA) approach with 176 patients who underwent conventional open thyroidectomy from April 2009 to June 2011.

Postoperative hypesthesia/paresthesia and discomfort of the neck and anterior chest were evaluated regularly for 1.5 years using a questionnaire with a scale from 0 to 4. **RESULTS:** There were no differences in neck discomfort or hypesthesia/paresthesia between the two groups. Neck discomfort and hypesthesia/paresthesia returned to preoperative levels by postoperative years 1.0 and 1.5, respectively, in both groups. Anterior chest discomfort and paresthesia/hypesthesia were higher in the robotic group than the open group. They returned to preoperative levels by postoperative year 1 in the robotic group and within 3 months in the open group.

**CONCLUSIONS:** Long-term sensory disturbance and discomfort of the neck does not differ between robotic thyroidectomy and conventional open thyroidectomy. However, anterior chest discomfort and sensory disturbance are greater and require longer times to recover after robotic thyroidectomy. Minimizing dissection of the anterior chest should be considered to reduce discomfort and sensory disturbance after robotic thyroidectomy by a GUAB/GUA approach.

PubMed-ID: [24510245](https://pubmed.ncbi.nlm.nih.gov/24510245/)

<http://dx.doi.org/10.1007/s00268-014-2456-8>

### **Follicular Thyroid Cancers Demonstrate Dual Activation of PKA and MTOR As Modeled by Thyroid-Specific Deletion of Prkar1a and Pten in Mice.**

*J Clin Endocrinol Metab*, 99(5):E804-E812.

Pringle DR, Vasko VV, Yu L, Manchanda PK, Lee AA, Zhang X, Kirschner JM, Parlow AF, Saji M, Jarjoura D, Ringel MD, La Perle KM, Kirschner LS. 2014.

**CONTEXT:** Thyroid cancer is the most common form of endocrine cancer, and it is a disease whose incidence is rapidly rising. Well-differentiated epithelial thyroid cancer can be divided into papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC). Although FTC is less common, patients with this condition have more frequent metastasis and a poorer prognosis than those with PTC. **OBJECTIVE:** The objective of this study was to characterize the molecular mechanisms contributing to the development and metastasis of FTC. **DESIGN:** We developed and characterized mice carrying thyroid-specific double knockout of the Prkar1a and Pten tumor suppressor genes and compared signaling alterations observed in the mouse FTC to the corresponding human tumors. **SETTING:** The study was conducted at an academic research laboratory. Human samples were obtained from academic hospitals. **PATIENTS:** Deidentified, formalin-fixed, paraffin-embedded (FFPE) samples were analyzed from 10 control thyroids, 30 PTC cases, five follicular variant PTC cases, and 10 FTC cases.

**INTERVENTIONS:** There were no interventions. **MAIN OUTCOME MEASURES:** Mouse and patient samples were analyzed for expression of activated cAMP response element binding protein, AKT, ERK, and mammalian target of rapamycin (mTOR). Murine FTCs were analyzed for differential gene expression to identify genes associated with metastatic progression. **RESULTS:** Double Prkar1a-Pten thyroid knockout mice develop FTC and recapitulate the histology and metastatic phenotype of the human disease. Analysis of signaling pathways in FTC showed that both human and mouse tumors exhibited strong activation of protein kinase A and mTOR. The development of metastatic disease was associated with the overexpression of genes required for cell movement. **CONCLUSIONS:** These data imply that the protein kinase A and mTOR signaling cascades are important for the development of follicular thyroid carcinogenesis and may suggest new targets for therapeutic intervention.

Mouse models paralleling the development of the stages of human FTC should provide important new tools for understanding the mechanisms of FTC development and progression and for evaluating new therapeutics.

PubMed-ID: [24512487](https://pubmed.ncbi.nlm.nih.gov/24512487/)

<http://dx.doi.org/10.1210/jc.2013-3101>

### **Refining Calcium Test for the Diagnosis of Medullary Thyroid Cancer: Cutoffs, Procedures, and Safety.**

*J Clin Endocrinol Metab*, 99(5):1656-64.

Mian C, Perrino M, Colombo C, Cavedon E, Pennelli G, Ferrero S, De LS, Sarais C, Cacciatore C, Manfredi GI, Verga U, Iacobone M, De PL, Pelizzo MR, Vicentini L, Persani L, Fugazzola L. 2014.

**CONTEXT:** Calcitonin (CT) measurement is crucial to the early diagnosis and the follow-up of medullary thyroid cancer (MTC). If the evaluation of stimulated CT levels is required, a provocative test can be performed, being the high-dose Ca test recently reintroduced in clinical practice. **OBJECTIVE:** Our objective was to identify gender-specific thresholds for MTC diagnosis in a large series of patients who underwent the Ca test.

**PATIENTS AND METHODS:** A total of 91 patients (49 females and 42 males) underwent the Ca test (calcium

gluconate, 25 mg/kg) before thyroidectomy and both basal CT (bCT) and stimulated CT (sCT) were compared with histological results by receiver operating characteristic plot analyses. To evaluate possible side effects of Ca administration, cardiac function has been extensively studied. RESULTS: bCT levels were found to harbor the same accuracy as sCT in the preoperative diagnosis of MTC. The best Ca thresholds for the identification of MTC were >26 and >68 for bCT and >79 and >544 pg/mL for sCT in females and males, respectively. The high tolerability and safety of the Ca test was demonstrated and advice offered to be followed before and during the test. CONCLUSIONS: Gender-specific bCT and sCT cutoffs for the identification of C-cell hyperplasia and/or MTC have been defined. The bCT and sCT were found to have a similar accuracy, indicating that serum CT assays with improved functional sensitivity may likely decrease the relevance of the stimulation test in several conditions. Finally, systematic cardiac monitoring confirms the safety of the Ca test.

PubMed-ID: [24552221](https://pubmed.ncbi.nlm.nih.gov/24552221/)

<http://dx.doi.org/10.1210/jc.2013-4088>

### **Genome-Wide Copy Number Analysis in a Family With P.G533C RET Mutation and Medullary Thyroid Carcinoma Identified Regions Potentially Associated With a Higher Predisposition to Lymph Node Metastasis.**

*J Clin Endocrinol Metab*, 99(6):E1104-E1112.

Araujo AN, Moraes L, Franca MI, Hakonarson H, Li J, Pellegrino R, Maciel RM, Cerutti JM. 2014.

CONTEXT: Our group described a p.G533C RET gene mutation in a large family with multiple endocrine neoplasia type 2 syndrome. Clinical heterogeneity, primarily associated with the presence of lymph node metastases, was observed among the p.G533C carriers. OBJECTIVE: The aim of this study was to use single-nucleotide polymorphism-array technology to identify copy number variations (CNVs), which are present in the constitutional DNA and associated with the established clinical and pathological features of aggressive medullary thyroid carcinoma (MTC), primarily the presence of lymph node metastasis. DESIGN: Fifteen p.G533C carriers with MTC were chosen for the initial screening. The subjects were divided into two groups according the presence (n = 8) or absence (n = 7) of lymph node metastasis. Peripheral blood DNA was independently hybridized using a genome-wide single-nucleotide polymorphism Array 6.0 platform. The results were analyzed using both Genotyping Console and PennCNV software. To identify the possible candidate regions associated with the presence of lymph node metastasis, cases (metastatic MTC) were compared with controls (nonmetastatic MTC). The identified CNVs were validated by quantitative PCR in an extended cohort (n = 32). RESULTS: Using two different algorithms, we identified nine CNV regions that may contribute to susceptibility to lymph node metastasis. The validation step confirmed that a CNV loss impacting the FMN2 gene was potentially associated with a greater predisposition to lymph node metastasis in this family (P = .0179). Finally, we sought to investigate whether the development of lymph node metastasis might not depend on a single CNV but rather a combination of various CNVs. These analyses defined a CNV pattern related to a more aggressive phenotype in this family, with CNV deletions being enriched in the metastatic group (P = .0057). CONCLUSION: Although heritable specific RET mutations are important to determine cancer risk, germline CNVs in disease-affected individuals may predispose them to MTC aggressiveness.

PubMed-ID: [24601688](https://pubmed.ncbi.nlm.nih.gov/24601688/)

<http://dx.doi.org/10.1210/jc.2013-2993>

### **Low-Activity (124)I-PET/Low-Dose CT Versus (131)I Probe Measurements in Pretherapy Assessment of Radioiodine Uptake in Benign Thyroid Diseases.**

*J Clin Endocrinol Metab*, 99(6):2138-45.

Westphal JG, Winkens T, Kuhnelt C, Freesmeyer M. 2014.

CONTEXT: Radioiodine therapy of benign thyroid diseases requires pretherapy assessment of radioactive iodine uptake (RAIU) for reliable therapy planning. OBJECTIVE: Our objective was to assess RAIU by low-activity (124)I-positron emission tomography/low-dose computed tomography ((124)I-PET/CT) in comparison with standard (131)I probe measurements. DESIGN/SETTING: This prospective comparative study was conducted at the Jena University Hospital, Jena, Germany, in a referral center setting. PATIENTS: A total of 79 patients with benign thyroid diseases were screened, 40 of whom met the inclusion criteria (stable TSH, free T3 and free T4 levels; no thyroid-specific medication, no iodine contamination) and 24 of whom agreed to participate by signing an informed consent. INTERVENTIONS: All patients received the standard (131)I scintillation probe uptake test 30 hours after administration of 3 MBq (131)I. Seven days later, all patients were subjected to (124)I-PET/CT uptake measurement 30 hours after administration of 1 MBq (124)I. MAIN OUTCOME MEASURES: The decay-corrected uptake values of both techniques were compared. Additionally, 3 different volume-of-interest-based evaluation methods in PET/CT (whole neck [WN], automatic isocontour [IC], and manually contoured [MC]) were evaluated. RESULTS: The (131)I probe measurement and (124)I-PET.WN method provided very similar mean RAIU (30.7% +/- 10.3%; 31.7% +/- 8.9%), resulting in a significant positive correlation (r = 0.93, P < .001).

Compared with (124)I-PET.WN, the (124)I-PET.IC (29.8% +/- 8.6%) and the (124)I-PET.MC (24.5% +/- 7.1%) demonstrated lower uptake values. CONCLUSIONS: Using activities as low as 1 MBq, the (124)I-PET.WN method shows a good correlation with conventional (131)I probe measurement. Thus, (124)I-PET/CT is a suitable alternative for pretherapy RAIU evaluations. This may offer potential additional benefits such as PET/ultrasound fusion imaging and CT volumetry.

PubMed-ID: [24606104](https://pubmed.ncbi.nlm.nih.gov/24606104/)

<http://dx.doi.org/10.1210/jc.2013-4390>

### **Clinical Significance of the BRAF V600E Mutation in Multifocal Papillary Thyroid Carcinoma in Korea.**

*Surgery*, 155(4):689-95.

Ahn HY, Chung YJ, Kim BS, Kang KH, Seok JW, Kim HS, Park SJ, Cho BY. 2014.

BACKGROUND: We examined the frequency of the BRAF(V600E) mutation and compared the clinicopathologic features based on the BRAF(V600E) mutation status in multifocal papillary thyroid carcinoma (PTC). METHODS: A total 85 patients who were diagnosed with multifocal PTC were enrolled. We confirmed the status of the BRAF(V600E) mutation in each tumor focus by the real-time polymerase chain reaction technique. RESULTS: Among the 85 patients, 49 (57.6%), 34 (40.0%), and 2 (2.4%) patients were determined to have all BRAF(V600E)-positive, mixed BRAF(V600E), and all BRAF(V600E)-negative in their tumor foci, respectively. When we compared clinicopathologic features according to the BRAF(V600E) mutation status of the dominant tumor, the BRAF(V600E) -positive group (n = 70) showed more extrathyroidal invasion in the dominant tumor (32.9% vs 6.7%, P = .041) and more lymph node metastasis (67.2% vs 40.0%, P = .049) than the BRAF(V600E) -negative group (n = 15). Considering all tumor foci, the all BRAF(V600E) mutation group exhibited a younger population (P = .039), showed increased extrathyroidal invasion (38.8% vs 14.7%, P = .017) and lymph node metastasis (71.4% vs 48.4%, P = .038), and received more radioactive iodine therapy (79.2% vs 52.9%, P = .012) than the mixed BRAF(V600E) mutation group. A larger tumor size and heavier preoperative body weight was positively correlated with the relative expression of BRAF(V600E) mutation calculated by 2(- big up tri, open big up tri, openCt) method. CONCLUSION: Most of the Korean patients with multifocal PTC had the BRAF(V600E) mutation in one or more tumor foci, and all BRAF(V600E)-positive multifocal PTC showed more aggressive features.

PubMed-ID: [24612623](https://pubmed.ncbi.nlm.nih.gov/24612623/)

<http://dx.doi.org/10.1016/j.surg.2013.12.025>

### **Novel Thyroidectomy Difficulty Scale Correlates With Operative Times.**

*World J Surg*, 38(8):1984-9.

Schneider DF, Mazeh H, Oltmann SC, Chen H, Sippel RS. 2014.

BACKGROUND: The aim of this study was to evaluate a new thyroidectomy difficulty scale (TDS) for its inter-rater agreement, correspondence with operative times, and correlation with complications. METHODS: We developed a four item, 20-point TDS. Following cases where two board-certified surgeons participated, each surgeon completed a TDS, blinded to the other's responses. Paired sets of TDS scores were compared. The relationship between operative time and TDS scores was analyzed with linear regression. Multiple regression evaluated the association of TDS scores and other clinical data with operative times. RESULTS: A total of 119 patients were scored using TDS. In this cohort, 22.7% suffered from hyperthyroidism, 37.8% experienced compressive symptoms, and 58.8% had cancer. The median total TDS score was 8, and both surgeons' total scores exhibited a high degree of correlation. Overall, 87.4% of the two raters' total scores were within one point of each other. Patients with hyperthyroidism received higher median scores than euthyroid patients (10 vs. 8, p < 0.01). Similarly, patients who suffered a complication had higher scores than those without complications (10 vs. 8, p = 0.04). TDS scores demonstrated a linear relation with operative times (R<sup>2</sup> = 0.36, p < 0.01). Cases with a score of >=14 took 41.0% longer compared to cases with scores of <=5 (p < 0.01). In the multiple regression analysis, TDS scores independently predicted the operative time (p < 0.01). CONCLUSION: The TDS is an accurate tool whose scores correlate with more difficult thyroidectomies as measured by complications and operative times.

PubMed-ID: [24615607](https://pubmed.ncbi.nlm.nih.gov/24615607/)

<http://dx.doi.org/10.1007/s00268-014-2489-z>

### **Incidental Thyroid Nodules: Incidence, Evaluation, and Outcome.**

*Otolaryngol Head Neck Surg*, 150(6):939-42.

Chaikhoutdinov I, Mitzner R, Goldenberg D. 2014.

OBJECTIVE: To examine patients with incidentally discovered thyroid nodules (IDTNs) with a focus on identification, evaluation, surgical intervention, and rates of malignancy. STUDY DESIGN: Case series with chart review. SETTING: Tertiary care medical center. SUBJECTS AND METHODS: A total of 1408 patients were

identified by cross-referencing thyroid diagnosis codes with ultrasound (US) codes between July 2008 and June 2009. Information regarding demographics, follow-up, and outcomes was extracted from the medical record. RESULTS: A total of 249 patients with IDTNs were identified. Most were discovered on computed tomography (CT) scans (59.8%); the most common indication for obtaining imaging was for evaluation of an unrelated malignancy (26.9%). Malignant IDTNs were identified on 23.8% of positron emission tomography/CT scans and 6.8% of CT scans. Initial evaluation of IDTNs was performed by US in 62.2% and by US with fine-needle aspiration (FNA) in 36.1% of patients. The most common pathology on FNA of IDTNs was benign follicular nodule (64.1%) followed by papillary thyroid cancer (PTC; 13.5%); however, 31.7% of all cytology indicated suspicion for malignancy. Fifty-five patients (22.1%) were treated surgically. On final surgical pathology, 33 malignancies were present, of which 28 were PTC. The overall malignancy rate for incidental thyroid nodules was 13.3%. CONCLUSION: We identified a malignancy of at least 13.3% in IDTNs, reaffirming that IDTNs should undergo thorough workup.

PubMed-ID: [24618501](https://pubmed.ncbi.nlm.nih.gov/24618501/)

<http://dx.doi.org/10.1177/0194599814524705>

### **Development and Characterization of a Differentiated Thyroid Cancer Cell Line Resistant to VEGFR-Targeted Kinase Inhibitors.**

*J Clin Endocrinol Metab*, 99(6):E936-E943.

Isham CR, Netzel BC, Bossou AR, Milosevic D, Cradic KW, Grebe SK, Bible KC. 2014.

BACKGROUND: Vascular endothelial growth factor-targeted kinase inhibitors have emerged as highly promising therapies for radioiodine-refractory metastatic differentiated thyroid cancer. Unfortunately, drug resistance uniformly develops, limiting their therapeutic efficacies and thereby constituting a major clinical problem.

APPROACH AND METHODS: To study acquired drug resistance and elucidate underlying mechanisms in this setting, BHP2-7 human differentiated thyroid cancer cells were subjected to prolonged continuous in vitro selection with 18  $\mu$ M pazopanib, a clinically relevant concentration; acquisition of pazopanib resistance was serially assessed, with the resulting resistant cells thereafter subcloned and characterized to assess potential mechanisms of acquired pazopanib resistance. RESULTS: Stable 2- to 4-fold in vitro pazopanib resistance emerged in response to pazopanib selection associated with similar in vitro growth characteristics but with markedly more aggressive in vivo xenograft growth. Selected cells were cross-resistant to sunitinib and to a lesser extent sorafenib but not to MAPK kinase (MEK1/2) inhibition by GSK1120212. Genotyping demonstrated acquisition of a novel activating KRAS codon 13 GGC to GTT (glycine to valine) mutation, consistent with the observed resistance to upstream vascular endothelial growth factor receptor inhibition yet sensitivity to downstream MAPK kinase (MEK1/2) inhibition. CONCLUSIONS: Selection of thyroid cancer cells with clinically utilized therapeutics can lead to acquired drug resistance and altered in vivo xenograft behavior that can recapitulate analogous drug resistance observed in patients. This approach has the potential to lead to insights into acquired treatment-related drug resistance in thyroid cancers that can be subjected to subsequent validation in serially collected patient samples and that has the potential to yield preemptive and responsive approaches to dealing with this important clinical problem.

PubMed-ID: [24628546](https://pubmed.ncbi.nlm.nih.gov/24628546/)

<http://dx.doi.org/10.1210/jc.2013-2658>

### **Role of Salvage Targeted Therapy in Differentiated Thyroid Cancer Patients Who Failed First-Line Sorafenib.**

*J Clin Endocrinol Metab*, 99(6):2086-94.

Dadu R, Devine C, Hernandez M, Waguespack SG, Busaidy NL, Hu MI, Jimenez C, Habra MA, Sellin RV, Ying AK, Cote GJ, Sherman SI, Cabanillas ME. 2014.

CONTEXT: Sorafenib, a tyrosine kinase inhibitor, is a common first-line therapy for advanced differentiated thyroid cancer (DTC). However, responses are not durable and drug toxicity remains a problem. OBJECTIVE: The objective of the study was to determine the efficacy of salvage therapy after first-line sorafenib failure. DESIGN: This was a retrospective review at M. D. Anderson Cancer Center from January 2005 to May 2013. PATIENTS: The study included patients with metastatic DTC who received salvage therapy after their initial sorafenib failure (group 2). PATIENTS who received first-line sorafenib only (group 1) were evaluated for comparison of overall survival (OS). OUTCOME MEASURES: Progression-free survival, best response, and median OS were measured. RESULTS: Sixty-four patients with metastatic, radioactive iodine refractory DTC were included; 35 were in group 1 and 25 were in group 2, and the groups were well balanced. Median OS of all 64 patients receiving first line sorafenib was 37 months; median OS was significantly longer with salvage therapy compared with sorafenib alone (58 vs 28 months,  $P = .013$ ). In group 2, 17 patients were evaluable for best response, although two patients had toxicity with sorafenib, which was discontinued before restaging. Best responses with first-line sorafenib were partial response in 2 of 15 (13%), stable disease in 10 of 15 (67%), and

progressive disease in 3 of 15 (20%) patients. With salvage therapy, partial responses were seen in 7 of 17 (41%) and stable disease in 10 of 17 (59%) patients. Median progression-free survival was 7.4 months with first-line sorafenib and 11.4 months with salvage therapy. Salvage therapy included sunitinib (n = 4), pazopanib (n = 3), cabozantinib (n = 4), lenvatinib (n = 3), and vemurafenib (n = 3). CONCLUSIONS: Other targeted agents are effective salvage treatments after sorafenib failure, despite similar mechanisms of action, and should be offered to patients who are able to receive salvage therapy.

PubMed-ID: [24628550](https://pubmed.ncbi.nlm.nih.gov/24628550/)

<http://dx.doi.org/10.1210/jc.2013-3588>

### **Multinodular Goiter in Children: an Important Pointer to a Germline DICER1 Mutation.**

*J Clin Endocrinol Metab*, 99(6):1947-8.

Rath SR, Bartley A, Charles A, Powers N, Baynam G, Jones T, Priest JR, Foulkes WD, Choong CS. 2014.

PubMed-ID: [24628552](https://pubmed.ncbi.nlm.nih.gov/24628552/)

<http://dx.doi.org/10.1210/jc.2013-3932>

### **A Nomogram for Predicting Malignancy in Thyroid Nodules Diagnosed As Atypia of Undetermined Significance/Follicular Lesions of Undetermined Significance on Fine Needle Aspiration.**

*Surgery*, 155(6):1006-13.

Yoon JH, Lee HS, Kim EK, Moon HJ, Kwak JY. 2014.

BACKGROUND: We hypothesized that a nomogram constructed of clinical and imaging variables could be applied to predicting the risk of malignancy in thyroid nodules diagnosed as atypia of undetermined significance/follicular lesions of undetermined significance (AUS/FLUS) on ultrasonographic fine-needle aspiration (US-FNA). METHODS: This retrospectively designed study included 393 thyroid nodules in 392 patients (mean age, 49 +/- 12 years), which were diagnosed as AUS/FLUS with US-FNA during the study period. Medical records, US images, and cytopathology results were reviewed and analyzed. The 393 thyroid nodules were divided into training and validation sets. Logistic regression analysis was performed to predict the probability of malignancy, and nomograms were constructed using the training set and subsequently applied to the validation set. RESULTS: Three sets of nomograms were constructed separately using clinical factors and (1) individual US features; (2) final assessment of US; and (3) the number of suspicious US features. All 3 sets of nomograms built were proven accurate and discriminative, these nomograms had an area under the receiver operating characteristic curve (AUC) of 0.817 (95% confidence interval [CI], 0.757-0.877) when using clinical factors and individual US features, an AUC of 0.769 (95% CI, 0.705-0.833) when using final assessment, and an AUC of 0.779 (95% CI, 0.718-0.840) when using the number of suspicious US features. The AUC of each validation set was 0.754 (95% CI, 0.659-0.850), 0.757 (95% CI, 0.661-0.853), and 0.721 (95% CI, 0.621-0.820), respectively. CONCLUSION: Nomograms constructed in our study using US can be utilized in predicting the probability of malignancy in thyroid nodules diagnosed as AUS/FLUS on US-FNA, and may help in selecting patients who are at high risk for malignancy.

PubMed-ID: [24630147](https://pubmed.ncbi.nlm.nih.gov/24630147/)

<http://dx.doi.org/10.1016/j.surg.2013.12.035>

### **Pemberton's Sign: Explained Nearly 70 Years Later.**

*J Clin Endocrinol Metab*, 99(6):1949-54.

De Filippis EA, Sabet A, Sun MR, Garber JR. 2014.

CONTEXT: Pemberton's sign is used to evaluate venous obstruction in patients with goiters. The sign is positive when bilateral arm elevation causes facial plethora. It has been attributed to a "cork effect" resulting from the thyroid obstructing the thoracic inlet, thereby increasing pressure on the venous system. According to some, the "cork effect" is caused by the thyroid descending into the thoracic inlet during arm elevation. According to others, the obstruction is due to elevation of the thoracic inlet against the thyroid. OBJECTIVE: We studied a 36-year-old man with a positive Pemberton's sign secondary to a goiter extending to the substernal region. DESIGN AND INTERVENTION: Clinical, biochemical, and radiological assessments were done. Magnetic resonance angiography of the neck was performed while the patient's arms were elevated and at his sides. After the imaging studies were completed, the patient underwent thyroidectomy. RESULTS: Magnetic resonance angiography demonstrated that there was no craniocaudal movement of the goiter relative to the thoracic inlet. However, the lateral aspect of the clavicle moved medially and inferiorly, obstructing the right external jugular vein and subclavian vein confluence. CONCLUSIONS: In the present case, we demonstrated that when eliciting Pemberton's sign, facial plethora and venous engorgement were due to the clavicles moving and compressing venous vasculature against the enlarged thyroid and not to a "cork effect." Rather, the clavicular motion observed during arm elevation could be compared to the movement of a "nutcracker" compressing major venous structures within a narrowed thoracic inlet against a relatively fixed and enlarged thyroid.

PubMed-ID: [24646105](https://pubmed.ncbi.nlm.nih.gov/24646105/)  
<http://dx.doi.org/10.1210/jc.2013-4240>

### **Post-Operative Neck Ultrasound and Risk Stratification in Differentiated Thyroid Cancer Patients With Initial Lymph Node Involvement.**

*Eur J Endocrinol*, 170(6):837-46.

Lepoutre-Lussey C, Maddah D, Golmard JL, Russ G, Tissier F, Tresallet C, Menegaux F, Aurengo A, Leenhardt L. 2014.

OBJECTIVE: Cervical ultrasound (US) scan is a key tool for detecting metastatic lymph nodes (N1) in patients with papillary thyroid cancer (PTC). N1-PTC patients are stratified as intermediate-risk and high-risk (HR) patients, according to the American Thyroid Association (ATA) and European Thyroid Association (ETA) respectively. The aim of this study was to assess the value of post-operative cervical US (POCUS) in local persistent disease (PD) diagnosis and in the reassessment of risk stratification in N1-PTC patients. DESIGN: Retrospective cohort study. METHODS: Between 1997 and 2010, 638 N1-PTC consecutive patients underwent a systematic POCUS. Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of POCUS for the detection of PD were evaluated and a risk reassessment using cumulative incidence functions was carried out. RESULTS: After a median follow-up of 41.6 months, local recurrence occurred in 138 patients (21.6%), of which 121 were considered to have PD. Sensitivity, specificity, NPV, and PPV of POCUS for the detection of the 121 PD were 82.6, 87.4, 95.6, and 60.6% respectively. Cumulative incidence of recurrence at 5 years was estimated at 26% in ETA HR patients, 17% in ATA intermediate-risk patients, and 35% in ATA HR patients respectively. This risk fell to 9, 8, and 11% in the above three groups when the POCUS result was normal and to <6% when it was combined with thyroglobulin results at ablation. CONCLUSION: POCUS is useful for detecting PD in N1-PTC patients and for stratifying individual recurrence risk. Its high NPV could allow clinicians to tailor follow-up recommendations to individual needs.

PubMed-ID: [24659355](https://pubmed.ncbi.nlm.nih.gov/24659355/)

<http://dx.doi.org/10.1530/EJE-13-0888>

### **Therapy of Endocrine Disease: Antithyroid Drug Use in Early Pregnancy and Birth Defects: Time Windows of Relative Safety and High Risk?**

*Eur J Endocrinol*, 171(1):R13-R20.

Laurberg P, Andersen SL. 2014.

BACKGROUND: Antithyroid drugs (ATDs) may have teratogenic effects when used in early pregnancy.

OBJECTIVE: To review the association between the time period of ATD exposure in early pregnancy and the development of birth defects. METHODS: We identified publications on birth defects after early pregnancy exposure to the ATDs methimazole (MMI; and its prodrug carbimazole (CMZ)) and propylthiouracil (PTU). Cases of birth defects after ATD treatment had been initiated or terminated within the first 10 weeks of pregnancy were identified and studied in detail. RESULTS: A total of 92 publications were read in detail. Two recent large controlled studies showed ATD-associated birth defects in 2-3% of exposed children, and MMI/CMZ-associated defects were often severe. Out of the total number of publications, 17 included cases of birth defects with early pregnancy stop/start of ATD treatment, and these cases suggested that the high risk was confined to gestational weeks 6-10, which is the major period of organogenesis. Thus, the cases reported suggest that the risk of birth defects could be minimized if pregnant women terminate ATD intake before gestational week 6. CONCLUSION: Both MMI and PTU use in early pregnancy may lead to birth defects in 2-3% of the exposed children. MMI-associated defects are often severe. Proposals are given on how to minimize the risk of birth defects in fertile women treated for hyperthyroidism with ATDs.

PubMed-ID: [24662319](https://pubmed.ncbi.nlm.nih.gov/24662319/)

<http://dx.doi.org/10.1530/EJE-14-0135>

### **Laser Ablation and 131-Iodine: a 24-Month Pilot Study of Combined Treatment for Large Toxic Nodular Goiter.**

*J Clin Endocrinol Metab*, 99(7):E1283-E1286.

Chianelli M, Bizzarri G, Todino V, Misischi I, Bianchini A, Graziano F, Guglielmi R, Pacella CM, Gharib H, Papini E. 2014.

CONTEXT: It is normally recognized that the preferred treatment in large toxic thyroid nodules should be thyroidectomy. OBJECTIVE: The aim of the study was to assess the efficacy of combined laser ablation treatment (LAT) and radioiodine 131 (131I) treatment of large thyroid toxic nodules with respect to rapidity of control of local symptoms, of hyperthyroidism, and of reduction of administered 131I activity in patients at refusal or with contraindications to surgery. DESIGN AND SETTING: We conducted a pilot study at a single center specializing in thyroid care. PATIENTS: Fifteen patients were treated with LAT, followed by 131I (group A), and a

series of matched consecutive patients were treated by 131I only (group B). INTERVENTION(S): Laser energy was delivered with an output power of 3 W (1800 J per fiber per treatment) through two 75-mm, 21-gauge spinal needles. Radioiodine activity was calculated to deliver 200 Gy to the hyperfunctioning nodule. MAIN OUTCOME MEASURE(S): Thyroid function, thyroid peroxidase antibody, thyroglobulin antibody, ultrasound, and local symptoms were measured at baseline and up to 24 months. RESULTS: Nodule volume reduction at 24 months was: 71.3 +/- 13.4 vs 47.4 +/- 5.5%, group A (LAT+131I) vs group B (131I), respectively; P < .001). In group A (LAT+131I), a reduction in radioiodine-administered activity was obtained (-21.1 +/- 8.1%). Local symptom score demonstrated a more rapid reduction in group A (LAT+131I). In three cases, no 131I treatment was needed after LAT. CONCLUSIONS: In this pilot study, combined LAT/131I treatment induced faster and greater improvement of local and systemic symptoms compared to 131I only. This approach seems a possible alternative to thyroidectomy in patients at refusal of surgery.

PubMed-ID: [24684455](https://pubmed.ncbi.nlm.nih.gov/24684455/)

<http://dx.doi.org/10.1210/jc.2013-2967>

### **Cost-Effectiveness of Molecular Testing for Thyroid Nodules With Atypia of Undetermined Significance Cytology.**

*J Clin Endocrinol Metab*, 99(8):2674-82.

Lee L, How J, Tabah RJ, Mitmaker EJ. 2014.

CONTEXT: Novel molecular diagnostics, such as the gene expression classifier (GEC) and gene mutation panel (GMP) testing, may improve the management for thyroid nodules with atypia of undetermined significance (AUS) cytology. The cost-effectiveness of an approach combining both tests in different practice settings in North America is unknown. OBJECTIVE: The aim of the study was to determine the cost-effectiveness of two diagnostic molecular tests, singly or in combination, for AUS thyroid nodules. DESIGN AND SETTING: We constructed a microsimulation model to investigate cost-effectiveness from US (Medicare) and Canadian healthcare system perspectives. PATIENTS: Low-risk patients with AUS thyroid nodules were simulated. INTERVENTIONS: We examined five management strategies: 1) routine GEC; 2) routine GEC + selective GMP; 3) routine GMP; 4) routine GMP + selective GEC; and 5) standard management. MAIN OUTCOME MEASURES: Lifetime costs and quality-adjusted life-years were measured. RESULTS: From the US perspective, the routine GEC + selective GMP strategy was the dominant strategy. From the Canadian perspective, routine GEC + selective GMP cost and additional CAN\$24 030 per quality-adjusted life-year gained over standard management, and was dominant over the other strategies. Sensitivity analyses reported that the decisions from both perspectives were sensitive to variations in the probability of malignancy in the nodule and the costs of the GEC and GMP. The probability of cost-effectiveness for routine GEC + selective GMP was low. CONCLUSIONS: In the US setting, the most cost-effective strategy was routine GEC + selective GMP. In the Canadian setting, standard management was most likely to be cost effective. The cost of these molecular diagnostics will need to be reduced to increase their cost-effectiveness for practice settings outside the United States.

PubMed-ID: [24684467](https://pubmed.ncbi.nlm.nih.gov/24684467/)

<http://dx.doi.org/10.1210/jc.2014-1219>

### **[Surgical Relevance of New Biomarkers in Papillary Carcinoma of the Thyroid] Chirurgische Relevanz Neuer Biomarker Beim Papillaren Schilddrusenkarzinom.**

*Chirurg*, 85(5):447.

Dralle H. 2014.

PubMed-ID: [24696317](https://pubmed.ncbi.nlm.nih.gov/24696317/)

<http://dx.doi.org/10.1007/s00104-014-2747-5>

### **In Search of an Unstimulated Thyroglobulin Baseline Value in Low-Risk Papillary Thyroid Carcinoma Patients Not Receiving Radioactive Iodine Ablation.**

*Thyroid*, 24(7):1127-33.

Angell TE, Spencer CA, Rubino BD, Nicoloff JT, LoPresti JS. 2014.

BACKGROUND: The clinical use of serum thyroglobulin (Tg) as a tumor marker in papillary thyroid cancer (PTC) patients following total thyroidectomy continues to evolve, due in part to the introduction of more sensitive (second generation) Tg immunometric assays (Tg(2G)IMA, functional sensitivity  $\leq$  0.10 ng/mL), and the implementation of new recommendations against radioactive iodine ablation (RAIA) for patients at the lowest risk of recurrence. As a result, there is a need to establish the optimal timing and interpretation of serum Tg values while on levothyroxine-induced suppression of thyrotropin (TSH) in thyroidectomized PTC patients with a thyroid remnant. This study examines the pattern of decline and eventual baseline value of unstimulated Tg (uTg) concentrations following total thyroidectomy in patients with low-risk PTC who did not receive RAIA. METHODS:

The medical records of consecutive patients with thyroid cancer seen at the Los Angeles County + USC Medical Center were retrospectively reviewed. Serial uTg and TSH values from Tg-antibody negative low-risk PTC patients treated with total thyroidectomy and no RAI were analyzed. Patients were stratified by degree of TSH suppression to assess the effect on uTg. Serial postoperative uTg values were evaluated for the temporal pattern of decline and ultimate baseline. Patients with medullary thyroid cancer (MTC) were studied as a surgical reference group. RESULTS: Records from 577 consecutive thyroid cancer patients were reviewed, of which 36 met all criteria for inclusion. By 6 months, uTg fell to <0.5 ng/mL in 61% of patients and all patients demonstrated uTg < 0.5 ng/mL 2 years after surgery. During a median follow up of 5.7 years, uTg values remained below this level. The median uTg values in patients with papillary microcarcinoma, PTC, and MTC were similar at 0.11, 0.12, and 0.09 ng/mL, respectively. Further decline in uTg was not observed once the TSH was <0.5 mIU/L. CONCLUSIONS: The uTg values during TSH suppression in Tg antibody-negative, low-risk PTC patients who did not receive RAI were below 0.5 ng/mL by 6 months postoperatively in most cases and remained stable over the duration of patient follow-up.

PubMed-ID: [24697314](https://pubmed.ncbi.nlm.nih.gov/24697314/)

<http://dx.doi.org/10.1089/thy.2013.0691>

### **Germline Alterations in *RASAL1* in Cowden Syndrome Patients Presenting With Follicular Thyroid Cancer and in Individuals With Apparently Sporadic Epithelial Thyroid Cancer.**

*J Clin Endocrinol Metab*, 99(7):E1316-E1321.

Ngeow J, Ni Y, Tohme R, Song CF, Bebek G, Eng C. 2014.

CONTEXT: *RASAL1* has recently been identified as an important tumor suppressor for sporadic thyroid tumorigenesis, particularly for follicular thyroid cancer (FTC) and anaplastic thyroid cancer. Thyroid cancer is an important component of Cowden syndrome (CS). Patients with germline *PTEN* mutations have an overrepresentation of FTC over other histological subtypes. OBJECTIVE: To determine the prevalence of germline *RASAL1* mutations in *PTEN* mutation-positive and wild type CS patients. SETTING AND DESIGN: We reviewed our prospective database of more than 3000 CS/CS-like patients and retrospectively identified a subset of patients who presented with thyroid cancer for *RASAL1* mutation analysis. We reviewed data from The Cancer Genome Atlas (TCGA) sporadic papillary thyroid cancer (PTC) database with germline data for *RASAL1* mutations to determine the prevalence of germline *RASAL1* mutations in CS-related thyroid cancer patients. RESULTS: We scanned 155 CS/CS-like patients with thyroid cancer for germline *RASAL1* mutations. Of the 155 patients, 39 had known germline pathogenic *PTEN* mutations (*PTEN*(mut+)) and 116 were *PTEN* mutation negative (*PTEN*(WT)). Among these 155 patients, we identified *RASAL1* germline alterations suspected as being deleterious in two patients. Both were patients with *PTEN*(WT) who had FTC (2/48, 4.1%). This was in contrast to patients with *PTEN*(mut+) who had thyroid cancer (0/39). Of 339 sporadic patients with PTC from the TCGA study, 62 (18%) had germline *RASAL1* variants predicted to be deleterious. TCGA patients with follicular-variant PTC were statistically overrepresented (21/62, 34%) among patients with deleterious *RASAL1* variants compared with those without (57/277, 21%). CONCLUSIONS: Germline *RASAL1* alterations are uncommon in patients with CS but may not be infrequent in patients with apparently sporadic follicular-variant PTC.

PubMed-ID: [24712574](https://pubmed.ncbi.nlm.nih.gov/24712574/)

<http://dx.doi.org/10.1210/jc.2014-1225>

### **Treatment Approach, Surveillance, and Outcome of Well-Differentiated Thyroid Cancer in Childhood and Adolescence.**

*Thyroid*, 24(7):1121-6.

Markovina S, Grigsby PW, Schwarz JK, DeWees T, Moley JF, Siegel BA, Perkins SM. 2014.

BACKGROUND: Well-differentiated thyroid carcinoma in children and adolescents is a rare disease with favorable prognosis despite regional and distant metastasis at presentation in many patients. Treatment recommendations are varied and there is little consensus on follow-up guidelines for these patients. METHODS: Medical records of patients less than 22 years of age treated at our institution were reviewed. One hundred twelve patients treated between 1969 and 2009 were selected for further analysis. Effects of patient and tumor characteristics on progression-free survival (PFS) were evaluated along with the predictive value of whole-body (131)I scintigraphy in the follow-up setting. RESULTS: Overall survival at 20 years and 30 years was 100% and 94.4%, respectively. PFS at 10, 20, and 30 years was 71%, 62%, and 55%, respectively. Although male patients and younger patients presented with more advanced disease, sex, and age at diagnosis had no effect on risk of PFS. Additionally, neither the presence of vascular invasion, capsular extension, positive margins, nor soft tissue invasion had an effect on PFS. Mean time to recurrence in patients who underwent immediate postoperative (131)I therapy was 3.8 years compared to 14.1 years in patients who either never received (131)I therapy or were treated in the salvage setting ( $p < 0.0001$ ). Negative posttreatment whole-body (131)I scintigraphy was strongly predictive for decreased risk of recurrence, especially in patients with three consecutive negative scans.

CONCLUSIONS: Pediatric patients are more likely to present with advanced disease and for this reason, the majority of patients treated at our institution receive postoperative (131)I. Long-term surveillance is required in this population because of the risk of late recurrences. Whole-body (131)I scintigraphy is useful for risk stratification; after three consecutive negative scans, the risk of recurrence is low.

PubMed-ID: [24731094](https://pubmed.ncbi.nlm.nih.gov/24731094/)

<http://dx.doi.org/10.1089/thy.2013.0297>

#### **A NSQIP Risk Assessment for Thyroid Surgery Based on Comorbidities.**

*J Am Coll Surg*, 218(6):1231-7.

Abraham CR, Ata A, Carsello CB, Chan TL, Stain SC, Beyer TD. 2014.

BACKGROUND: Thyroid surgery is associated with low mortality and morbidity and often is performed in an ambulatory setting. The majority of patients undergoing thyroidectomy have an uncomplicated outcome, but common comorbidities may increase mortality and morbidity. Due to low complication rates, studies using single surgeon or single institutional data to identify risk factors for adverse outcomes may be limited by inadequate patient volume. STUDY DESIGN: This retrospective cohort study used data from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP). The study group included all thyroidectomy patients over a 6-year period (2005 to 2010). Common patient comorbidities were identified and analyzed using logistic regression. Risk of adverse outcomes was calculated for single and multiple comorbidities. Statistical significance was set at  $p < 0.05$ . RESULTS: The study group included 38,577 consecutive patients. Thirty-day mortality and postoperative morbidity were 0.06% and 1.49%, respectively. The risk factors independently associated with morbidity included hypertension, diabetes, advanced age greater than 70 years, COPD, dialysis, malignant thyroid disease, and surgical approach (total thyroidectomy). Substernal thyroidectomy, hypertension, diabetes, age greater than 70 years, COPD, and dialysis were significant predictors (unadjusted) of mortality. Multiple comorbidities resulted in significant cumulative risk. The presence of 3 or more comorbidities was associated with a postoperative morbidity of 5.1% ( $p < 0.001$ ) and mortality as high as 12.5%. CONCLUSIONS: Thyroid surgery is generally safe. Common comorbidities significantly increase the risk of adverse outcomes and death. Clinically applicable risk calculation based on overall health may improve patient selection, surgical management, and informed consent.

PubMed-ID: [24745620](https://pubmed.ncbi.nlm.nih.gov/24745620/)

<http://dx.doi.org/10.1016/j.jamcollsurg.2014.01.055>

#### **Voice Outcomes After Total Thyroidectomy, Partial Thyroidectomy, or Non-Neck Surgery Using a Prospective Multifactorial Assessment.**

*J Am Coll Surg*, 219(1):152-63.

Vicente DA, Solomon NP, Avital I, Henry LR, Howard RS, Helou LB, Coppit GL, Shriver CD, Buckenmaier CC, Libutti SK, Shaha AR, Stojadinovic A. 2014.

BACKGROUND: Voice alteration remains a significant complication of thyroid surgery. We present a comparison of voice outcomes between total thyroidectomy (TT), partial thyroidectomy (PT), and non-neck (NN) surgery using a multifactorial voice-outcomes classification tool. STUDY DESIGN: Patients with normal voice ( $n = 112$ ) were enrolled between July 2004 and March 2009. The patients underwent TT ( $n = 54$ ), PT ( $n = 35$ ), or NN ( $n = 23$ ) surgery under general endotracheal anesthesia as part of a prospective observational study involving serial multimodality voice evaluation preoperatively, and at 2 weeks, 3 months, and 6 months postoperatively. Patients with adverse voice outcomes were grouped into the negative voice outcomes (NegVO) category, including patients with objective (abnormality on videolaryngostroboscopy and substantial voice dysfunction) and subjective (normal videolaryngostroboscopy but with notable voice impairment) NegVO. Voice outcomes were compared among study groups. RESULTS: Negative voice outcomes occurred in 46% (95% CI, 34-59%) and 14% (95% CI, 6-30%) of TT and PT groups, respectively. No NegVOs were observed after NN surgery. Early NegVOs were more common in the TT group than in the NN or PT groups ( $p < 0.001$ ). Most voice disturbances resolved by 6 months (TT 84%; PT 92%) with no difference in NegVO among all groups ( $p = 0.23$ ). Black race and significant changes in certain voice outcomes measures at the 2-week follow-up visit were identified as predictors of late (3 to 6 months) NegVO. CONCLUSIONS: This comprehensive voice outcomes study revealed that the extent of thyroidectomy impacts voice outcomes in the early postoperative period, and identified risk factors for late NegVO in post-thyroidectomy patients who should be considered for early voice rehabilitation referral.

PubMed-ID: [24745621](https://pubmed.ncbi.nlm.nih.gov/24745621/)

<http://dx.doi.org/10.1016/j.jamcollsurg.2014.03.019>

### **Possible Targets for Nonimmunosuppressive Therapy of Graves' Orbitopathy.**

*J Clin Endocrinol Metab*, 99(7):E1183-E1190.

Zhang L, Grennan-Jones F, Draman MS, Lane C, Morris D, Dayan CM, Tee AR, Ludgate M. 2014.

CONTEXT: Graves' orbitopathy (GO) is caused by expansion of the orbital contents by excess adipogenesis and overproduction of hyaluronan (HA). Immunosuppressive and antiinflammatory treatments of GO are not always effective and can have side effects, whereas targeting GO-associated tissue remodeling might be a more logical therapeutic strategy. Previously we reported that signaling cascades through IGF1 receptor and thyrotropin receptor within orbital preadipocytes/fibroblasts drove adipogenesis and HA production. Our current study combined the stimulation of IGF1 receptor and thyrotropin receptor increase of HA accumulation, which we hypothesize is by activation of phosphatidylinositol 3-kinase (PI3K)-1A/PI3K1B, respectively. The central aim of this study was to investigate whether PI3K/mammalian target of rapamycin complex 1 (mTORC1) inhibitors affected adipogenesis and/or HA production within orbital preadipocyte/fibroblasts. METHODS: Human orbital preadipocytes were treated with/without inhibitors, LY294002 (PI3K1A/mTORC1), AS-605240 (PI3K1B), or PI103 (PI3K1A/mTORC1) in serum-free medium for 24 hours or cultured in adipogenic medium for 15 days. Quantitative PCR was used to measure hyaluronan synthases (HAS2) transcripts and the terminal adipogenesis differentiation marker lipoprotein lipase. HA accumulation in the medium was measured by an ELISA. RESULTS: Unlike AS-605240, both LY294002 (10 µM) and PI-103 (5 µM) significantly decreased HAS2 transcripts/HA accumulation and adipogenesis. Because PI-103 and LY294002 are dual PI3K/mTOR inhibitors, we investigated the inhibition of mTORC1 (rapamycin 100 nM), which significantly decreased adipogenesis but had no effect on HAS2 transcripts/HA, implicating PI3K-1A in the latter. CONCLUSIONS: The combined inhibition of PI3K1A and mTORC1 signaling in vitro decreased both HA accumulation and adipogenesis. Because PI3K and mTOR inhibitors are clinically used to treat other conditions, they have the potential to be repositioned to be used as an alternative nonimmunosuppressive therapy of GO.

PubMed-ID: [24758182](https://pubmed.ncbi.nlm.nih.gov/24758182/)

<http://dx.doi.org/10.1210/jc.2013-4182>

### **Telomerase-Dependent and Independent Telomere Maintenance and Its Clinical Implications in Medullary Thyroid Carcinoma.**

*J Clin Endocrinol Metab*, 99(8):E1571-E1579.

Wang N, Xu D, Sofiadis A, Hoog A, Vukojevic V, Backdahl M, Zedenius J, Larsson C. 2014.

CONTEXT: Telomere maintenance via telomerase activation and the alternative lengthening of telomeres (ALT) mechanism was assessed in medullary thyroid carcinoma. SETTING AND DESIGN: In total, 42 medullary thyroid carcinomas (MTC) were studied including 24 rearranged during transfection (RET)-mutated cases. Relative telomerase reverse transcriptase (TERT) expression, splice forms, and telomere length were determined by PCR-based methods, and telomerase activity by ELISA. The ALT mechanism was detected by Southern blot analysis and immunofluorescence. RESULTS: TERT expression and telomerase activity were detected in 21/42 tumors (50%), and was independent of the common somatic M918T RET mutation. Mean telomere length was shorter in MTCs compared with thyroids. Telomerase activation was associated with large tumor size ( $P = .027$ ), advanced clinical stage ( $P = .0001$ ), and short survival ( $P = .0001$ ). Full-length TERT and the alpha(-) and beta(-)-deletion forms were revealed, and the full-length form was associated with short survival ( $P = .04$ ). A subset of cases without telomerase activation showed involvement of the ALT mechanism, which was associated with a low MIB-1 proliferation index ( $P = .024$ ). CONCLUSIONS: Stabilization of telomeres by telomerase activation occurs in half of the MTCs and by the ALT mechanism in a subset of cases. Telomerase activation may be used as an additional prognostic marker in medullary thyroid carcinoma.

PubMed-ID: [24758186](https://pubmed.ncbi.nlm.nih.gov/24758186/)

<http://dx.doi.org/10.1210/jc.2014-1158>

### **Small Medullary Thyroid Carcinoma: Post-Operative Calcitonin Rather Than Tumour Size Predicts Disease Persistence and Progression.**

*Eur J Endocrinol*, 171(1):117-26.

Saltiki K, Rentziou G, Stamatelopoulos K, Georgiopoulos G, Stavrianos C, Lambrinouadaki E, Alevizaki M. 2014.

OBJECTIVE: Recently, small medullary thyroid carcinomas (smallMTCs;  $\leq 1.5$  cm) are frequently diagnosed, occasionally as incidental findings in surgical specimens. Their clinical course varies. We examined tumour size as a predictor of clinical behaviour. DESIGN: A retrospective study. METHODS: A total of 128 smallMTC patients (35.2% males and 45% familial) were followed up for 0.9-30.9 years. According to tumour size (cm), patients were classified into four groups: group 1, 0.1-0.5 (n=33); group 2, 0.6-0.8 (n=33); group 3, 0.8-1.0 (n=29) and group 4, 1.1-1.5 (n=33). RESULTS: Pre- and post-operative calcitonin levels were positively associated with the tumour size ( $P < 0.001$ ). Capsular and lymph node invasion were more frequent in groups 3 and 4 ( $P < 0.03$ ); the stage was more advanced and the outcome was less favourable with an increasing tumour

size ( $P < 0.001$ ). Groups 1 and 2 patients were more frequently cured (group 1, 87.8%; group 2, 72.7%; group 3, 68.9%; and group 4, 48.5%;  $P = 0.002$ ). The 10-year probability of lack of disease progression according to the tumour size differed between patients with tumour sizes of 0.1-1.0 and 1.1-1.5 cm (96.6%, 81.3%,  $\chi^2 = 4.03$ ,  $P = 0.045$  for log-rank test). Post-operative calcitonin was the only predictor significantly associated with the 10-year progression of disease. Post-operative calcitonin levels  $\geq 4.65$  pg/ml predicted disease persistence (sensitivity 93.8% and specificity 90%) and  $\geq 14.5$  pg/ml predicted disease progression (sensitivity 100%, specificity 82%, receiver operating characteristic curve analysis). **CONCLUSIONS:** Tumour size may be of clinical importance only in patients with MTCs  $> 1$  cm in size. Post-operative calcitonin is a more important predictor than size for disease progression.

PubMed-ID: [24760539](https://pubmed.ncbi.nlm.nih.gov/24760539/)

<http://dx.doi.org/10.1530/EJE-14-0076>

### **No Adverse Affect in Clinical Outcome Using Low Preablation Diagnostic (131)I Activity in Differentiated Thyroid Cancer: Refuting Thyroid-Stunning Effect.**

*J Clin Endocrinol Metab*, 99(7):2433-40.

Yap BK, Murby B. 2014.

**CONTEXT:** Published studies of thyroid stunning due to preablation (131)I scanning in the treatment of differentiated thyroid cancer after thyroidectomy had shown inconsistent clinical impact. **OBJECTIVE:** The objective of the study was to evaluate the clinical outcome in patients who were given a low diagnostic (131)I activity (1.1 mCi or 40 MBq) 6 days prior to radioiodine ablation (RAI). **DESIGN/SETTING:** Two cohorts of patients were treated in a cancer referral center in 2004-2011. The eligibility criteria were as follows: 1) diagnosis of differentiated thyroid cancer; 2) total or near total thyroidectomy; 3) no distant metastasis; and 4) receiving 82.4 mCi or greater (3050 MBq) therapeutic (131)I activity. **PATIENTS/INTERVENTIONS:** Three hundred five consecutive patients treated in 2004-2008 (group A) had a diagnostic activity 1.1 mCi of (131)I prior to RAI. The second cohort treated in 2009-2011 (group B) consisted of 237 patients who did not undergo diagnostic (131)I scanning prior to RAI. **MAIN OUTCOME MEASURES:** The tumor recurrence rate at 3 years and quantitative assessment using diagnostic whole-body radioiodine scans and TSH-stimulated thyroglobulin levels at 3-12 months after RAI were measured. **RESULTS:** The 3-year recurrence-free survival rates were 96.4% in both groups, with 4.3% in group A and 3.4% in group B having tumor recurrence ( $P = .91$ ). The ablation success rates measured by diagnostic whole-body radioiodine scans were 97.6% and 100% and by stimulated thyroglobulin were 85.3% and 85.8% in group A and B, respectively ( $P = .62$ ). **CONCLUSIONS:** The use of low diagnostic (131)I activity (1.1 mCi) given 6 days prior to RAI was safe and convenient without adversely affecting the long-term clinical outcome.

PubMed-ID: [24762114](https://pubmed.ncbi.nlm.nih.gov/24762114/)

<http://dx.doi.org/10.1210/jc.2014-1405>

### **High-Sensitivity BRAF Mutation Analysis: BRAF V600E Is Acquired Early During Tumor Development but Is Heterogeneously Distributed in a Subset of Papillary Thyroid Carcinomas.**

*J Clin Endocrinol Metab*, 99(8):E1530-E1538.

de BD, Cesari V, Visani M, Casadei GP, Cremonini N, Gandolfi G, Sancisi V, Ragazzi M, Pession A, Ciarrocchi A, Tallini G. 2014.

**CONTEXT:** The homogeneous distribution of BRAF V600E in papillary thyroid carcinoma (PTC) has been called into question by recent reports. These studies claim that BRAF V600E is heterogeneous and is limited to tumor cell subsets in the majority of PTCs. **OBJECTIVE:** The objective of the study was to understand the allele distribution of BRAF V600E by evaluating the percentage of mutated neoplastic cells in a group of PTCs using two different highly sensitive analytical approaches: allele-specific locked nucleic acid PCR and 454 next-generation sequencing targeted to BRAF exon 15. **STUDY DESIGN:** BRAF V600E was investigated using allele-specific locked nucleic acid PCR on 155 consecutive samples of PTC. Mutated cases were reanalyzed by 454 next-generation sequencing and immunohistochemistry. Because the evaluation of genetic heterogeneity in tumor samples can be profoundly biased by contamination with normal cells, all mutation frequency data were normalized to the real amount of neoplastic cells within each tumor. **RESULTS:** Eighty-five of 155 PTCs (54.8%) were BRAF V600E mutated. The distribution of mutated neoplastic cells within the tumor was as follows: greater than 80% in 37 of 85 (43.5%), 30-80% in 39 of 85 (45.9%), and less than 30% in 9 of 85 (10.6%). In most of the PTCs with less than 80% BRAF V600E-positive neoplastic cells, the mutation was present in large neoplastic cell subpopulations. Tumors with less than 30% mutated neoplastic cells were smaller than tumors with a percentage of mutated cells greater than 80% or between 30% and 80% ( $P < .05$ ). **CONCLUSIONS:** BRAF V600E is heterogeneously distributed in some PTCs. The large BRAF V600E neoplastic cell subpopulations found in mutated cases is consistent with the view that the BRAF V600E is acquired early during PTC development.

PubMed-ID: [24780046](https://pubmed.ncbi.nlm.nih.gov/24780046/)  
<http://dx.doi.org/10.1210/jc.2013-4389>

**Morbidity of Central Neck Dissection: Primary Surgery Vs Reoperation. Results of a Case-Control Study.**  
*Langenbecks Arch Surg*, 399(6):747-53.

Lombardi CP, Raffaelli M, De CC, Sessa L, Bellantone R. 2014.

**PURPOSE:** Complication rate in reoperative central neck node surgery is one of the main arguments to favor prophylactic central neck dissection at first operation in patients with papillary thyroid carcinoma. We evaluated if reoperative central neck dissection implies an increased postoperative morbidity. Secondarily, we aimed also to verify the effectiveness of the surgical resection of reoperative central neck dissection. **METHODS:** Forty-one patients who underwent reoperative central neck dissection after initial thyroidectomy for papillary thyroid carcinoma between January 2008 and May 2012 were compared to 41 controls who underwent central neck dissection at initial operation. **RESULTS:** The two groups were well matched for age, sex, and pN stage ( $P = 0.296$ ,  $0.199$ , and  $1.000$ , respectively). Three patients had distant metastases at presentation. No significant difference was found concerning mean number of removed nodes ( $P = 0.064$ ). No significant difference was found between the reoperative and the control groups concerning transient hypocalcemia (17 vs 19, respectively) ( $P = 0.901$ ) and transient recurrent nerve palsy (2 vs 2) ( $P = 0.608$ ). Follow-up was completed in 69 out of all the included patients (85.2 %). At a mean follow-up of 33 months, two patients (2.9 %) experienced nodal recurrence. **CONCLUSIONS:** Morbidity of central neck dissection is similar for primary surgery and reoperation. In high-volume centers, reoperative central neck dissection can be safely accomplished when needed, allowing to achieve locoregional control in most of patients.

PubMed-ID: [24781962](https://pubmed.ncbi.nlm.nih.gov/24781962/)  
<http://dx.doi.org/10.1007/s00423-014-1201-y>

**The Effect of Surgeon Experience on the Detection of Metastatic Lymph Nodes in the Central Compartment and the Pathologic Features of Clinically Unapparent Metastatic Lymph Nodes: What Are We Missing When We Don't Perform a Prophylactic Dissection of Central Compartment Lymph Nodes in Papillary Thyroid Cancer?**

*Thyroid*, 24(8):1282-8.

Scherl S, Mehra S, Clain J, Dos Reis LL, Persky M, Turk A, Wenig B, Husaini H, Urken ML. 2014.

**BACKGROUND:** Prophylactic central neck dissection (PCND) for papillary thyroid cancer (PTC) is controversial. Recent publications suggest that the number and size of nodes and the presence of extranodal extension (ENE) are important features for risk stratification of lymph node metastases. We analyzed these features in clinically unapparent nodes that would not otherwise be removed. We also investigated the impact of surgeon experience on the ability to detect metastatic lymph nodes intraoperatively. **METHODS:** Forty-seven patients with well-differentiated PTC, with no preoperative evidence of central metastases, were included in this study. Intraoperatively, clinically apparent disease was determined by inspection and palpation by the senior surgeon and a fellow/senior resident, and recorded in a blinded fashion. Rate of occult metastases based on intraoperative evaluation were tabulated for each group of surgeons. Histopathologic features of occult nodes were analyzed to determine what clinicians would be missing by foregoing a PCND, and how that would have impacted the patient management. **RESULTS:** The rate of occult metastases, based on senior surgeon assessment, was 26%, and did not differ significantly from fellow/senior resident assessment. The level of agreement between these two surgeon groups was moderate ( $k=0.665$ ). Analysis of the false negative cases revealed that the size of the largest undetected node ranged from 0.1 to 1.3 cm; 36% of patients with occult metastases demonstrated five or more positive nodes, and 27% showed ENE. **DISCUSSION:** Clinical assessment based on intraoperative inspection and palpation had poor sensitivity and specificity in identifying metastatic central nodes, regardless of the level of experience of the surgeon. There was moderate agreement between surgeons of different experience levels. Sensitivity improved significantly with larger size of positive nodes, but not with the presence of multiple positive nodes or presence of ENE. In foregoing PCND in this patient population, our results suggest that treating clinicians miss potentially virulent disease with a large number of occult positive central nodes and occult nodes with ENE. This is the first report to address the pathologic features of clinically nonevident central nodes showing a high incidence of clinically relevant, adverse histologic features, as well as the impact of surgeon experience in performing the important intraoperative determination of whether there are clinically evident nodes that require removal.

PubMed-ID: [24787362](https://pubmed.ncbi.nlm.nih.gov/24787362/)  
<http://dx.doi.org/10.1089/thy.2013.0600>

### **Initial Presentation and Late Results of Treatment of Post-Chernobyl Papillary Thyroid Carcinoma in Children and Adolescents of Belarus.**

*J Clin Endocrinol Metab*, 99(8):2932-41.

Fridman M, Savva N, Krasko O, Mankovskaya S, Branovan DI, Schmid KW, Demidchik Y. 2014.

**BACKGROUND:** The aim of this population-based study was to evaluate the clinical and pathological characteristics and outcome of papillary thyroid carcinoma (PTC) that have arisen in the Belarusian childhood population exposed to the radioactive fallout from the Chernobyl accident within a long-term period. **PATIENTS AND METHODS:** The long-term treatment results were investigated in 1078 children and adolescents (<19 years old) with PTC who were surgically treated during the years 1990 through 2005. **RESULTS:** Patients had high rates of metastatic PTC at presentation, with 73.8% of cases having lymph node involvement and 11.1% having distant spread. The most influential factor for lymph node metastases at initial treatment was lymphatic vessel invasion ( $P < .0001$ ) and for distant metastases, lateral lymph node involvement ( $P < .0001$ ). The overall survival was 96.9% +/- 0.9% with a median follow-up of 16.21 years, and 20-year event-free survival and relapse-free survival were 87.8% +/- 1.6% and 92.3% +/- 0.9%, respectively. Patients had significantly lower probability of both loco-regional ( $P < .001$ ) and distant relapses ( $P = .005$ ) after total thyroidectomy (TT) and radioactive iodine therapy (RAI). For loco-regional relapses after TT, only RAI influenced the prognosis significantly ( $P < .001$ ). For distant relapses after TT, the refusal to treat with RAI (hazard ratio [HR] = 9.26), vascular invasion (HR = 8.68), and age at presentation (HR = 6.13) were significant risk factors. For loco-regional relapses after non-TT, the principal risk factors were age less than 15 years old at presentation (HR = 5.34) and multifocal growth of tumor (HR = 5.19). For distant relapses after non-TT, the lateral neck metastases were the only unfavorable factor (HR = 9.26). **CONCLUSION:** The outcome of PTC both in children and in adolescents exposed to the post-Chernobyl radioiodine fallout was rather favorable. TT with RAI is recommended for minimizing loco-regional or distant relapses.

PubMed-ID: [24823453](https://pubmed.ncbi.nlm.nih.gov/24823453/)

<http://dx.doi.org/10.1210/jc.2013-3131>

### **[Extent of Resection in Grave's Disease]**

#### **Resektionsausmass Beim Morbus Basedow.**

*Chirurg*, 85(6):541.

Dralle H. 2014.

PubMed-ID: [24824006](https://pubmed.ncbi.nlm.nih.gov/24824006/)

<http://dx.doi.org/10.1007/s00104-014-2780-4>

### **Utility of Serum Procalcitonin for Screening and Risk Stratification of Medullary Thyroid Cancer.**

*J Clin Endocrinol Metab*, 99(8):2986-94.

Machens A, Lorenz K, Dralle H. 2014.

**CONTEXT:** The clinical utility of procalcitonin has not been demonstrated across the whole spectrum of medullary thyroid cancer (MTC). **OBJECTIVE:** This serum biomarker validation study aimed at defining the diagnostic accuracy of procalcitonin for screening and risk stratification of MTC and delineating biochemical thresholds predictive of lymph node involvement in the neck and mediastinum. **DESIGN AND SETTING:** This was a retrospective analysis at a tertiary referral center. **PATIENTS:** Included in this study were 457 consecutive patients with previously untreated MTC, 112 of whom had procalcitonin and calcitonin serum levels determined before the initial operation. **INTERVENTION:** The intervention was compartment-oriented surgery. **MAIN OUTCOME MEASURES:** Main outcome measures included primary tumor diameter, extrathyroidal extension, lymph node metastases, distant metastases, and biochemical cure. **RESULTS:** Receiver operating characteristics analyses revealed similar diagnostic accuracy for procalcitonin vs the current calcitonin standard, yielding comparable areas under the curve for primary tumors at thresholds of 10 (0.94 vs 0.93) and 40 (0.92 vs 0.84) mm; extrathyroidal extension (0.84 vs 0.83), lymph node metastasis (0.88 vs 0.86), and distant metastasis (0.93 vs 0.91). Lymph node metastases were present in the ipsilateral lateral neck with procalcitonin levels  $\leq 1.0$  ng/mL and the ipsilateral central neck with procalcitonin levels  $\leq 0.25$  ng/mL. Above a threshold of 1.0 ng/mL, lymph node metastases emerged in the contralateral central and lateral neck and above 5.0 ng/mL also in the upper mediastinum. When procalcitonin levels exceeded 1, 5, 10, and 50 ng/mL, biochemical cure rates declined to no more than 71%, 36%, 23%, and 10%, respectively. **CONCLUSION:** Serum procalcitonin, having comparable diagnostic accuracy, has great potential to replace serum calcitonin as a new standard of care in the management of MTC because it does not need to be kept cool on ice or frozen and is easier to manage at the community level.

PubMed-ID: [24840813](https://pubmed.ncbi.nlm.nih.gov/24840813/)

<http://dx.doi.org/10.1210/jc.2014-1278>

**[Importance of PET for Surgery of Recurrent Thyroid Cancer]  
Bedeutung Der PET Fur Die Chirurgie Des Schilddrusenkarzinomrezidivs.**

*Chirurg*, 85(6):481-6.

Haane C, Colombo-Benkman M. 2014.

BACKGROUND: The early detection of recurrent thyroid cancer and focussed surgery are essential for patients' prognosis. Using I-131 whole body scintigraphy is often not sufficient to detect recurrent carcinoma making other imaging methods necessary to identify the tumor. Recent studies showed that positron emission tomography-computed tomography (PET/CT) is able to identify recurrent carcinoma and metastasis at an early stage.

OBJECTIVE: The aim of this study was an evaluation of the impact of PET/CT on diagnostic and operation strategies in recurrent thyroid cancer. METHODS: A review of the literature was carried out combined with a case report from the daily practice. Furthermore, flow charts were created to clarify the aftercare procedure.

RESULTS: In patients with recurrent thyroid cancer PET/CT significantly increased the identification of recurrent tumors and metastases. Depending on the subtype of cancer, different tracers are used. The use of a metabolically active tracer which shows the increase of tumor metabolism and the morphological correlation of the tumor using a CT scan enable preoperative planning for a focussed surgical approach. CONCLUSIONS: The PET/CT procedure should be an integral part of the aftercare procedure in thyroid cancer for early identification of recurrent tumors and to enable focussed surgery.

PubMed-ID: [24840933](https://pubmed.ncbi.nlm.nih.gov/24840933/)

<http://dx.doi.org/10.1007/s00104-013-2667-9>

**Cervical Cancer Mortality in India.**

*Lancet*, 383(9931):1804.

Suba EJ, Raab SS. 2014.

PubMed-ID: [24856023](https://pubmed.ncbi.nlm.nih.gov/24856023/)

[http://dx.doi.org/10.1016/S0140-6736\(14\)60877-1](http://dx.doi.org/10.1016/S0140-6736(14)60877-1)

**Cervical Cancer Mortality in India - Authors' Reply.**

*Lancet*, 383(9931):1804-5.

Sankaranarayanan R, Esmy PO, Rajkumar R, Muwonge R, Swaminathan R. 2014.

PubMed-ID: [24856024](https://pubmed.ncbi.nlm.nih.gov/24856024/)

[http://dx.doi.org/10.1016/S0140-6736\(14\)60878-3](http://dx.doi.org/10.1016/S0140-6736(14)60878-3)

**Impact of Prophylactic Central Compartment Neck Dissection on Locoregional Recurrence of Differentiated Thyroid Cancer in Clinically Node-Negative Patients: a Retrospective Study of a Large Clinical Series.**

*Surgery*, 155(6):998-1005.

Conzo G, Calo PG, Sinisi AA, De BA, Pasquali D, Iorio S, Tartaglia E, Mauriello C, Gambardella C, Cavallo F, Medas F, Polistena A, Santini L, Avenia N. 2014.

BACKGROUND: In clinically node-negative patients with differentiated thyroid cancer (DTC), indications for routine central lymph node dissection (RCLD) are the subject of intensive research, and surgeons are divided between the pros and cons of this surgery. To better define the role of neck dissection in the treatment of DTC, we analyzed retrospectively the results in three centers in Italy. METHODS: The clinical records of 752 clinically node-negative patients with DTC who underwent operative treatment between January 1998 and December 2005 in three endocrine surgery referral units were evaluated retrospectively. The complications and medium- and long-term outcomes of total thyroidectomy (TT) alone (performed in 390 patients: group A) and TT combined with bilateral RCLD (362 patients: group B) were analyzed and compared. RESULTS: The incidence of permanent hypoparathyroidism and permanent unilateral vocal folds was 1% and 0.8% in group A and 3.6% and 1.7% in the group B, respectively. Bilateral temporary recurrent nerve palsy was observed in one of the 362 patients in group B. After a follow-up of 9.5 +/- 3.5 years (mean +/- SD), the locoregional recurrence rate with positive cervical lymph nodes was not substantially significantly different between the two groups.

CONCLUSION: In our series, TT combined with bilateral RCLD was associated with a greater rate of transient and permanent complications. Similar incidences of locoregional recurrence were reported in the two groups of patients. Considering the recent trend toward routine central lymphadenectomy, further studies are needed to evaluate the benefits of these different approaches.

PubMed-ID: [24856120](https://pubmed.ncbi.nlm.nih.gov/24856120/)

<http://dx.doi.org/10.1016/j.surg.2014.02.010>

### **The Incidence of Papillary Thyroid Carcinoma and Outcomes in Operative Patients According to Their Body Mass Indices.**

*Surgery*,

Tresallet C, Seman M, Tissier F, Buffet C, Lupinacci RM, Vuarnesson H, Leenhardt L, Menegaux F. 2014. BACKGROUND: The connection between high body mass index (BMI), risk of papillary thyroid carcinoma (PTC), and the aggressiveness of PTC is still debated. We aimed to establish the relationship between excess BMI and the risk of PTC in an operative population, and the impact of obesity on histopathologic aggressiveness of PTC and on the outcome of patients. METHODS: All consecutive patients who underwent thyroid operation from June 2002 to December 2009 were reviewed in this retrospective study. BMI groupings were based on standardized categories: normal-weight, overweight, and obesity. We performed a total thyroidectomy with lymph node dissection in patients with preoperative or operative diagnosis of PTC. Radioiodine ablation was performed in every N1 patient, in case of tumor size greater than 10 mm, and if there was extrathyroidal invasion. During a median follow-up of 6.2 years, patients who were retreated by operation or 131I were considered to have a persistent (<18 months of the initial operative treatment) or recurrent (>=18 months) disease. RESULTS: Of 6,684 patients who had a thyroid gland resection, we identified 1,216 (18.2%) patients with PTC. Patients who were overweight or obese were not at greater risk of PTC than normal-weight subjects. Indications for operation or radioiodine therapy were similar in the three BMI groups. During follow-up, 86 patients (7.1%) experienced persistent (4.5%) or recurrent (2.5%) disease. When excluding micro-PTCs (<=10 mm), we found an association between recurrent or residual locoregional thyroid cancer and BMI: 18.7% in obese patients versus 8.5% if BMI <25 kg/m<sup>2</sup> and 9.8% if 25 >= BMI < 30 kg/m<sup>2</sup> (P = .03). This difference was clearly marked for persistence. When adjusted for other cofounder factors, we observed that BMI was an independent factor associated with the risk of postoperative locoregional event (odds ratio 3.8, 95% confidence interval 1.6-8.8), with sex, age, lymph node metastasis, and tumor bilaterality. CONCLUSION: In macro-PTC, obese patients had an increased risk of developing a locoregional event during the follow-up, specifically a persistence of the disease. According to these results, overweight and obese patients with macro-PTC should be monitored more carefully for early detection of cancer persistence.

PubMed-ID: [24878452](https://pubmed.ncbi.nlm.nih.gov/24878452/)

<http://dx.doi.org/10.1016/j.surg.2014.04.020>

### **A Prospective Comparison of Patient Body Image After Robotic Thyroidectomy and Conventional Open Thyroidectomy in Patients With Papillary Thyroid Carcinoma.**

*Surgery*, 156(1):117-25.

Lee S, Kim HY, Lee CR, Park S, Son H, Kang SW, Jeong JJ, Nam KH, Chung WY, Park CS. 2014. BACKGROUND: Body image is associated with self-esteem and identity and has a close relationship with quality of life (QoL). We compared the impact of surgical scars on the patient's perception of body image between conventional open thyroidectomy (OT) and robotic thyroidectomy (RT) in female papillary thyroid carcinoma patients. METHODS: From October 2009 to December 2010, we enrolled prospectively 116 papillary thyroid carcinoma patients who underwent total thyroidectomy at the Yonsei University Health System (Seoul, Korea). Of these 116 patients, 56 had OT and 60 RT. Their scars were assessed using the Vancouver Scar Scale (VSS), and psychometric properties were evaluated using the Body Image Scale (BIS) questionnaire postoperatively. Both groups were compared using cross-sectional and time-series methods. RESULTS: Mean age was significantly younger in the RT group. Regarding scar quality, the OT group showed superiority in scar pigmentation and the total VSS score during the early postoperative period, but the VSS score improved over time and was similar between both groups at 9 months. The RT group had better scores regarding most of the BIS items, a trend that remained relatively constant over time. In patients with noticeable scars (VSS >= 2) at 9 months, the RT group had better BIS scores regarding almost all items, including "self-conscious," "physical attractiveness," "feeling of less feminine," "sexual attractiveness," "dissatisfaction with body, scar and appearance when dressed," and "avoidance of people due to appearance." CONCLUSION: RT provides a better self-body image and improves QoL compared with conventional OT by avoiding a noticeable cervical scar.

PubMed-ID: [24878453](https://pubmed.ncbi.nlm.nih.gov/24878453/)

<http://dx.doi.org/10.1016/j.surg.2014.02.007>

### **The Impact of Nodal Status on Outcome in Older Patients With Papillary Thyroid Cancer.**

*Surgery*, 156(1):137-46.

Nixon IJ, Wang LY, Palmer FL, Tuttle RM, Shaha AR, Shah JP, Patel SG, Ganly I. 2014.

BACKGROUND: The impact of clinically or radiologically detected nodal metastases on survival in patients with papillary thyroid cancer (PTC) is controversial but seems more important and relevant in older patients. The objective of this study was to determine the impact of clinically or radiologically detected nodal metastases on outcome in patients 45 years of age or older. METHODS: Retrospective analysis of 834 patients 45 years or

older who underwent operation for PTC between 1986 and 2005. RESULTS: With a median follow up of 77 months, the 5 year disease-specific survival (DSS) and recurrence-free survival (RFS) were 99% and 94%, respectively. Patients with clinically N+ nodes with pathologic confirmation were stratified into pN0/Nx, pN1a, and pN1b, respectively. Five-year DSS was 100%, 100%, and 91% for pN0/Nx, pN1a, and pN1b disease;  $P < .001$ . Patients with pN1b disease had poorer distant RFS compared with pN0/Nx and pN1a patients (84%, 99%, and 99%;  $P < .001$ ). The presence of pN1b disease was an independent predictor of worse DSS and distant RFS on multivariate analysis, conferring a 10-fold increased risk of distant metastases and death. All cause-specific deaths were due to distant metastases. CONCLUSION: Older patients with PTC and N1b disease at presentation have poorer DSS compared with patients with pN0/Nx or N1a disease. The cause of death in these patients is due to distant metastases rather than locoregional recurrence.

PubMed-ID: [24878458](https://pubmed.ncbi.nlm.nih.gov/24878458/)

<http://dx.doi.org/10.1016/j.surg.2014.03.027>

### **Time to Reconsider Thyroid Cancer Screening in Fukushima.**

*Lancet*, 383(9932):1883-4.

Shibuya K, Gilmour S, Oshima A. 2014.

PubMed-ID: [24881983](https://pubmed.ncbi.nlm.nih.gov/24881983/)

[http://dx.doi.org/10.1016/S0140-6736\(14\)60909-0](http://dx.doi.org/10.1016/S0140-6736(14)60909-0)

### **Utility of Serum Thyroglobulin Measurements After Prophylactic Thyroidectomy in Patients With Hereditary Medullary Thyroid Cancer.**

*Surgery*, 156(2):394-8.

Seib CD, Harari A, Conte FA, Duh QY, Clark OH, Gosnell JE. 2014.

INTRODUCTION: Prophylactic thyroidectomy can be curative for patients with hereditary medullary thyroid cancer (MTC) caused by RET proto-oncogene mutations. Calcitonin is a sensitive tumor marker used to follow patients. We suggest that thyroglobulin (Tg) levels should also be monitored postoperatively in these patients. METHODS: We reviewed patients with RET mutations who underwent prophylactic thyroidectomy between 1981 and 2011 at an academic endocrine surgery center. Patients were excluded if they had no postoperative Tg levels recorded. RESULTS: Of the 22 patients who underwent prophylactic thyroidectomy, 14 were included in the final analysis. The average age at thyroidectomy was 9.8 years (range, 4-29). Tg levels were detectable 1.5 months to 31 years postoperatively in 11 patients (79%), all of whom were <15 years old at thyroidectomy. Median thyroid-stimulating hormone (TSH) was 2.5 mIU/L and 13.4 mIU/L in patients with undetectable and detectable Tg, respectively. Of those with detectable Tg, 5 had cervical ultrasonographic examination: Two showed no residual tissue in the thyroid bed, and 3 showed remnant thyroid tissue. CONCLUSION: Tg levels can identify patients with remnant thyroid tissue after prophylactic thyroidectomy. Ultrasonography can determine whether thyroid tissue remains posterolaterally that is at risk of MTC recurrence. Maintaining normal TSH may prevent growth of remaining thyroid follicular cells.

PubMed-ID: [24882762](https://pubmed.ncbi.nlm.nih.gov/24882762/)

<http://dx.doi.org/10.1016/j.surg.2014.03.037>

### **Second-Line Treatment for Advanced Thyroid Cancer: an Indication in Need of Randomized Clinical Trials.**

*J Clin Endocrinol Metab*, 99(6):1995-7.

Cohen AB, Brose MS. 2014.

PubMed-ID: [24893137](https://pubmed.ncbi.nlm.nih.gov/24893137/)

<http://dx.doi.org/10.1210/jc.2014-2236>

### **A Clinical Algorithm for Fine-Needle Aspiration Molecular Testing Effectively Guides the Appropriate Extent of Initial Thyroidectomy.**

*Ann Surg*, 260(1):163-8.

Yip L, Wharry LI, Armstrong MJ, Silbermann A, McCoy KL, Stang MT, Ohori NP, LeBeau SO, Coyne C, Nikiforova MN, Bauman JE, Johnson JT, Tublin ME, Hodak SP, Nikiforov YE, Carty SE. 2014.

OBJECTIVE: To test whether a clinical algorithm using routine cytological molecular testing (MT) promotes initial total thyroidectomy (TT) for clinically significant thyroid cancer (sTC) and/or correctly limits surgery to lobectomy when appropriate. BACKGROUND: Either TT or lobectomy is often needed to diagnose differentiated thyroid cancer. Determining the correct extent of initial thyroidectomy is challenging. METHODS: After implementing an algorithm for prospective MT of in-house fine-needle aspiration biopsy specimens, we conducted a single-institution cohort study of all patients (N = 671) with nonmalignant cytology who had thyroidectomy between October 2010 and March 2012, cytological diagnosis using 2008 Bethesda criteria, and 1 or more indications for

thyroidectomy by 2009 American Thyroid Association guidelines. sTC was defined by histological differentiated thyroid cancer of 1 cm or more and/or lymph node metastasis. Cohort 2 patients did not have MT or had unevaluable results. In cohort 1, MT for a multigene mutation panel was performed for nonbenign cytology, and positive MT results indicated initial TT. RESULTS: MT guidance was associated with a higher incidence of sTC after TT (P = 0.006) and a lower rate of sTC after lobectomy (P = 0.03). Without MT results, patients with indeterminate (follicular lesion of undetermined significance/follicular or oncocytic neoplasm) cytology who received initial lobectomy were 2.5 times more likely to require 2-stage surgery for histological sTC (P < 0.001). In the 501 patients with non-sTC for whom lobectomy was the appropriate extent of surgery, lobectomy was correctly performed more often with routine preoperative MT (P = 0.001). CONCLUSIONS: Fine-needle aspiration biopsy MT for BRAF, RAS, PAX8-PPARgamma, and RET-PTC expedites optimal initial surgery for differentiated thyroid cancer, facilitating succinct definitive management for patients with thyroid nodules.

PubMed-ID: [24901361](https://pubmed.ncbi.nlm.nih.gov/24901361/)

<http://dx.doi.org/10.1097/SLA.0000000000000215>

### **Thyroidectomy in Patients With a High BMI: a Safe Surgery?**

*Eur J Endocrinol*, 171(1):99-105.

Finel JB, Mucci S, Branger F, Venara A, Lenaoures P, Rodien P, Hamy A. 2014.

OBJECTIVE: To study and compare the specific postoperative complications of thyroidectomy in a population with a BMI  $\geq 25$  with a population having a BMI below 25. DESIGN: A prospective study was carried out from September 2010 to January 2013. METHODS: Postoperative calcemia, laryngeal mobility, bleeding or infectious complications, postoperative hospital stay, and operation time were studied and compared statistically by a chi(2)-test or Student's t-test. RESULTS: A total of 240 patients underwent total thyroidectomy and 126 underwent a partial thyroidectomy. Of them, 168 patients had a BMI below 25 and 198 patients had a BMI  $\geq 25$ . There was no statistically significant difference in the occurrence of early or permanent hypoparathyroidism, recurrent laryngeal nerve palsy, bleeding complications, or postoperative duration of hospital stay. There was, however, a significant operative time in patients with a BMI  $\geq 25$ . CONCLUSION: Despite the longer operative time, thyroidectomy (total or partial) can be performed safely in patients with a BMI  $\geq 25$ .

PubMed-ID: [24913199](https://pubmed.ncbi.nlm.nih.gov/24913199/)

<http://dx.doi.org/10.1530/EJE-14-0063>

### **Predicting Hypocalcemia After Thyroidectomy in Children.**

*Surgery*, 156(1):130-6.

Freire AV, Ropelato MG, Ballerini MG, Acha O, Bergada I, de Papendieck LG, Chiesa A. 2014.

BACKGROUND AND AIMS: Hypocalcemia after thyroidectomy is caused by parathyroid trauma. There are no studies regarding the usefulness of intact parathyroid hormone (PTH) as a monitor of postoperative hypoparathyroidism tool in pediatrics. We evaluated the diagnostic accuracy of intra- and postoperative PTH to predict the risk of developing post thyroidectomy hypocalcemia in children. METHODS: A prospective longitudinal cohort study was conducted in 32 pediatric patients (3.2-17.6 years old) undergoing total thyroidectomy. Intact PTH measured by the assays (Immulite Immunoassay System [ICMA] or electrochemoluminescence assay [ECLIA]) at 5 (PTH-5) and 60 (PTH-60) minutes after thyroid removal were considered as predicting variables. The postoperative outcome was hypocalcemia (endpoint variable). Patients were clinically and biochemically monitored regularly for 48 hours after surgery. RESULTS: Of the patients, 47% developed hypocalcemia (15% symptomatic). An ICMA PTH-5 of  $\leq 14$  pg/mL or an ECLIA PTH-5 of  $\leq 16$  pg/mL predicted hypocalcemia with a sensitivity of 80%, specificity of 100%, positive predictive value (PPV) of 100%, and diagnostic efficiency (DE) of 91%. Using the same cutoff values, PTH-60 presented a sensitivity of 93%, specificity of 82%, PPV of 81%, and DE of 87%. Adjusting for variation in the assays and combining intra- and postoperative PTH determinations, we developed an algorithm that improved sensitivity, specificity, and DE. CONCLUSION: PTH is useful for predicting hypocalcemia after total thyroidectomy in children. The use of our proposed strategy should be considered to (a) initiate preventive treatment in patients identified at high risk for hypocalcemia, (b) shorten the duration of hospitalization, and (c) reduce the clinical and biochemical controls in those who remained normocalcemic.

PubMed-ID: [24929763](https://pubmed.ncbi.nlm.nih.gov/24929763/)

<http://dx.doi.org/10.1016/j.surg.2014.02.016>

### **Radio-Guided Selective Compartment Neck Dissection Improves Staging in Papillary Thyroid Carcinoma: a Prospective Study on 345 Patients With a 3-Year Follow-Up.**

*Surgery*, 156(1):147-57.

Carcoforo P, Portinari M, Feggi L, Panareo S, De TA, Zatelli MC, Trasforini G, Degli UE, Forini E, Feo CV. 2014.

**BACKGROUND:** Prospective uncontrolled study to investigate in papillary thyroid carcinoma (PTC) patients: (1) Distribution of lymph node metastases within the neck compartments, (2) factors predicting lymph nodes metastases, and (3) disease recurrence after thyroidectomy associated with radio-guided selective compartment neck dissection (RSCND). **METHODS:** We studied 345 consecutive PTC patients operated on between February 2004 and October 2011 at the S. Anna University Hospital, Ferrara (Italy). Patients with cervical lymph node metastases on preoperative ultrasonography and fine needle aspiration cytology were excluded. All patients underwent total thyroidectomy associated with SLN identification followed by RSCND in the SLN compartment, without SLN frozen section. **RESULTS:** In patients with lymph node metastases, metastatic nodes were not in the central neck compartment in 22.6% of the cases. The presence of infiltrating or multifocal PTC was a predicting factor for lymph nodes metastases. The median follow-up was 35.5 months. RSCND was associated with a false-negative rate of 1.1%, a persistent disease rate of 0.6%, and a recurrent disease rate of 0.9%. The permanent dysphonia rate was 1.3%. **CONCLUSION:** RSCND associated with total thyroidectomy may improve: (1) the locoregional lymph node staging, and (2) the identification of the site of lymphatic drainage within the neck compartments. Thus, considering the high false-negative rate of sentinel lymph node biopsy (SLNB), a radio-guided technique in PTC patients may guide the lymphadenectomy (ie, RSCND) to increase the metastatic yield and improve staging of the disease rather than avoid prophylactic lymphadenectomy (ie, SLNB). PubMed-ID: [24929764](https://pubmed.ncbi.nlm.nih.gov/24929764/)  
<http://dx.doi.org/10.1016/j.surg.2014.03.045>

**Risk Factors for Hematoma After Thyroidectomy: Results From the Nationwide Inpatient Sample.**  
*Surgery*, 156(2):399-404.

Weiss A, Lee KC, Brumund KT, Chang DC, Bouvet M. 2014.

**BACKGROUND:** Hematoma after thyroidectomy is a potentially lethal complication. We sought to evaluate risk factors for hematoma formation using the Nationwide Inpatient Sample. We hypothesized that certain risk factors could be identified and that this information would be useful to surgeons. **METHODS:** The Nationwide Inpatient Sample database was queried for patients who underwent thyroidectomy from 1998 to 2010. Bivariate analysis was used to compare patients with and without hematoma. Logistic regression was performed to identify important predictors of hematoma. **RESULTS:** There were 150,012 patients. The rate of hematoma was 1.25%. Female sex and high-volume hospitals were important for decreased hematoma risk (odds ratio 0.61 [0.54-0.69] and 0.71 [0.56-0.83], respectively). Black race, age >45 years, inflammatory thyroid disease, partial thyroidectomy, chronic kidney disease, and bleeding disorders increased the risk of hematoma (odds ratio 1.37, 1.44, 1.59, 1.69, 1.8, 3.38; respectively). Overall mortality was 0.32% for the entire group and 1.34% in patients with postoperative hematoma (P < .001). Patients with hematoma after thyroidectomy were 2.94 [1.76-4.9] times more likely to die than those without hematoma. **CONCLUSION:** We identified risk factors associated with postoperative hematoma after thyroidectomy. Such information should be useful for surgeons for predicting patients at risk for this potentially lethal complication.

PubMed-ID: [24947642](https://pubmed.ncbi.nlm.nih.gov/24947642/)

<http://dx.doi.org/10.1016/j.surg.2014.03.015>

**Improvement of Quality of Life in Patients With Benign Goiter After Surgical Treatment.**

*Langenbecks Arch Surg*, 399(6):755-64.

Bukvic BR, Zivaljevic VR, Sipetic SB, Diklic AD, Tausanovic KM, Paunovic IR. 2014.

**PURPOSE:** A quality of life (QoL) assessment is considered an important outcome measure in the treatment of benign thyroid diseases. The aims of this study were to analyze the impact of different surgical treatments on QoL in patients with benign thyroid diseases and to evaluate factors correlating with the QoL outcomes.

**METHODS:** A prospective longitudinal study was conducted. One hundred thirty-two patients met the inclusion/exclusion criteria and completed the disease-specific questionnaire, thyroid patient-reported outcome (ThyPRO), before surgery and after 6 months. Preoperative and postoperative QoL outcomes were compared and correlating factors were analyzed. **RESULTS:** Indication for surgery was euthyroid goiter, toxic goiter, and suspicious malignant thyroid disease in 58.3, 29.5, and 12.1 % of the patients, respectively. None of the patients had overtly toxic goiter. There were 65.2 % of the patients who underwent total thyroidectomy, while 34.8 % underwent hemithyroidectomy. The total postoperative complication rate was 5.3 %. QoL improved significantly after surgical treatment, independent of the extent of performed surgery. The most affected domain, pre- and postoperative, was for tiredness. QoL improvement was significant for women in all domains, while for men, it was significant in only three domains (goiter symptoms, emotional susceptibility, and cosmetic complaints) and in overall QoL. Younger patients had significantly better cognitive functioning and daily life, while elderly patients had significantly less cosmetic complaints. The factors that significantly correlated with improvement of QoL in different domains were lower education level, duration of disease, and microcarcinoma at final histology. **CONCLUSION:** QoL in patients with benign thyroid diseases improves significantly after operative treatment,

independent of the extent of the operation.  
PubMed-ID: [25002182](https://pubmed.ncbi.nlm.nih.gov/25002182/)  
<http://dx.doi.org/10.1007/s00423-014-1221-7>

### **A Single Parathyroid Hormone Level Obtained 4 Hours After Total Thyroidectomy Predicts the Need for Postoperative Calcium Supplementation.**

*J Am Coll Surg*, 219(4):757-64.

Carr AA, Yen TW, Fareau GG, Cayo AK, Misustin SM, Evans DB, Wang TS. 2014.

**BACKGROUND:** Parathyroid hormone (PTH) levels after total thyroidectomy have been shown to predict the development of symptomatic hypocalcemia and the need for calcium supplementation. This study aimed to determine whether a PTH level drawn 4 hours postoperatively is as effective as a level drawn on postoperative day 1 (POD1) in predicting this need. **STUDY DESIGN:** This is a single-institution retrospective review of 4-hour and POD1 PTH levels in patients who underwent total thyroidectomy from January 2012 to September 2012. If POD1 PTH was  $\geq 10$  pg/mL, patients did not routinely receive supplementation; if PTH was  $< 10$  pg/mL, patients received oral calcium with or without calcitriol. **RESULTS:** Of 77 patients, 20 (26%) had a 4-hour PTH  $< 10$  pg/mL; 18 (90%) of these patients had a POD1 PTH  $< 10$  pg/mL. No patient with a 4-hour PTH  $\geq 10$  pg/mL had a POD1 PTH  $< 10$  pg/mL. All 18 patients with POD1 PTH  $< 10$  pg/mL received calcium supplementation. Three additional patients received supplementation due to reported symptoms or surgeon preference. A 4-hour PTH  $\geq 10$  pg/mL compared with a POD1 PTH had a similar ability to predict which patients would not need calcium supplementation; sensitivity was 98% vs 98%, specificity was 90% vs 86%, and negative predictive value was 95% vs 95%. Of 21 patients who received supplementation, 13 (62%) also received calcitriol, including 9 patients (69%) with a 4-hour PTH  $< 6$  pg/mL. **CONCLUSIONS:** A single PTH level obtained 4 hours after total thyroidectomy that is  $\geq 10$  pg/mL accurately identifies patients who do not need calcium supplementation or additional monitoring of serum calcium levels. Same-day discharge, if deemed safe, can be accomplished with or without calcium supplementation based on the 4-hour PTH level. Greater consideration should be given to calcitriol supplementation in patients with a 4-hour PTH  $< 6$  pg/mL.

PubMed-ID: [25053220](https://pubmed.ncbi.nlm.nih.gov/25053220/)

<http://dx.doi.org/10.1016/j.jamcollsurg.2014.06.003>

### **Can Ultrasound Be Used to Predict Malignancy in Patients With a Thyroid Nodule and an Indeterminate Fine-Needle Aspiration Biopsy?**

*Surgery*, 156(4):967-70.

Khoncarly SM, Tamarkin SW, McHenry CR. 2014.

**PURPOSE:** The purpose of this study was to evaluate whether ultrasonography is helpful in predicting malignancy in patients with a thyroid nodule and atypia/follicular lesion of undetermined significance (AFLUS). **METHODS:** All patients with a preoperative ultrasound who underwent thyroidectomy for a nodule with AFLUS comprised the study population. A blinded review of gray-scale and color-Doppler sonographic images of the thyroid nodule was performed by an expert sonographer; results were compared with the original interpretation and were correlated with histopathology. All images were reviewed for hypoechogenicity, irregular margins, shape that was taller than wide, micro and macrocalcifications, absent halo, and intranodular hypervascularity. **RESULTS:** From 2010 to 2012, 61 patients underwent thyroidectomy for AFLUS with an ultrasound examination for review; 6 (10%) with cancer. Nodule shape that was taller than wide, was associated with cancer ( $P < .05$ ). The original sonographer commented on an average of two of seven features important in assessment of a thyroid nodule. **CONCLUSION:** With the exception of nodule height greater than width, sonographic criteria were not helpful in deciding which patients with AFLUS should undergo thyroidectomy. Thyroidectomy is recommended in lieu of repeat biopsy for a nodule that is taller than wide. Standardized sonographic reporting should be implemented.

PubMed-ID: [25074360](https://pubmed.ncbi.nlm.nih.gov/25074360/)

<http://dx.doi.org/10.1016/j.surg.2014.06.043>

### **Endoscopic Thyroid Surgery Via a Breast Approach: a Single Institution's Experiences.**

*BMC Surg*, 14:49.

Kim YS, Joo KH, Park SC, Kim KH, Ahn CH, Kim JS. 2014.

**BACKGROUND:** Thyroid carcinoma in young women is rapidly increasing, and cosmesis plays an important role in thyroid operations. Various endoscopic thyroid surgery approaches have been performed, and their application has recently been extended. We performed endoscopic thyroid surgeries via a breast approach since 1999. Herein, we evaluate the safety of this approach and identify the outcomes for differentiated thyroid carcinoma. **METHODS:** A total of 452 consecutive patients with thyroid and parathyroid disease underwent endoscopic thyroidectomy via a breast approach at Uijeongbu St. Mary's Hospital between November 1999 and

December 2012. The inclusion criteria for endoscopic thyroidectomy included a benign tumour less than 4 cm in diameter, malignant thyroid nodules less than 2 cm, and no evidence of lymph node metastasis or local invasion. We analysed the clinicopathologic data and surgical factors of this approach. RESULTS: The mean age of the patients was 38.4 +/- 10.6 years (range 11-73 years). The mean tumour size was 2.12 +/- 1.17 cm (range 0.1-4 cm). The final tumour pathologies included papillary carcinoma (n = 120), follicular carcinoma (n = 8), nodular hyperplasia (n = 266), follicular adenoma (n = 43), and Huthle cell adenoma (n = 4). The mean postoperative hospital stay was 3.8 +/- 1.3 days (range 1-17 days). Temporary and permanent hypoparathyroidism requiring calcium and vitamin D supplementation developed in 32 (7.1%) and 4 (0.9%) patients, respectively. Transient vocal cord paresis occurred in 20 (4.4%) patients. CONCLUSIONS: For patients with benign and low-risk malignant thyroid disease, endoscopic thyroidectomy via a breast approach is a safe, feasible, and minimally invasive surgical method with minimal complications.

PubMed-ID: [25095889](https://pubmed.ncbi.nlm.nih.gov/25095889/)

<http://dx.doi.org/10.1186/1471-2482-14-49>

# Parathyroids

## Meta-Analyses

### **Parathyroid Carcinoma.**

*Surg Oncol*, 23(2):107-14.

Al-Kurd A, Mekel M, Mazeh H. 2014.

Parathyroid carcinoma is a rare form of endocrine malignancy accounting for only a small minority of cancer cases. Due to the rarity of this cancer, there are no generalized guidelines for its management; however, surgery remains to be the mainstay therapy. The purpose of this article is to review and summarize the available literature on parathyroid carcinoma, while discussing proposed staging systems and the role of available adjuvant therapies.

PubMed-ID: [24742584](https://pubmed.ncbi.nlm.nih.gov/24742584/)

<http://dx.doi.org/10.1016/j.suronc.2014.03.005>

## Randomized controlled trials

### **Vitamin D-Binding Protein Levels Do Not Influence the Effect of Vitamin D Repletion on Serum PTH and Calcium: Data From a Randomized, Controlled Trial.**

*J Clin Endocrinol Metab*, 99(7):2494-9.

Ponda MP, McGee D, Breslow JL. 2014.

CONTEXT: Vitamin D deficiency, defined by the total serum 25-hydroxyvitamin D [25(OH)D] level, is common and more prevalent among Blacks than whites. Vitamin D-binding protein (DBP) levels vary with race and may modulate "bioavailable" levels of 25(OH)D. OBJECTIVE: To determine the effect of DBP levels on the functional response to vitamin D. SETTING AND DESIGN: A randomized, placebo-controlled trial of vitamin D repletion for 2 mo, which took place at an outpatient research unit. Participants included 150 vitamin D-deficient (25(OH)D <20 ng/mL) adults. Participants were randomly assigned to receive either 50,000 IU of vitamin D3 or placebo weekly for 8 weeks. This is a post-hoc analysis using DBP, 25(OH)D, PTH, and calcium levels. RESULTS: Blacks had lower total 25(OH)D (12 vs 15 ng/mL,  $P < .001$ ) and DBP levels (119 vs 234  $\mu\text{g/mL}$ ,  $P < .001$ ) than non-Blacks. DBP levels were similar before and after vitamin D3 or placebo treatment ( $r = 0.98$ ,  $P < .001$ ). Baseline total 25(OH)D levels were a significant determinant of baseline PTH levels ( $P < .001$ ). The change in total 25(OH)D was associated with the change in PTH ( $P < 0.001$ ) and calcium levels ( $P < .05$ ). In contrast, DBP levels were not a determinant of baseline PTH ( $P = .57$ ) nor significantly related to changes in either PTH ( $P = .53$ ) or calcium levels ( $P = .88$ ). CONCLUSIONS: DBP levels are stable in Blacks and non-Blacks, and do not change with correction of vitamin D deficiency. Even for individuals with total 25(OH)D levels < 20 ng/mL, Blacks have significantly lower DBP levels than non-Blacks. However, within this range of total 25(OH)D, DBP levels do not influence the effect of vitamin D repletion on PTH or calcium levels.

PubMed-ID: [24712573](https://pubmed.ncbi.nlm.nih.gov/24712573/)

<http://dx.doi.org/10.1210/jc.2014-1181>

## Consensus Statements/Guidelines

- None -

## Other Articles

### **Incidental Parathyroidectomy During Thyroid Surgery Using Capsular Dissection Technique.**

*Otolaryngol Head Neck Surg*, 150(5):754-61.

Prazenica P, O'Driscoll K, Holy R. 2014.

OBJECTIVE: To identify incidence, preoperative features, surgical factors, and postoperative events of incidental parathyroidectomy (IP) during thyroidectomy. STUDY DESIGN: A total of 1068 consecutive patients who underwent thyroidectomy performed by a single surgeon between January 2003 and April 2012 were enrolled in

retrospective study with prospectively collected data. SETTING: University hospital. SUBJECTS AND METHODS: To assess the impact of IP on study variables, patients were stratified into 2 study groups: IP group and non-IP group. Univariate and multivariate analyses identified significant correlates of IP. RESULTS: In all, 5.4% patients experienced IP. Significant difference ( $P < .001$ ) was in incidence of temporary hypocalcemia between IP group (36.2%) and non-IP group (16.8%). Multivariable logistic regression model identified total thyroidectomy (odds ratio 3.937, 95% confidence interval [CI] 1.462-10.601,  $P = .007$ ) and Graves' disease (odds ratio 2.192, 95% CI 1.157-4.158,  $P = .016$ ) as risk-adjusted factors associated with IP. Multivariate analysis of repeated measures identified statistically significant difference of repeated total calcium level ( $P < .001$ ) and ionized calcium level ( $P = .020$ ) between study groups. CONCLUSION: IP during thyroidectomy might be potential complication. Total thyroidectomy, Graves' disease, longer operation time, and identification 3 and more parathyroid glands seemed to be predictive factors for IP. IP is significantly associated with temporary hypocalcemia, but not with permanent hypoparathyroidism.

PubMed-ID: [24496742](https://pubmed.ncbi.nlm.nih.gov/24496742/)

<http://dx.doi.org/10.1177/0194599814521365>

### **The Small Abnormal Parathyroid Gland Is Increasingly Common and Heralds Operative Complexity.**

*World J Surg*, 38(6):1274-81.

McCoy KL, Chen NH, Armstrong MJ, Howell GM, Stang MT, Yip L, Carty SE. 2014.

BACKGROUND: Over decades, improvements in presymptomatic screening and awareness of surgical benefits have changed the presentation and management of primary hyperparathyroidism (PHPT). Unrecognized multiglandular disease (MGD) remains a major cause of operative failure. We hypothesized that during parathyroid surgery the initial finding of a mildly enlarged gland is now frequent and predicts both MGD and failure. METHODS: A prospective database was queried to examine the outcomes of initial exploration for sporadic PHPT using intraoperative PTH monitoring (IOPTH) over 15 years. All patients had follow-up  $\geq 6$  months (mean = 1.8 years). Cure was defined by normocalcemia at 6 months and microadenoma by resected weight of  $< 200$  mg. RESULTS: Of the 1,150 patients, 98.9 % were cured and 15 % had MGD. The highest preoperative calcium level decreased over time ( $p < 0.001$ ) and varied directly with adenoma weight ( $p < 0.001$ ). Over time, single adenoma weight dropped by half ( $p = 0.002$ ) and microadenoma was increasingly common ( $p < 0.01$ ). MGD risk varied inversely with weight of first resected abnormal gland. Microadenoma required bilateral exploration more often than macroadenoma (48 vs. 18 %,  $p < 0.01$ ). When at exploration the first resected gland was  $< 200$  mg, the rates of MGD (40 vs. 11 %,  $p = 0.001$ ), inadequate initial IOPTH drop (67 vs. 79 %,  $p = 0.002$ ), operative failure (6.6 vs. 0.7 %,  $p < 0.001$ ), and long-term recurrence (1.6 vs. 0.3 %,  $p = 0.007$ ) were higher. CONCLUSIONS: Single parathyroid adenomas are smaller than in the past and require more complex pre- and intraoperative management. During exploration for sporadic PHPT, a first abnormal gland  $< 200$  mg should heighten suspicion of MGD and presages a tenfold higher failure rate.

PubMed-ID: [24510243](https://pubmed.ncbi.nlm.nih.gov/24510243/)

<http://dx.doi.org/10.1007/s00268-014-2450-1>

### **Bilateral Neck Exploration in Patients With Primary Hyperparathyroidism and Discordant Imaging Results: a Single-Centre Study.**

*Eur J Endocrinol*, 170(5):719-25.

Philippon M, Guerin C, Taieb D, Vaillant J, Morange I, Brue T, Conte-Devolx B, Henry JF, Slotema E, Sebag F, Castinetti F. 2014.

INTRODUCTION: Focused parathyroidectomy is the treatment of choice for patients with concordant positive imaging. Bilateral cervical exploration is performed for cases with discordant imaging, yet more than 70% of those cases are the result of a single-gland disease. As focused parathyroidectomy is generally costless and harmless, for cases with discordant imaging, we tried to determine whether preoperative characteristics can lead to a diagnosis of single-gland disease. METHODS: This study included 182 patients treated for primary hyperparathyroidism by bilateral exploration from 2009 to 2012 at La Timone Hospital, Marseille, France. We classified patients based on preoperative images and pathological results (single-gland or multiglandular disease). We then compared the demographical, laboratory and imaging results. We also asked a senior nuclear medicine practitioner who was blind to the ultrasound and pathological results to perform a second reading. RESULTS: Of the total number of patients, 15.4% had negative, 54.4% discordant and 30.2% concordant imaging. After reviewing the scintigraphy results, 8% of the cases with discordant imaging would have been classified as concordant with ultrasound. Subtraction scintigraphy obtained better results than dual-phase scintigraphy (concordance with ultrasound in 50 vs 31% with classical scintigraphy). For the cases of discordant imaging, no predictive factors of single-gland disease could be identified. Ultrasound and scintigraphy were similarly effective in determining the correct location of the abnormal gland. CONCLUSION: Discordant results of preoperative imaging modalities do not discriminate between uniglandular and multiglandular diseases in

hyperparathyroidism. Diagnostic differentiation between the different causes of hyperparathyroidism requires improvements in imaging techniques and might benefit from subtraction scintigraphy.

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<http://dx.doi.org/10.1530/EJE-13-0796>

### **[Localization of Parathyroid Adenomas With C11-Methionine PET-CT]**

#### **C-11-Methionin-PET/CT Zur Lokalisation Von Nebenschilddrüsenadenomen.**

*Chirurg*, 85(7):601-6.

Weber T, Luster M. 2014.

**BACKGROUND AND OBJECTIVES:** In primary hyperparathyroidism (pHPT) preoperative localization of parathyroid adenomas enables focussed unilateral parathyroidectomy. Ultrasound and sestamibi scintigraphy are the recommended standard procedures for primary diagnostics of pHPT and C-11 methionine positron emission tomography computed tomography (Met-PET/CT) is the latest technique for localization of hyperfunctioning parathyroid glands. **METHODS:** This review presents the results of Met-PET/CT on the basis of a selective literature search using the keywords "primary hyperparathyroidism and methionine", "primary hyperparathyroidism and PET", "parathyroid adenomas and methionine" and "parathyroid adenomas and PET". **RESULTS:** Localization of single gland adenomas can be achieved with Met-PET/CT in 79-91 % of cases. The advantages of this procedure are a high sensitivity even in operations for recurrences or concomitant thyroid nodules and an accurate detection even with atypical localizations. In multiglandular disease a localization of more than one hyperfunctioning gland remains difficult. Potential limitations of the method include the restricted availability and the relatively high costs of Met-PET/CT. **CONCLUSIONS:** Using Met-PET/CT hyperfunctioning parathyroid glands can be exactly localized in most patients with pHPT. Indications for this procedure are mostly when preoperative standard tests are negative and in parathyroid surgery for recurrences.

PubMed-ID: [24599386](https://pubmed.ncbi.nlm.nih.gov/24599386/)

<http://dx.doi.org/10.1007/s00104-013-2695-5>

### **Surgical Treatment of Patients With Mildly Elevated Parathormone and Calcium Levels.**

*World J Surg*, 38(6):1289-95.

Parikh PP, Allan BJ, Lew JI. 2014.

**BACKGROUND:** Patients with mildly elevated parathormone (PTH) and calcium levels consistent for primary hyperparathyroidism (pHPT) may present with more underlying multiglandular disease (MGD) and higher operative failure and recurrence rates than those with conventional, or "classic" pHPT. This study compared the clinical characteristics and surgical outcomes of patients with biochemically mild versus conventional pHPT. **METHODS:** A series of 707 consecutive patients underwent initial targeted parathyroidectomy with intraoperative parathormone monitoring (IPM) at a single institution. Biochemically mild (BM) pHPT was defined as PTH > 65 and <100 pg/ml with serum calcium >10.4 and <11 mg/dl. Conventional pHPT was defined as calcium >=11 mg/dl and PTH >= 100 pg/ml. Prospectively collected data for all patients, including operative indication, preoperative laboratory values, imaging, IPM dynamics, and postoperative laboratory values were retrospectively reviewed. Additional assessments included presence of MGD, bilateral neck exploration (BNE), single-gland volume, and operative failure or success, and recurrence. **RESULTS:** Of 60 patients with BM-pHPT, 46 reported preoperative bone pain, kidney stones, fatigue, and/or mental disturbances. The remaining 14 BM-pHPT patients underwent parathyroidectomy based on published asymptomatic guidelines. Patients with BM-pHPT had significantly more kidney stones, MGD, and BNE. Average single-gland volume and postoperative PTH levels were significantly lower in BM-pHPT patients. There were no significant differences between groups regarding preoperative localization accuracy, IPM dynamics, or operative success/failure, recurrence rates. **CONCLUSIONS:** BM-pHPT patients had more MGD requiring BNE but achieved operative success rates similar to those of patients with conventional disease. IPM successfully identifies MGD in BM-pHPT patients, who should be counseled regarding more extensive operations than limited parathyroidectomy.

PubMed-ID: [24615605](https://pubmed.ncbi.nlm.nih.gov/24615605/)

<http://dx.doi.org/10.1007/s00268-014-2487-1>

### **The Impact of Obesity on the Presentation of Primary Hyperparathyroidism.**

*J Clin Endocrinol Metab*, 99(7):2359-64.

Tran H, Grange JS, Adams-Huet B, Nwariaku FE, Rabaglia JL, Woodruff SL, Holt SA, Maalouf NM. 2014.

**CONTEXT:** Obesity has been associated with elevated serum PTH (sPTH) in the general population. Obesity may also alter the clinical presentation in patients with primary hyperparathyroidism (PHPT). **OBJECTIVES:** The objectives of the study were to compare the clinical presentation of obese (OB) vs nonobese (NO) PHPT patients and to assess the impact of obesity on the presentation of PHPT independent of serum calcium and PTH. **PATIENTS:** Consecutive PHPT patients who underwent parathyroidectomy between 2003 and 2012 by a

single surgical group participated in the study. SETTING: The study was conducted at an academic medical center. DESIGN: Cross-sectional review of records of preoperative demographic, historical, laboratory, and densitometry findings and intraoperative pathological findings were compared in OB vs NO patients. MAIN OUTCOME MEASURES: The prevalence of nephrolithiasis and osteoporosis was measured. RESULTS: Two hundred forty-seven PHPT patients were included in this analysis. Fifty percent were OB and 79% were women. Mean body mass index was 25.3 +/- 3.3 and 36.0 +/- 5.2 kg/m<sup>2</sup> in the NO and OB groups, respectively. Age, gender, and race distribution was similar between the two groups. Serum calcium was similar between the groups (11.0 +/- 0.7 mg/dL in NO vs 11.1 +/- 0.9 mg/dL in OB, P = .13), whereas sPTH was higher in OB (151 +/- 70 vs 136 +/- 69 pg/mL, P = .03). The OB group exhibited higher prevalence of hypercalciuria (urine calcium > 400 mg per 24 h) (41% vs 23% in NO, P = .01) and nephrolithiasis (36% vs 21% in NO, P = .03). Despite higher sPTH, OB patients showed higher bone mineral density and a lower rate of osteoporosis (21% vs 35%, P = .05). Differences in the prevalence of hypercalciuria and osteoporosis between the groups persisted after adjustment for age, race, estimated glomerular filtration rate, gender, sPTH, and calcium. CONCLUSIONS: In PHPT patients, obesity is a risk factor for hypercalciuria and nephrolithiasis and is protective against osteoporosis. The impact of parathyroidectomy on the clinical features of obese PHPT patients merits further evaluation.

PubMed-ID: [24684459](https://pubmed.ncbi.nlm.nih.gov/24684459/)

<http://dx.doi.org/10.1210/jc.2013-3903>

### **Initial Surgery for Benign Primary Hyperparathyroidism: an Analysis of 1,300 Patients in a Teaching Hospital.**

*World J Surg*, 38(8):2011-8.

Karakas E, Schneider R, Rothmund M, Bartsch DK, Schlosser K. 2014.

BACKGROUND: Success rates of initial surgery for primary hyperparathyroidism (pHPT) are greater than 95 % in specialized centers, mostly referring to single-surgeon experiences. The present study was performed to identify changes in clinical manifestations, diagnostic procedures, surgical strategies, and outcome of initial parathyroid interventions in a teaching hospital during the past 25 years with special regard to the surgical expertise. METHODS: Clinical data of patients who underwent an initial neck exploration for benign pHPT between 1985 and 2010 at the University hospital Marburg were retrospectively evaluated. All data were analyzed particularly with regard to the implementation of additional pre- and intraoperative procedures and to the particular surgical strategy. In addition, operative results were furthermore analyzed with regard to the experience of the responsible surgeons. RESULTS: An initial neck exploration for benign pHPT was performed in 1,300 patients. Of these, 1,035 patients had a bilateral cervical exploration (BCE) and 265 patients had a focused, minimally invasive parathyroidectomy (MIP). Cure rates did not differ between focused surgeries and BCE (98.9 vs. 98.3%, p = 0.596) after a mean follow-up of 33.4 (+/- 44.3) months. Postoperative transient hypoparathyroidism was significantly lower in the MIP group (11 vs. 47%, p < 0.0001). The rate of permanent recurrent laryngeal nerve palsies (0.4 vs. 2%, p = 0.064) and nonsurgical complications (0 vs. 1.4%, p = 0.0875) tended to be lower in the MIP group. Success and complication rates of chief surgeons (n = 2), attending surgeons (n = 20), and residents (56 < 3 years, 30 > 3 years) were similar, despite a significantly shorter operating time in the chief surgeon group (p < 0.01). CONCLUSIONS: Despite the implementation of several diagnostic procedures and significant changes concerning the surgical strategy, high success rates of primary interventions for pHPT did not change over the past three decades. High success rates also can be achieved in a teaching hospital, provided that surgery is supervised by an experienced endocrine surgeon. MIP is the treatment of choice in patients with benign sporadic pHPT and positive preoperative localization studies.

PubMed-ID: [24696057](https://pubmed.ncbi.nlm.nih.gov/24696057/)

<http://dx.doi.org/10.1007/s00268-014-2520-4>

### **Transoral Parathyroid Surgery--a New Alternative or Nonsense?**

*Langenbecks Arch Surg*, 399(6):741-5.

Karakas E, Steinfeldt T, Gockel A, Mangalo A, Sesterhenn A, Bartsch DK. 2014.

PURPOSE: In recent years, several endoscopic techniques have been explored in thyroid and parathyroid surgery, but only few gained acceptance among patients and surgeons. Based on extensive human cadaver and animal studies, we developed a technique for transoral partial parathyroidectomy (TOPP), which was performed for the first time in a patient with primary hyperparathyroidism (pHPT). We now report on results and the acceptance of this new technique 2 years after its implementation. METHODS: A pilot study was initiated to recruit a total of 10 patients with benign sporadic pHPT and a preoperatively localized parathyroid adenoma eligible for initial parathyroidectomy. The study protocol was approved by the ethics committee, and an insurance for unforeseen complications and risks was procured. Data of all patients evaluated and operated were prospectively collected, and follow-up examinations were carried out for 19 months on average, which

included clinical examinations; ultrasonography; Ear, Nose, and Throat (ENT) investigations; and blood testing. RESULTS: Between January 2010 and May 2012, 75 patients with pHPT and a preoperative localized parathyroid adenoma were eligible for TOPP. After detailed information about the transoral procedure, only five (7 %) female patients consent to undergo TOPP. In three patients, a parathyroid adenoma could be removed via the transoral access, In two patients, the procedure had to be converted to the conventional technique. Median time until resection of a parathyroid adenoma was 122 min (range, 45-175). One patient had a transient recurrent laryngeal nerve palsy, while one patient suffered from a transient palsy of the right hypoglossal nerve and a slight but persisting dysgeusia. Three patients developed a hematoma of the mouth floor and swallowing problems. In four patients, the visual analog scale (VAS) pain score was high (>7) within the first 2 postoperative days. CONCLUSIONS: Although TOPP is feasible, it is poorly accepted by patients and its complication rate is high. Thus, TOPP is nonsense with currently available devices.

PubMed-ID: [24728604](https://pubmed.ncbi.nlm.nih.gov/24728604/)

<http://dx.doi.org/10.1007/s00423-014-1187-5>

### **Renal Impairment As a Surgical Indication in Primary Hyperparathyroidism: Do the Data Support This Recommendation?**

*J Clin Endocrinol Metab*, 99(8):2646-50.

Hendrickson CD, Castro Pereira DJ, Comi RJ. 2014.

CONTENT: Management of primary hyperparathyroidism has evolved over the past two decades, yet impaired renal function has consistently been a surgical indication. This recommendation has been based upon the historical association between primary hyperparathyroidism and renal impairment, and a review of the literature is needed to determine whether such a recommendation is warranted. EVIDENCE ACQUISITION AND SYNTHESIS: PubMed was utilized to identify English-language articles published between January 1990 and February 2014 using keywords related to hyperparathyroidism and renal function. The keywords were "primary hyperparathyroidism," "surgery," "parathyroidectomy," "kidney," "renal," "glomerular filtration rate," and "creatinine." Of the 1926 articles obtained with this search, all articles germane to the topic that quantified the relationship between primary hyperparathyroidism and renal function were included. All references within these articles were investigated for inclusion. When helpful, data tables were constructed to summarize the results succinctly. CONCLUSIONS: A secondary elevation of PTH levels has not been consistently shown to occur at the threshold currently indicated for surgical intervention. While renal impairment is seen with more significant disease, mild asymptomatic primary hyperparathyroidism has not been conclusively associated with renal impairment. Furthermore, there is no evidence to suggest that surgically curing primary hyperparathyroidism via a parathyroidectomy has any impact upon renal function.

PubMed-ID: [24758187](https://pubmed.ncbi.nlm.nih.gov/24758187/)

<http://dx.doi.org/10.1210/jc.2014-1379>

### **High Cardiac Background Activity Limits 99mTc-MIBI Radioguided Surgery in Aortopulmonary Window Parathyroid Adenomas.**

*BMC Surg*, 14:22.

Schwarzlmuller T, Brauckhoff K, Lovas K, Biermann M, Brauckhoff M. 2014.

BACKGROUND: Radioguided surgery using 99m-Technetium-methoxyisobutylisonitrile (99mTc-MIBI) has been recommended for the surgical treatment of mediastinal parathyroid adenomas. However, high myocardial 99mTc-MIBI uptake may limit the feasibility of radioguided surgery in aortopulmonary window parathyroid adenoma. CASE PRESENTATION: Two female patients aged 72 (#1) and 79 years (#2) with primary hyperparathyroidism caused by parathyroid adenomas in the aortopulmonary window were operated by transsternal radioguided surgery. After intravenous injection of 370 MBq 99mTc-MIBI at start of surgery, the maximum radioactive intensity (as counts per second) was measured over several body regions using a gamma probe before and after removal of the parathyroid adenoma. Relative radioactivity was calculated in relation to the measured ex vivo radioactivity of the adenoma, which was set to 1.0. Both patients were cured by uneventful removal of aortopulmonary window parathyroid adenomas of 4400 (#1) and 985 mg (#2). Biochemical cure was documented by intraoperative measurement of parathyroid hormone as well as follow-up examination. Ex vivo radioactivity over the parathyroid adenomas was 196 (#1) and 855 counts per second (#2). Before parathyroidectomy, relative radioactivity over the aortopulmonary window versus the heart was found at 1.3 versus 2.6 (#1) and 1.8 versus 4.8 (#2). After removal of the adenomas, radioactivity within the aortopulmonary window was only slightly reduced. CONCLUSION: High myocardial uptake of 99mTc-MIBI limits the feasibility of radioguided surgery in aortopulmonary parathyroid adenoma.

PubMed-ID: [24758398](https://pubmed.ncbi.nlm.nih.gov/24758398/)

<http://dx.doi.org/10.1186/1471-2482-14-22>

### **Robotic Surgery for Primary Hyperparathyroidism.**

*Surg Endosc*, 28(9):2702-7.

Karagkounis G, Uzun DD, Mason DP, Murthy SC, Berber E. 2014.

**BACKGROUND:** Open cervical parathyroidectomy is the standard of care for the treatment of primary hyperparathyroidism (PHP). However, in patients with a history of keloid or hypertrophic scar formation, the cosmetic result may sometimes be unsatisfactory. Furthermore, in the presence of mediastinal glands, a more morbid approach is sometimes necessary, involving a sternal split or thoracotomy. Robotic parathyroidectomy, either transaxillary or transthoracic, could be an alternative in both settings. **METHODS:** Between 2008 and 2013, 14 patients with PHP and a well-localized single adenoma underwent robotic transaxillary cervical (TAC) (n = 8) or transthoracic mediastinal (TTM) (n = 6) parathyroidectomy at an academic tertiary medical center and their outcomes were analyzed. **RESULTS:** All 14 operations were completed successfully as planned. For TAC and TTM parathyroidectomies, mean operative time was 184 and 168 min, respectively. With the exception of one TTM patient, intraoperative PTH determination indicated a >50 % drop in all patients 10 min after excision and no patients presented with recurrent disease on follow-up. Average length of hospital stay was 1 day after TAC parathyroidectomy and 2.2 days after TTM. On a visual analog pain scale (0-10), average pain scores after TAC were 6/10 on postoperative day 1 and 1/10 on day 14, compared to 7.7/10 and 1.5/10, respectively, after TTM. Complications included development of seroma in 1 patient in the TAC group and pericardial and pleural effusion in 1 patient in the TTM cohort. **CONCLUSIONS:** This initial study shows that robotic TAC and TTM parathyroidectomy are feasible in selected PHP patients with preoperatively well-localized disease. Although the TAC approach offers a potential cosmetic benefit in patients with a history of keloid or hypertrophic scar formation, a more generalized use cannot be recommended based on current evidence. The robotic TTM approach presents a minimally invasive alternative to resections previously performed through thoracotomy and sternotomy.

PubMed-ID: [24771196](https://pubmed.ncbi.nlm.nih.gov/24771196/)

<http://dx.doi.org/10.1007/s00464-014-3531-9>

### **Normocalcemic Hyperparathyroidism: Preoperatively a Disease, Postoperatively Cured?**

*Am J Surg*, 207(5):673-80.

Stuart HC, Harvey A, Pasiaka JL. 2014.

**BACKGROUND:** Up to 44% of primary hyperparathyroidism patients have elevated parathyroid hormone (ePTH) with normal calcium postparathyroidectomy (PTx). The question is whether the surgical approach affects the incidence of this phenomenon. **METHODS:** Patients with hyperparathyroidism and presumed single-gland disease on preoperative imaging who underwent PTx between 1994 and 2008 were identified and contacted for long-term follow-up. PTx was either a focused approach (minimally invasive approach [MIP]) or a bilateral neck exploration (BNE). **RESULTS:** In total, 171 patients had PTH measured postoperatively (95 MIP and 76 BNE); 30 of 171 (17%) had ePTH with normal calcium (MIP 21 [22%] and BNE 9 [12%], P = .08). This occurred within 2 years in 48% and 67% and after 2 years in 52% and 33%, MIP vs BNE, respectively. Four patients recurred, 2 MIP and 2 BNE. **CONCLUSIONS:** There is a trend toward a higher incidence of ePTH in patients having undergone an MIP. The etiology of ePTH is multifactorial but may represent an early recurrence.

PubMed-ID: [24791626](https://pubmed.ncbi.nlm.nih.gov/24791626/)

<http://dx.doi.org/10.1016/j.amjsurg.2014.01.005>

### **Total Parathyroidectomy With Trace Amounts of Parathyroid Tissue Autotransplantation As the Treatment of Choice for Secondary Hyperparathyroidism: a Single-Center Experience.**

*BMC Surg*, 14:26.

He Q, Zhuang D, Zheng L, Fan Z, Zhou P, Zhu J, Duan S, Li Y, Ge Y, Lv Z, Cao L. 2014.

**BACKGROUND:** The aim of the study was to evaluate total parathyroidectomy with trace amounts of parathyroid tissue (30 mg) as a surgical option in secondary hyperparathyroidism (sHPT) treatment. **METHODS:** From January 2008 to March 2012, 47 patients underwent parathyroidectomy. Comparisons of demographic data, symptoms, and preoperative or postoperative biochemistry were made between total parathyroidectomy with trace amounts of parathyroid tissue autotransplantation group and total parathyroidectomy group. **RESULTS:** Out of 47 cases, 45 had successful operation. 187 parathyroid glands identified at the initial operation were reported in 47 patients. 43 patients had been diagnosed with parathyroid hyperplasia, and 4 patients had a benign adenoma. After operation, pruritus, bone pain and muscle weakness disappeared, also serum PTH and serum phosphate were declined markedly as well. After discharge, two patients (in total parathyroidectomy group) were readmitted because of postoperative hypoparathyroidism. Graft-dependent recurrence was not observed in an average follow-up of 42 months. **CONCLUSIONS:** Total parathyroidectomy with sternocleidomastoid muscle trace amounts of parathyroid tissue autotransplantation is considered to be a feasible, safe and effective surgical option for the patients with sHPT.

### **A Novel Technique to Improve the Diagnostic Yield of Negative Sestamibi Scans.**

*Surgery*, 156(3):584-90.

Nagar S, Walker DD, Embia O, Kaplan EL, Grogan RH, Angelos P. 2014.

**INTRODUCTION:** Minimally invasive parathyroidectomy is successful in achieving cure for most patients with primary hyperparathyroidism. Most surgeons rely on preoperative imaging as part of the workup for localization. Ultrasonography and sestamibi are the 2 most commonly used preoperative imaging studies. When these 2 studies are positive and concordant the preoperative localization is straightforward. However, when  $\geq 1$  of these studies is negative, the preoperative localization is suspect. We hypothesize that the yield of useful localizing information from "negative" sestamibi scans can be increased in certain situations. Specifically, in cases where the thyroid lobe length seen on sestamibi is discordant from the lobe length of the ultrasonography, this often represents a "hidden" parathyroid adenoma. If our hypothesis is correct, this could lead to decreased resource utilization in cases of nonlocalized parathyroid adenomas. **METHODS:** We retrospectively analyzed our database of patients with primary hyperparathyroidism who underwent parathyroidectomy from 2005 to 2011. The anteroposterior views of early phase sestamibi were analyzed for thyroid lobe lengths. A ratio of the length of the right lobe to left lobe was calculated. The thyroid lobe lengths on ultrasonography were measured and similar ratios were calculated. The difference in ratios between sestamibi and ultrasonography was calculated for each patient. A difference in ratios from sestamibi and ultrasonography that corresponded with a "hidden" parathyroid on the side of the additional length on sestamibi at the time of surgery was considered a positive finding. When the difference in ratios from the 2 images did not correspond with a "hidden" parathyroid at the time of operation, it was considered a negative finding. **RESULTS:** There were 59 patients with single-gland disease, negative sestamibi, and images available for review. There were 32 patients (54%) with the positive finding of a "hidden" parathyroid corresponding with a difference in thyroid lobe length ratios from sestamibi and ultrasonography. The overall mean difference in ratios between sestamibi and ultrasonography was  $0.37 \pm 0.32$ . The mean ratio difference in the group of patients with a negative "hidden" parathyroid was  $0.11 \pm 0.02$ , and the mean ratio difference in the group of patients with a positive "hidden" parathyroid was  $0.58 \pm 0.05$  ( $P < .001$ ). When a difference in ratios of  $\geq 0.23$  was obtained, this predicted a "hidden" parathyroid with a sensitivity of 93.8% and specificity of 85.2%. There were 39 patients with multigland disease, negative sestamibi, and images available for review. None of these patients had a ratio difference of  $\geq 0.23$ . The mean ratio difference for patients with multigland disease was significantly lower than that of the single-gland disease ( $0.08 \pm 0.06$  vs  $0.37 \pm 0.32$ ;  $P < .001$ ). **CONCLUSION:** Discordance between thyroid lobe lengths on the early phase sestamibi compared with ultrasonography has led to successful preoperative identification of parathyroid adenomas, even though the sestamibi was traditionally read as negative. This finding has not been previously described, seems to be reliable, and can lead to improved preoperative localization and decreased resource utilization in this subset patients.

PubMed-ID: [24931283](https://pubmed.ncbi.nlm.nih.gov/24931283/)

<http://dx.doi.org/10.1016/j.surg.2014.05.020>

### **Trends in the Frequency and Quality of Parathyroid Surgery: Analysis of 17,082 Cases Over 10 Years.**

*Ann Surg*,

Abdulla AG, Ituarte PH, Harari A, Wu JX, Yeh MW. 2014.

**OBJECTIVE::** To examine trends in the frequency and quality of surgery for primary hyperparathyroidism (PHPT) in California during the period of 1999 to 2008. **BACKGROUND::** The quality of surgery for PHPT can be measured by the complication rate and the success rate of surgery. A fraction of patients with failed initial surgery undergo reoperation. **METHODS::** Data on patients undergoing parathyroidectomy (PTx) were obtained from the California Office of Statewide Health Planning and Development. Renal transplant recipients and dialysis patients were excluded. Hospitals were categorized by case volume: Very low: 1 to 4 operations annually; Low: 5 to 9; Medium, 10 to 19; High: 20 to 49; Very high: 50 or more. Complication rates and the percentage of cases requiring reoperation were analyzed. **RESULTS::** A total of 17,082 cases were studied. Annual case volume grew from 990 to 2746 (177% increase) over the study period, corresponding to a 147% increase in the per capita PTx rate. The proportion of cases performed by very high-volume hospitals increased from 6.4% to 20.5% ( $P < 0.001$ ). The overall complication rate declined from 8.7% to 3.8% ( $P < 0.001$ ). Complication rates were inversely related to hospital volume (very high volume, 3.9% vs very low volume, 5.2%,  $P < 0.05$ ). Reoperation was performed in 363 patients (2.1%). The reoperation rate increased from 0.91% to 2.73% during the study period ( $P < 0.01$ ). The reoperation rate was inversely and nonlinearly related to hospital volume, as described by the equation  $\% \text{ reoperation} = 100/(\text{total hospital case volume})$ . **CONCLUSIONS::** Surgery for PHPT has grown safer and more common over time. High-volume centers have lower rates of

complication and reoperation.

PubMed-ID: [24950283](https://pubmed.ncbi.nlm.nih.gov/24950283/)

<http://dx.doi.org/10.1097/SLA.0000000000000812>

### **Long-Term Outcome After Parathyroidectomy for Lithium-Induced Hyperparathyroidism.**

*Br J Surg*, 101(10):1252-6.

Norlen O, Sidhu S, Sywak M, Delbridge L. 2014.

**BACKGROUND:** The accepted management of lithium-associated hyperparathyroidism (LiHPT) is open four-gland parathyroid exploration (OPTX). This approach has recently been the subject of controversy. A recent study has shown very high long-term recurrence rates after OPTX, whereas some have promoted unilateral focused parathyroidectomy as appropriate management. The aim was to evaluate long-term outcomes after surgery for LiHPT and to assess the accuracy of preoperative imaging. **METHODS:** This was a retrospective cohort study that comprised all patients undergoing initial surgery for LiHPT between 1990 and 2013. The cumulative recurrence rate was calculated by the Kaplan-Meier method. The sensitivity and specificity of sestamibi scintigraphy and ultrasound imaging for identification of single-gland versus multigland disease was investigated using intraoperative assessment as reference. **RESULTS:** Of 48 patients, 45 had OPTX and three underwent focused parathyroidectomy. Multiglandular disease was documented in 27 patients and 21 had a single adenoma. The median follow-up was 5.9 (range 0.3-22) years and 16 patients died during follow-up. The 10-year cumulative recurrence rate was 16 (95 per cent confidence interval 2 to 29) per cent. No permanent complications occurred after primary surgery for LiHPT. Twenty-four patients had at least one preoperative ultrasound or sestamibi scan. For concordant sestamibi scintigraphy and ultrasound imaging, the sensitivity and specificity for identifying single-gland versus multigland disease was five of nine and five of eight respectively. **CONCLUSION:** Surgery provided a safe and effective management option for patients with LiHPT in this series, with a long-term cure rate of well over 80 per cent.

PubMed-ID: [25043401](https://pubmed.ncbi.nlm.nih.gov/25043401/)

<http://dx.doi.org/10.1002/bjs.9589>

### **The Biochemical Severity of Primary Hyperparathyroidism Correlates With the Localization Accuracy of Sestamibi and Surgeon-Performed Ultrasound.**

*J Am Coll Surg*,

Hughes DT, Sorensen MJ, Miller BS, Cohen MS, Gauger PG. 2014.

**BACKGROUND:** Minimally invasive parathyroidectomy for primary hyperparathyroidism is dependent on preoperative localization, commonly with ultrasound and sestamibi imaging. This study sought to determine if preoperative serum calcium and parathyroid hormone (PTH) levels correlate with localization sensitivity and positive predictive value (PPV). **STUDY DESIGN:** This is a retrospective analysis of a prospective database of 1,910 patients with primary hyperparathyroidism from 2002 to 2013, who had surgeon-performed ultrasound and/or sestamibi for preoperative localization. The sensitivity and PPV of ultrasound and sestamibi were analyzed by degree of preoperative serum calcium and parathyroid hormone level perturbation. **RESULTS:** In 1,910 parathyroidectomy patients, ultrasound was localizing in 1,411 of 1,644 (86%) and sestamibi in 802 of 1,165 (69%) ( $p < 0.01$ ). The PPV of ultrasound was 1,135 of 1,411 (80%) and sestamibi was 705 of 802 (88%) ( $p < 0.01$ ). Using logistic regression analysis, there was statistically significant positive correlation between localization and preoperative serum calcium for both sestamibi (odds ratio [OR] 1.21 [95% CI 1.00 to 1.47;  $p < 0.05$ ]) and ultrasound (OR 1.29 [95% CI 1.03 to 1.60;  $p < 0.05$ ]). There was a weak, but statistically significant positive correlation of PTH with sestamibi localization (OR 1.00 [95% CI 1.00 to 1.01;  $p < 0.05$ ]). There was no statistically significant correlation between the PPV and serum calcium or PTH for either study. When patients were divided into quartiles of preoperative serum calcium and PTH levels, localization rates and PPV of both ultrasound and sestamibi increased with higher calcium and PTH levels. Surgeon-performed ultrasound had higher localization rates than sestamibi, with lower calcium and PTH values. Sestamibi demonstrated higher PPV values across all quartiles. **CONCLUSIONS:** Surgeon-performed ultrasound and sestamibi have higher localization rates and PPV, with increasing preoperative serum calcium and PTH levels. Surgeon-performed ultrasound may be a better initial test for patients with lower calcium ( $<10.5$  mg/dL) and PTH ( $<90$  pg/mL) values due to significantly higher localization rates; however, a localizing sestamibi has higher PPV.

PubMed-ID: [25086814](https://pubmed.ncbi.nlm.nih.gov/25086814/)

<http://dx.doi.org/10.1016/j.jamcollsurg.2014.06.020>

# Adrenals

## Meta-Analyses

- None -

## Randomized controlled trials

- None -

## Consensus Statements/Guidelines

### **Pheochromocytoma and Paraganglioma: an Endocrine Society Clinical Practice Guideline.**

*J Clin Endocrinol Metab*, 99(6):1915-42.

Lenders JW, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH, Naruse M, Pacak K, Young WF, Jr. 2014.

**OBJECTIVE:** The aim was to formulate clinical practice guidelines for pheochromocytoma and paraganglioma (PPGL). **PARTICIPANTS:** The Task Force included a chair selected by the Endocrine Society Clinical Guidelines Subcommittee (CGS), seven experts in the field, and a methodologist. The authors received no corporate funding or remuneration. **EVIDENCE:** This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe both the strength of recommendations and the quality of evidence. The Task Force reviewed primary evidence and commissioned two additional systematic reviews. **CONSENSUS PROCESS:** One group meeting, several conference calls, and e-mail communications enabled consensus. Committees and members of the Endocrine Society, European Society of Endocrinology, and American Association for Clinical Chemistry reviewed drafts of the guidelines. **CONCLUSIONS:** The Task Force recommends that initial biochemical testing for PPGLs should include measurements of plasma free or urinary fractionated metanephrines. Consideration should be given to preanalytical factors leading to false-positive or false-negative results. All positive results require follow-up. Computed tomography is suggested for initial imaging, but magnetic resonance is a better option in patients with metastatic disease or when radiation exposure must be limited. (123)I-metaiodobenzylguanidine scintigraphy is a useful imaging modality for metastatic PPGLs. We recommend consideration of genetic testing in all patients, with testing by accredited laboratories. Patients with paraganglioma should be tested for SDHx mutations, and those with metastatic disease for SDHB mutations. All patients with functional PPGLs should undergo preoperative blockade to prevent perioperative complications. Preparation should include a high-sodium diet and fluid intake to prevent postoperative hypotension. We recommend minimally invasive adrenalectomy for most pheochromocytomas with open resection for most paragangliomas. Partial adrenalectomy is an option for selected patients. Lifelong follow-up is suggested to detect recurrent or metastatic disease. We suggest personalized management with evaluation and treatment by multidisciplinary teams with appropriate expertise to ensure favorable outcomes.

PubMed-ID: [24893135](https://pubmed.ncbi.nlm.nih.gov/24893135/)

<http://dx.doi.org/10.1210/jc.2014-1498>

## Other Articles

### **LH, Progesterone, and TSH Can Stimulate Aldosterone in Vitro: a Study on Normal Adrenal Cortex and Aldosterone Producing Adenoma.**

*Horm Metab Res*, 46(5):318-21.

Nicolini G, Balzan S, Morelli L, Iacconi P, Sabatino L, Ripoli A, Fommei E. 2014.

Endocrine factors different from ACTH or angiotensin II can stimulate aldosterone secretion and have a role in the pathophysiology of hyperaldosteronism. Aldosterone may increase in luteotropic/progestogenic and in hypothyroid states; LH and, occasionally, TSH receptors have been detected in normal adrenal cortex and aldosterone-producing adenoma. The aim of the study was to compare adrenal contents of LH and TSH

receptors between normal cortex and aldosterone-producing adenoma and to evaluate the ability of LH, its product progesterone, and TSH to stimulate aldosterone secretion in vitro from primary adrenocortical cells. Surgical aldosterone-producing adenoma fragments from 19 patients and adrenal cortex fragments from 10 kidney donors were used for Western blotting and cell cultures. LH (n=26), TSH (n=19) and progesterone (n=8) receptor proteins were investigated; LH receptor-mRNA was also tested in 8 samples. Aldosterone responses in vitro to LH, progesterone, and TSH stimulation were assayed. LH and TSH receptors were more expressed in adenoma than normal cortex ( $p < 0.01$ ,  $p < 0.05$ , respectively); progesterone receptor was observed in 6/8 samples. Aldosterone increased after in vitro stimulation with LH (5/12 adenoma, 1/7 normal cells), progesterone (4/5 adenoma, 5/6 normal cells), and TSH (3/5 adenoma and 3/5 normal cells). LH and TSH receptors were more expressed in aldosterone producing adenoma than normal adrenal cortex. LH, progesterone, and TSH can stimulate aldosterone in vitro. Similar mechanisms could participate in vivo in the aldosterone increase in lutetotropic, progestogenic, or hypothyroid states and may exist in both normal adrenal cortex and adenoma in responsive individuals.

PubMed-ID: [24297486](https://pubmed.ncbi.nlm.nih.gov/24297486/)

<http://dx.doi.org/10.1055/s-0033-1358733>

### **Adrenal Metastectomy Is Safe in Selected Patients.**

*World J Surg*, 38(6):1336-42.

Romero Arenas MA, Sui D, Grubbs EG, Lee JE, Perrier ND. 2014.

**BACKGROUND:** The benefit of adrenalectomy (ADX) for adrenal metastasis is not established. We evaluated outcomes after ADX for patients with adrenal metastasis. **METHODS:** We retrospectively analyzed the records of 90 patients who underwent ADX for metastatic disease. Overall survival (OS) after ADX was calculated using the Kaplan-Meier method. Clinical factors were evaluated for associations with OS using a Cox regression model, and with operative factors using the Wilcoxon two-sample or Fisher's exact test. **RESULTS:** The most common primary tumor types were melanoma (35, 39 %) and lung cancer (32, 35 %). A total of 49 (54 %) patients had isolated adrenal metastasis; 55 (61 %) underwent laparoscopic resection (LADX). Median OS was 2.46 years (range < 1 month-15 years), and 5-year survival rate was 38 % (6 % standard error). Most patients experienced disease progression (56, 62 %) despite achieving disease-free status following ADX (78, 86 %). When compared with the open approach, LADX was associated with smaller tumor size, as well as reduced blood loss, operative time, and length of stay (all  $p < 0.0001$ ), and no difference in OS ( $p = 0.4122$ ) or complications ( $p = 1$ ). Isolated adrenal bed recurrence was similar in LADX (N = 3, 5 %) and open ADX (N = 2, 6 %) ( $p = 1$ ), and did not affect OS ( $p = 0.2$ ). Larger tumors were associated with shorter median OS ( $p = 0.0014$ ). **CONCLUSIONS:** ADX for metastasis can be safely performed in selected patients. Some patients with adrenal metastasis achieve prolonged survival following ADX. Compared with an open approach, LADX has no measurable oncologic disadvantage, minimizes morbidity, and should be considered when tumor characteristics permit.

PubMed-ID: [24452292](https://pubmed.ncbi.nlm.nih.gov/24452292/)

<http://dx.doi.org/10.1007/s00268-014-2454-x>

### **Is Adrenal Venous Sampling Mandatory Before Surgical Decision in Case of Primary Hyperaldosteronism?**

*World J Surg*, 38(7):1749-54.

Pirvu A, Naem N, Baguet JP, Thony F, Chabre O, Chaffanjon P. 2014.

**BACKGROUND:** Primary hyperaldosteronism (PHA) is a cause of secondary arterial hypertension potentially curable by laparoscopic unilateral adrenalectomy. We describe the follow-up of these patients according to their medical or surgical treatment. **METHODS:** We report a retrospective single-center study of 91 patients with PHA from 1998 to 2012. Treatment was guided by computed tomography (CT) scans. Preoperative adrenal vein sampling (AVS) was performed when the CT scan did not show single solitary unilateral nodules on the adrenal glands. During the follow-up, we considered hypertension to be cured in patients with normal blood pressure without antihypertensive medication (AM), and improvement was defined by a decrease in AM. **RESULTS:** A total of 28 patients received only AM. Of the 62 patients who underwent a unilateral adrenalectomy, 46 (74 %) had an adrenal adenoma, 14 (22 %) a hyperplasia, and the adrenal gland was normal in two cases. Hypertension was cured in 24 cases (38 %), and 28 patients (45 %) showed improvement with a reduction in AM. Predictive factors for a cure were gender, age, number of preoperative AMs, preoperative arterial systolic blood pressure, and plasma renin activity. All patients who presented with hypokalemia were cured postoperatively. We performed 38 AVS and nine of these patients were operated on based on the AVS findings, with an improvement of 100 % of arterial blood pressure after surgery. **CONCLUSION:** Laparoscopic unilateral adrenalectomy for PHA cured or improved hypertension in 84 % of patients. Preoperative AVS is mandatory for surgical decision making if the CT scan shows bilateral or no lesions associated with PHA.

PubMed-ID: [24481990](https://pubmed.ncbi.nlm.nih.gov/24481990/)  
<http://dx.doi.org/10.1007/s00268-014-2461-y>

### **Age Below 40 or a Recently Proposed Clinical Prediction Score Cannot Bypass Adrenal Venous Sampling in Primary Aldosteronism.**

*J Clin Endocrinol Metab*, 99(6):E1035-E1039.

Riester A, Fischer E, Degenhart C, Reiser MF, Bidlingmaier M, Beuschlein F, Reincke M, Quinkler M. 2014. CONTEXT: Adrenal venous sampling (AVS) is used to distinguish bilateral from unilateral primary aldosteronism (PA). Due to its limited availability, clinical prediction scores have been proposed to diagnose unilateral disease without AVS. OBJECTIVE: Our goal was to test 2 recently proposed predictors of unilateral PA: 1) a clinical prediction score using imaging, serum potassium, and glomerular filtration rate and 2) the combination of visible unilateral adenoma on imaging and age <40 years. DESIGN AND SETTING: We used the data of all patients with PA of the prospective German Conn's Registry treated in Munich and Berlin since 2008. PATIENTS AND INTERVENTION: Of 205 patients with PA, 194 had a successful AVS and were included. MAIN OUTCOME MEASURES: Parameters were compared between patients with lateralized and nonlateralized AVS. Specificity and sensitivity of the proposed predictors were calculated. RESULTS: A total of 130 patients (67%) had unilateral PA according to AVS. Patients with unilateral PA showed a significantly lower estimated glomerular filtration rate compared with patients with bilateral disease ( $P < .05$ ). The cohorts differed significantly in potassium supplementation, serum potassium, baseline and post-saline plasma aldosterone, baseline aldosterone to renin ratio, and adenoma in imaging. The proposed prediction score had a sensitivity of 46% (58 of 127) and a specificity of 80% (53 of 66). In patients below 40 years ( $n = 28$ ), the prediction score achieved a specificity of 100%; however, relying only on imaging in this young cohort, the specificity dropped to 83%. CONCLUSIONS: The suggested prediction score has high accuracy only in young patients but cannot substitute for AVS in the elderly.

PubMed-ID: [24601689](https://pubmed.ncbi.nlm.nih.gov/24601689/)  
<http://dx.doi.org/10.1210/jc.2013-3789>

### **The Role of Adrenal Scintigraphy in the Diagnosis of Subclinical Cushing's Syndrome and the Prediction of Post-Surgical Hypoadrenalism.**

*World J Surg*, 38(6):1328-35.

Ricciato MP, Di D, V, Perotti G, Pontecorvi A, Bellantone R, Corsello SM. 2014.

BACKGROUND: Management of subclinical Cushing's syndrome (SCS) remains controversial; it is not possible to predict which patients would benefit from adrenalectomy. In the present study we aimed to evaluate the role of adrenocortical scintigraphy (ACS) in the management of patients with SCS. METHODS: The medical records of 33 consecutive patients with adrenal "incidentaloma" and proven or suspected SCS who underwent (131)I-19-iodocholesterol ACS between 2004 and 2010 were reviewed. Sixteen underwent laparoscopic adrenalectomy (surgical group-S-group) and 17 were medically managed (medical group-M-group). Follow-up evaluation was obtained by outpatient consultation. RESULTS: Overall 25 patients (15 in the S-group and 10 in the M-group) had concordant unilateral uptake at ACS (ACS+). In the S-group, the mean follow-up duration was 30.9 +/- 16.1 months and, irrespective of the presence of hormonal diagnosis of SCS, in patients who were ACS+ adrenalectomy resulted in a significant increase in HDL cholesterol and decreases in body mass index, glycemia, and blood pressure (BP). One patient reduced antihypertensive medication and three others were able to discontinue it altogether. Prolonged postoperative hypoadrenalism (PH) occurred in 14 patients in the S-group. The overall accuracy in predicting PH was 93.7 % for ACS and 68.7 % for laboratory findings. In the M-group, the mean follow-up duration was 31.5 +/- 26.3 months and no patient developed overt Cushing's syndrome, although ACS+ patients experienced a worsening in glycemia and diastolic BP. CONCLUSIONS: Adrenal scintigraphy seems the most accurate diagnostic test for SCS. It is able to predict the metabolic outcome and the occurrence of PH, identifying the patients who could benefit from adrenalectomy irrespective of hormonal diagnosis.

PubMed-ID: [24615601](https://pubmed.ncbi.nlm.nih.gov/24615601/)  
<http://dx.doi.org/10.1007/s00268-014-2482-6>

### **Borderline Resectable Adrenal Cortical Carcinoma: a Potential Role for Preoperative Chemotherapy.**

*World J Surg*, 38(6):1318-27.

Bednarski BK, Habra MA, Phan A, Milton DR, Wood C, Vauthey N, Evans DB, Katz MH, Ng CS, Perrier ND, Lee JE, Grubbs EG. 2014.

BACKGROUND: Adrenal cortical carcinoma (ACC) may have tumor or patient characteristics at presentation that argue against immediate surgery because of an unacceptable risk of morbidity/mortality, incomplete resection, or recurrence. This clinical stage can be characterized as borderline resectable ACC (BRACC). At

present, systemic therapies in ACC can reduce tumor burden in some patients, creating an opportunity in BRACC for a strategy of preoperative chemotherapy (ctx) followed by surgery. **MATERIALS AND METHODS:** A single-institution retrospective review was conducted of all patients considered for surgery for primary ACC. Patients with BRACC treated with preoperative ctx were categorized as follows: group A, imaging suggesting a need for multiorgan/vascular resection; group B, imaging suggesting potentially resectable oligometastases; and group C, patients having marginal performance status/comorbidities precluding immediate surgery. Both the disease-free survival (DFS) and the overall survival (OS) were compared in BRACC patients treated with preoperative ctx+surgery and those who had upfront surgery. **RESULTS:** Fifty-three patients with primary ACC were considered for surgery (median follow-up: 49.9 months). Thirty-eight patients (71.7 %) had initial surgery and 15 of them (28.3 %) were considered BRACC and received preoperative therapy. Of these 15 patients, 12 (80 %) received combination therapy with mitotane and etoposide/cisplatin-based ctx, 2 (13 %) received mitotane alone, and 1 (7 %) received ctx alone. Six patients were defined as group A, 5 as group B, and 4 as group C. Thirteen (87 %) BRACC patients underwent surgical resection. BRACC patients were younger but had more advanced disease than the patients having initial surgery (stage IV in 40 vs 2.6 % [p < 0.01]). By Response Evaluation Criteria In Solid Tumors criteria, 5 patients (38.5 %) had a partial response, 7 (53.8 %) had stable disease, and 1 (7.7 %) had disease that progressed. Postoperative mitotane use was similar between groups (p = .15). Median DFS for resected BRACC patients was 28.0 months [95 % confidence interval (CI), 2.9-not attained] vs 13 months (95 % CI, 5.8-46.9) (p = 0.40) for initial surgery patients. Five-year OS rates were also similar: 65 % for resected BRACC vs 50 % for initial surgery (p = 0.72). **CONCLUSIONS:** The favorable outcome of patients with BRACC, despite more advanced stage of disease compared to those treated with surgery first, together with uncommon disease progression, suggests a benefit of neoadjuvant treatment sequencing in patients with BRACC.

PubMed-ID: [24615603](https://pubmed.ncbi.nlm.nih.gov/24615603/)

<http://dx.doi.org/10.1007/s00268-014-2484-4>

#### **A Feminizing Adrenocortical Carcinoma in the Context of a Late Onset 21-Hydroxylase Deficiency.**

*J Clin Endocrinol Metab*, 99(6):1943-4.

Libe R, Arlt W, Louiset E, Waintrop C, Guibourdenche J, Sibony M, Clauser E, Groussin L. 2014.

PubMed-ID: [24654754](https://pubmed.ncbi.nlm.nih.gov/24654754/)

<http://dx.doi.org/10.1210/jc.2014-1342>

#### **EJE Prize 2014: Current and Evolving Treatment Options in Adrenocortical Carcinoma: Where Do We Stand and Where Do We Want to Go?**

*Eur J Endocrinol*, 171(1):R1-R11.

Ronchi CL, Kroiss M, Sbiera S, Deutschbein T, Fassnacht M. 2014.

Adrenocortical carcinoma (ACC) is not only a rare and heterogeneous disease but also one of the most aggressive endocrine tumors. Despite significant advances in the last decade, its pathogenesis is still only incompletely understood and overall therapeutic means are unsatisfactory. Herein, we provide our personal view of the currently available treatment options and suggest the following research efforts that we consider timely and necessary to improve therapy: i) for better outcome in localized ACCs, surgery should be restricted to experienced centers, which should then collaborate closely to address the key surgical questions (e.g. best approach and extent of surgery) in a multicenter manner. ii) For the development of better systemic therapies, it is crucial to elucidate the exact molecular mechanisms of action of mitotane. iii) A prospective trial is needed to address the role of cytotoxic drugs in the adjuvant setting in aggressive ACCs (e.g. mitotane vs mitotane+cisplatin). iv) For metastatic ACCs, new regimens should be investigated as first-line therapy. v) Several other issues (e.g. the role of radiotherapy and salvage therapies) might be answered - at least in a first step - by large retrospective multicenter studies. In conclusion, although it is unrealistic to expect that the majority of ACCs can be cured within the next decade, international collaborative efforts (including multiple translational and clinical studies) should allow significant improvement of clinical outcome of this disease. To this end, it might be reasonable to expand the European Network for the Study of Adrenal Tumors (ENSAT) to a truly worldwide international network - INSAT.

PubMed-ID: [24714084](https://pubmed.ncbi.nlm.nih.gov/24714084/)

<http://dx.doi.org/10.1530/EJE-14-0273>

#### **Risk Estimator for Adrenal Tumor Functionality.**

*World J Surg*, 38(8):2019-24.

Sadler C, Goldfarb M. 2014.

**BACKGROUND:** Adrenal lesions are a common imaging finding with a prevalence approaching 10%. Although guidelines recommend dedicated laboratory tests to rule out tumor functionality, many patients never undergo

this workup. This study investigates the use of demographic and clinical variables to create an easy scoring system for predicting adrenal tumor functionality (functional adrenal tumors, or FATs). **METHODS:** Altogether, 2,807 patients in the NSQIP 2005-2010 database underwent adrenalectomy as their principal operation and had a postoperative diagnosis consistent with an adrenal lesion/disorder. Patients were divided into two groups based on a postoperative diagnosis consistent with tumor functionality. Univariate and multivariate logistic regression analyses were performed to identify specific predictors of FATs and for Cushing's, Conn's, or pheochromocytoma. **RESULTS:** Overall, 13.2% (n = 402) of adrenalectomies performed were for FATs. Patients with a FAT were younger (age <40, p < 0.01), overweight (BMI > 30 kg/m<sup>2</sup>, p < 0.01), hypertensive (p < 0.001). They also had elevated white blood cells (WBC > 11, p < 0.001), serum creatinine (Cr > 1.25 mg/dl, p < 0.001), and sodium (Na > 143 mmol/L, p < 0.001). On multivariate regression, patients with these characteristics were 20.53 times (CI 15.79-25.27) more likely to have a FAT (model c-statistic 0.634, CI 0.605-0.663; Hosmer-Lemeshow test (H-L), p = 0.035). Patients who were younger (p < 0.001), female (p < 0.001), diabetic (p = 0.07), overweight (p = 0.027), with elevated WBCs (p < 0.001) and lower Cr (p < 0.001) were 63.62 times (CI 58.03-69.21) more likely to have Cushing's (model c-statistic 0.685, CI 0.648-0.722; H-L p = 0.954). **CONCLUSIONS:** After external validation, this risk estimator might be used to quantify the probability of tumor functionality in patients with incidental adrenal masses. Although predictive power may be limited, it helps identify patients at high risk for FATs that need more urgent referral to a specialist.

PubMed-ID: [24715043](https://pubmed.ncbi.nlm.nih.gov/24715043/)

<http://dx.doi.org/10.1007/s00268-014-2524-0>

### **Laparoscopic Transperitoneal Anterior Adrenalectomy in Pheochromocytoma: Experience in 62 Patients.**

*Surg Endosc*, 28(9):2683-9.

Paganini AM, Balla A, Guerrieri M, Lezoche G, Campagnacci R, D'Ambrosio G, Quaresima S, Antonica MV, Lezoche E. 2014.

**BACKGROUND:** Aim was to evaluate the results in 62 patients undergoing laparoscopic adrenalectomy (LA) for the treatment of pheochromocytoma (PHE), with a transperitoneal anterior approach for lesions on the right side, and with a transperitoneal anterior submesocolic approach in case of left-sided lesions. **METHODS:** Sixty-two patients underwent LA for the treatment of PHE at two centers in Rome and Ancona (Italy). Two patients had bilateral lesions, for a total of 64 adrenalectomies. Sporadic PHE occurred in 57 patients (91.9 %) and in 5 (8.0 %) it was familiar. Thirty-six patients (58.0 %) underwent right adrenalectomy, 24 (38.7 %) left adrenalectomy, and in 2 cases (3.2 %) LA was bilateral. In 38 cases of right adrenalectomy (59.3 %) and in 5 cases of left adrenalectomy (7.8 %), the approach was a transperitoneal anterior one. A transperitoneal anterior submesocolic approach was used in 21 left adrenalectomy cases (32.8 %). **RESULTS:** Mean operative time for right and left transperitoneal anterior LA was 101 min (range 50-240) and 163 min (range 50-190), respectively. Mean operative time for left transperitoneal anterior submesocolic LA was 92 min (range 50-195). For bilateral adrenalectomy, mean operative time was 210 min (range 200-220). Conversion to open surgery occurred in 2 cases (3.22 %) due to extensive adhesions (1) and hemorrhage (1). One major and three minor complications were observed. Mobilization occurred on the first postoperative day. Hospitalization was 4.8 days (range 2-19). The lesions had a mean diameter of 4.5 cm (range 0.5-10). **CONCLUSIONS:** Early identification with no gland manipulation prior to closure of the adrenal vein is the main advantages of the transperitoneal anterior approach. PHE may be treated safely and effectively by a laparoscopic transperitoneal anterior approach for right-sided lesions and with a transperitoneal anterior submesocolic approach for left-sided ones.

PubMed-ID: [24737532](https://pubmed.ncbi.nlm.nih.gov/24737532/)

<http://dx.doi.org/10.1007/s00464-014-3528-4>

### **Pitfalls in Genetic Analysis of Pheochromocytomas/Paragangliomas-Case Report.**

*J Clin Endocrinol Metab*, 99(7):2321-6.

Canu L, Rapizzi E, Zampetti B, Fucci R, Nesi G, Richter S, Qin N, Giache V, Bergamini C, Parenti G, Valeri A, Ercolino T, Eisenhofer G, Mannelli M. 2014.

**CONTEXT:** About 35% of patients with pheochromocytoma/paraganglioma carry a germline mutation in one of the 10 main susceptibility genes. The recent introduction of next-generation sequencing will allow the analysis of all these genes in one run. When positive, the analysis is generally unequivocal due to the association between a germline mutation and a concordant clinical presentation or positive family history. When genetic analysis reveals a novel mutation with no clinical correlates, particularly in the presence of a missense variant, the question arises whether the mutation is pathogenic or a rare polymorphism. **OBJECTIVE:** We report the case of a 35-year-old patient operated for a pheochromocytoma who turned out to be a carrier of a novel SDHD (succinate dehydrogenase subunit D) missense mutation. With no positive family history or clinical correlates, we decided to perform additional analyses to test the clinical significance of the mutation. **METHODS:** We

performed in silico analysis, tissue loss of heterozygosity analysis, immunohistochemistry, Western blot analysis, SDH enzymatic assay, and measurement of the succinate/fumarate concentration ratio in the tumor tissue by tandem mass spectrometry. RESULTS: Although the in silico analysis gave contradictory results according to the different methods, all the other tests demonstrated that the SDH complex was conserved and normally active. We therefore came to the conclusion that the variant was a nonpathogenic polymorphism.

CONCLUSIONS: Advancements in technology facilitate genetic analysis of patients with pheochromocytoma but also offer new challenges to the clinician who, in some cases, needs clinical correlates and/or functional tests to give significance to the results of the genetic assay.

PubMed-ID: [24758185](https://pubmed.ncbi.nlm.nih.gov/24758185/)

<http://dx.doi.org/10.1210/jc.2013-4453>

### **Withanolides Are Potent Novel Targeted Therapeutic Agents Against Adrenocortical Carcinomas.**

*World J Surg*, 38(6):1343-52.

Subramanian C, Zhang H, Gallagher R, Hammer G, Timmermann B, Cohen M. 2014.

BACKGROUND: Adrenocortical carcinoma (ACC) is a rare and aggressive malignancy with poor prognosis, as a majority of patients present with advanced disease. Current adjuvant strategies for metastatic patients include mitotane or other cytotoxic agents and carry a significant morbidity as well as a low (<10 %) 5-year survival.

Withanolides, including withaferin A, are novel chemotherapeutic agents with potent targeted effects in medullary thyroid cancer and a number of solid malignancies with low toxicity in vivo. We hypothesize that novel naturally derived withanolides will have potent targeted anti-cancer activity against ACCs. METHODS: In vitro cell viability of ACC cell lines (Y1 and SW13) was measured using MTS cell proliferation assay. Cell cycle and apoptotic analysis studied using annexin V/propidium iodide staining on flow cytometry (FC) and targeted molecular mechanisms of withanolide cytotoxicity were assessed using standard Western blot analysis.

RESULTS: All the withanolides potently reduced ACC cell viability on MTS assay with 7- to 185-fold higher selectivity than normal fibroblasts. Cell cycle analysis demonstrated a shift in cell cycle arrest from G1/G0 to G2/M with induction of apoptosis at nanomolar concentrations of withanolides. Unlike current ACC therapeutics, withanolides modulated expression of several key oncogenic pathway proteins in ACCs by Western blot, including Jagged 1, MAPK, and Akt/mTOR pathway proteins in a dose-dependent manner after 24 h drug treatment of SW13 cells. CONCLUSION: These results demonstrate the first evidence of the anticancer efficacy of withanolides in ACC cells and provide support for future translational evaluation of these compounds as novel therapeutic agents for ACC patients.

PubMed-ID: [24763440](https://pubmed.ncbi.nlm.nih.gov/24763440/)

<http://dx.doi.org/10.1007/s00268-014-2532-0>

### **Accuracy of Adrenal Imaging and Adrenal Venous Sampling in Predicting Surgical Cure of Primary Aldosteronism.**

*J Clin Endocrinol Metab*, 99(8):2712-9.

Lim V, Guo Q, Grant CS, Thompson GB, Richards ML, Farley DR, Young WF, Jr. 2014.

CONTEXT: The accurate distinction between unilateral and bilateral adrenal disease in patients with primary aldosteronism (PA) guides surgical management. Adrenal venous sampling (AVS), the criterion standard localization procedure, is not readily available at many centers throughout the world. OBJECTIVE: The objective of the study was to determine factors most consistent with surgically curable PA. DESIGN: This was a retrospective observational study. SETTING: The study was conducted at the Mayo Clinic (Rochester, Minnesota), a tertiary referral center. PATIENTS: All patients who underwent unilateral adrenalectomy for treatment of PA between January 1993 and December 2011 participated in the study. INTERVENTION: The intervention in the study was unilateral adrenalectomy. MAIN OUTCOME MEASURES: Variables associated with the prediction of unilateral disease were measured. RESULTS: Over 19 years, 263 patients underwent unilateral adrenalectomy for the treatment of PA. Long-term postoperative follow-up was obtained in 143 patients (54.4%). The overall effective cure rate of PA was 95.5% in those patients sent for adrenalectomy for presumptive unilateral disease. In patients with cured PA, defined as the resolution of autonomous aldosterone secretion, hypertension was cured in 53 (41.7%) and improved in 59 (46.5%) patients. PA was not cured with unilateral adrenalectomy in six patients (4.2%). Adrenal imaging and AVS were concordant to the surgically documented side in 58.6% and 97.1% of the patients, respectively. Although there was no statistically significant difference in mean age between the inaccurate vs the accurate adrenal imaging group, we found that the minimum age in the former was 35.1 years. CONCLUSIONS: Using adrenal imaging and AVS, the effective surgical cure rate for PA was 95.5%. Although the overall accuracy of computed tomography and magnetic resonance imaging in detecting unilateral adrenal disease was poor at 58.6%, adrenal imaging performed well in those patients younger than 35 years of age.

PubMed-ID: [24796926](https://pubmed.ncbi.nlm.nih.gov/24796926/)  
<http://dx.doi.org/10.1210/jc.2013-4146>

### **Ketoconazole As an Adrenal Steroidogenesis Inhibitor: Effectiveness and Risks in the Treatment of Cushing's Disease.**

*J Clin Endocrinol Metab*, 99(5):1586-8.

Newell-Price J. 2014.

PubMed-ID: [24802173](https://pubmed.ncbi.nlm.nih.gov/24802173/)

<http://dx.doi.org/10.1210/jc.2014-1622>

### **Transcutaneous Biopsy of Adrenocortical Carcinoma Is Rarely Helpful in Diagnosis, Potentially Harmful, but Does Not Affect Patient Outcome.**

*Eur J Endocrinol*, 170(6):829-35.

Williams AR, Hammer GD, Else T. 2014.

CONTEXT: Adrenocortical carcinoma (ACC) is a rare malignancy with high recurrence and mortality rates. The utility, sensitivity, and effect on patient outcome of transcutaneous adrenal biopsy (TAB) for single, large, adrenal masses are unclear. OBJECTIVE: This study evaluated the utility, diagnostic sensitivity, and effect on patient outcome of TAB in patients with ACC. DESIGN AND SETTING: We conducted a retrospective review of the electronic medical records of all ACC patients who were evaluated at the University of Michigan Health System from 1991 to 2011. We evaluated the sensitivity of TAB for tumors with the final pathological diagnosis of ACC. We compared the characteristics and survival of patients with stage I-III disease who underwent TAB with those who did not undergo TAB. RESULTS: A total of 75 ACC patients with TAB were identified. Complications occurred in at least 11% of patients and were mainly associated with bleeding. The maximum sensitivity of the procedure in diagnosing ACC was 70%. For stage I-III patients, baseline characteristics, stage at diagnosis, and adjuvant treatment with mitotane or radiation were not significantly different between the TAB (n=36) and the non-TAB (n=254) groups. There was no significant difference in recurrence-free (P=0.7) or overall survival (P=0.7) between patients who underwent TAB and those who did not. CONCLUSIONS: TAB of single, large, adrenal masses is usually unnecessary, exposes patients to risk, but does not affect recurrence-free or overall survival.

PubMed-ID: [24836548](https://pubmed.ncbi.nlm.nih.gov/24836548/)

<http://dx.doi.org/10.1530/EJE-13-1033>

### **Renaissance of (18)F-FDG Positron Emission Tomography in the Imaging of Pheochromocytoma/Paraganglioma.**

*J Clin Endocrinol Metab*, 99(7):2337-9.

Taieb D, Timmers HJ, Shulkin BL, Pacak K. 2014.

PubMed-ID: [24878044](https://pubmed.ncbi.nlm.nih.gov/24878044/)

<http://dx.doi.org/10.1210/jc.2014-1048>

### **Adrenal Function After Adrenalectomy for Subclinical Hypercortisolism and Cushing's Syndrome: a Systematic Review of the Literature.**

*J Clin Endocrinol Metab*, 99(8):2637-45.

Di DG, Berr CM, Fassnacht M, Beuschlein F, Reincke M. 2014.

CONTEXT: The postoperative course of patients with subclinical hypercortisolism (SH) is yet to be clarified. The aims are to review the prevalence and predictive factors of postoperative adrenal insufficiency and the time to recover a normal adrenocortical function in patients with SH and Cushing's syndrome (CS). EVIDENCE ACQUISITION: Using the PubMed database, we conducted a systematic review of the literature, selecting studies published from 1980 to 2013. EVIDENCE SYNTHESIS: Of the 1522 papers screened, 28 were selected (13 retrospective, 14 prospective, and one randomized controlled trial). The prevalence of postoperative adrenal insufficiency was 65.3% in 248 SH subjects and 99.7% in 377 CS patients. Patients with SH were reclassified according to the following diagnostic criteria: subjects defined by pathological dexamethasone test only (DEX), and those defined by the dexamethasone test with one (DEX+1) or two additional criteria (DEX+2); and they were compared with CS patients. The prevalence of adrenal insufficiency was 51.4, 60.6, 91.3, and 99.7%, respectively, with no significant difference between the two latter groups. The test with the best compromise between sensitivity (64%) and specificity (81%) in predicting adrenal insufficiency was the midnight serum cortisol. The time to achieve eucortisolism was lower in SH patients than in CS patients (6.5 vs 11.2 mo; P < .001). CONCLUSIONS: Adrenal insufficiency occurs in about half of the patients with SH if defined only by the pathological dexamethasone test. However, prevalence of adrenal insufficiency and time to recovery are tightly related to the degree of hypercortisolism and diagnostic criteria to define SH, which might help to better define

SH for future studies.

PubMed-ID: [24878052](#)

<http://dx.doi.org/10.1210/jc.2014-1401>

### **Favorable Long-Term Outcomes of Bilateral Adrenalectomy in Cushing's Disease.**

*Eur J Endocrinol*, 171(2):209-15.

Osswald A, Plomer E, Dimopoulou C, Milian M, Blaser R, Ritzel K, Mickisch A, Knerr F, Stanojevic M, Hallfeldt K, Schopohl J, Kuhn KA, Stalla G, Beuschlein F, Reincke M. 2014.

**OBJECTIVE:** Bilateral adrenalectomy (BADX) is an important treatment option for patients with Cushing's syndrome (CS). Our aim is to analyze the long-term outcomes, surgical, biochemical, and clinical as well as morbidity and mortality, of patients who underwent BADX. **DESIGN:** A total of 50 patients who underwent BADX since 1990 in two German centers were identified. Of them, 34 patients had Cushing's disease (CD), nine ectopic CS (ECS), and seven ACTH-independent bilateral adrenal hyperplasia (BAH). **METHODS:** Standardized follow-up examination was performed in 36 patients with a minimum follow-up time of 6 months after BADX and a median follow-up time of 11 years. **RESULTS:** Surgical morbidity and mortality were 6 and 4% respectively. All patients were found to be in remission after BADX. Almost all Cushing's-specific comorbidities except for psychiatric diseases improved significantly. Health-related quality of life remained impaired in 45.0% of female and 16.7% of male patients compared with a healthy population. The median number of adrenal crises per 100 patient-years was four. Nelson tumor occurred in 24% of CD patients after a median time span of 51 months. Long-term mortality after 10 years was high in ECS (44%) compared with CD (3%) and BAH (14%).

**CONCLUSIONS:** BADX is an effective and relatively safe treatment option especially in patients with CD. The majority of patients experience considerable improvement of Cushing's symptoms.

PubMed-ID: [24975318](#)

<http://dx.doi.org/10.1530/EJE-14-0214>

# NET

## Meta-Analyses

### **Combination of Cross-Sectional and Molecular Imaging Studies in the Localization of Gastroenteropancreatic Neuroendocrine Tumors.**

*Neuroendocrinology*, 99(2):63-74.

Toumpanakis C, Kim MK, Rinke A, Bergestuen DS, Thirlwell C, Khan MS, Salazar R, Oberg K. 2014. Molecular imaging modalities exploit aspects of neuroendocrine tumors (NET) pathophysiology for both diagnostic imaging and therapeutic purposes. The characteristic metabolic pathways of NET determine which tracers are useful for their visualization. In this review, we summarize the diagnostic value of all available molecular imaging studies, present data about their use in daily practice in NET centers globally, and finally make recommendations about the appropriate use of those modalities in specific clinical scenarios. Somatostatin receptor scintigraphy (SRS) continues to have a central role in the diagnostic workup of patients with NET, as it is also widely available. However, and despite the lack of prospective randomized studies, many NET experts predict that Gallium-68 ((68)Ga)-DOTA positron emission tomography (PET) techniques may replace SRS in the future, not only because of their technical advantages, but also because they are superior in patients with small-volume disease, in patients with skeletal metastases, and in those with occult primary tumors. Carbon-11 ((11)C)-5-hydroxy-L-tryptophan (5-HTP) PET and (18)F-dihydroxyphenylalanine ((18)F-DOPA) PET are new molecular imaging techniques of limited availability, and based on retrospective data, their sensitivities seem to be inferior to that of (68)Ga-DOTA PET. Glucagon-like-peptide-1 (GLP-1) receptor imaging seems promising for localization of the primary in benign insulinomas, but is currently available only in a few centers. Fluorine-18 ((18)F)-fluorodeoxyglucose ((18)F-FDG) PET was initially thought to be of limited value in NET, due to their usually slow-growing nature. However, according to subsequent data, (18)F-FDG PET is particularly helpful for visualizing the more aggressive NET, such as poorly differentiated neuroendocrine carcinomas, and well-differentiated tumors with Ki67 values >10%. According to limited data, (18)F-FDG-avid tumor lesions, even in slow-growing NET, may indicate a more aggressive disease course. When a secondary malignancy has already been established or is strongly suspected, combining molecular imaging techniques (e.g. (18)F-FDG PET and (68)Ga-DOTA PET) takes advantage of the diverse avidities of different tumor types to differentiate lesions of different origins. All the above-mentioned molecular imaging studies should always be reviewed and interpreted in a multidisciplinary (tumor board) meeting in combination with the conventional cross-sectional imaging, as the latter remains the imaging of choice for the evaluation of treatment response and disease follow-up.

PubMed-ID: [24458014](https://pubmed.ncbi.nlm.nih.gov/24458014/)

<http://dx.doi.org/10.1159/000358727>

### **A Systematic Review and Meta-Analysis of the Clinicopathologic Characteristics of Cystic Versus Solid Pancreatic Neuroendocrine Neoplasms.**

*Surgery*, 156(1):83-96.

Koh YX, Chok AY, Zheng HL, Tan CS, Goh BK. 2014.

**INTRODUCTION:** Cystic pancreatic neuroendocrine neoplasms (PNENs) are rare neoplasms, and presently, it is uncertain whether their behavior is similar or distinct from their solid counterparts. This study aimed to review systematically the present literature to compare the clinicopathologic characteristics of cystic PNENs versus their solid counterparts to determine whether cystic PNENs are likely to be a distinct entity from solid PNENs.

**METHODS:** Comparative studies of solid versus cystic PNENs studies were reviewed. Cystic and solid PNENs were compared on the basis of several clinicopathologic characteristics. **RESULTS:** Seven nonrandomized case control studies compared 152 cystic versus 915 solid PNENs. Pooled analysis demonstrated that the likelihood of PNENs to be located in the head/uncinate of the pancreas was lower for cystic than solid neoplasms (27.7% vs 45.5%, odds ratio [OR] 0.452, 95% confidence interval [95% CI] 0.304-0.673,  $P < .001$ ). Cystic PNENs were less likely to be functional (14% vs 24.4%, OR 0.405, 95% CI 0.221-0.742,  $P = .003$ ) and were more likely to be benign/uncertain rather than malignant compared with solid PNENs (90.3% vs 65.9%, OR 3.151, 95% CI 1.297-7.652,  $P = .011$ ). Cystic PNENs were more likely to have a mitotic count <2 per 10 hpf and a Ki67 index <2% (93.3% vs 72.7%, OR 4.897, 95% CI 2.139-11.209,  $P < .001$  and 82.4% vs 54.1%, OR 4.079, 95% CI 2.177-7.641,  $P < .001$ ), respectively. Cystic neoplasms were also less likely to have regional lymph node metastases than solid neoplasms (11.2% vs 28.9%, OR 0.387, 95% CI 0.219-0.685,  $P = .001$ ). In this meta-analysis, there was no difference in the 5-year overall survival and 5-year disease-free survival between cystic vs solid PNENs (92.0% vs 86.8%,  $P = .214$ ) and (98.1% vs 83.9%,  $P = .185$ ). **CONCLUSION:** These findings suggest that cystic PNENs tend to be biologically less aggressive compared with their solid counterparts; more data, however, with

respect to molecular analysis are required to establish whether cystic and solid PNENs were distinct pathologic entities.

PubMed-ID: [24878455](#)

<http://dx.doi.org/10.1016/j.surg.2014.03.026>

## Randomized controlled trials

- None -

## Consensus Statements/Guidelines

- None -

## Other Articles

### **The Presence of SDHB Mutations Should Modify Surgical Indications for Carotid Body Paragangliomas.**

*Ann Surg*, 260(1):158-62.

Ellis RJ, Patel D, Prodanov T, Nilubol N, Pacak K, Kebebew E. 2014.

**OBJECTIVE:** The aim of this study was to determine whether the genetic background of the disease should be incorporated into treatment decision making. **BACKGROUND:** Carotid body paragangliomas are rare tumors that often affect patients with genetic mutations of the succinate dehydrogenase complex (SDHx). Despite growing evidence that germ line genetic mutations alter the aggressiveness of paragangliomas, treatment decisions are currently based only on clinical symptoms and tumor size in patients with carotid body paragangliomas.

**METHODS:** Retrospective analysis of 34 patients with carotid body paragangliomas who underwent genetic testing and surgical treatment. Recurrence was defined by the return of locoregional disease and/or development of distant metastases. Clinical characteristics and genetic testing results were analyzed as predictors of patient outcomes.

**RESULTS:** Thirty-four patients underwent 41 primary carotid body paraganglioma resections (median follow-up time of 42 months, range: 1-293). Overall survival was 91.2%. Twelve patients had germ line mutations in SDHB, 17 in SDHD, and 5 carried no known mutation. Surgical resection of larger tumors was associated with higher operative complications (odds ratio: 5.4,  $P = 0.05$ ). Tumor size at resection was significantly smaller in patients with SDHB mutations than in patients with non-SDHB mutations (2.1 vs 3.3 cm,  $P = 0.02$ ). Patients with a mutation in the SDHB gene also had significantly worse disease-free survival compared with patients without an SDHB gene mutation ( $P = 0.03$ ). **CONCLUSIONS:** Mutations in the SDHB gene are associated with worse disease-free survival after resection in patients with carotid body paragangliomas despite earlier intervention. This suggests that a more aggressive surgical approach is warranted in patients with SDHB mutations.

PubMed-ID: [24169168](#)

<http://dx.doi.org/10.1097/SLA.0000000000000283>

### **Comment on "Predicting Aggressive Behavior in Nonfunctioning Pancreatic Neuroendocrine".**

*Surgery*, 155(3):582-4.

Gaujoux S, Sauvanet A, Partelli S, Falconi M, Ruszniewski P. 2014.

PubMed-ID: [24462075](#)

<http://dx.doi.org/10.1016/j.surg.2013.11.004>

### **Role of Ki-67 Proliferation Index in the Assessment of Patients With Neuroendocrine Neoplasias Regarding the Stage of Disease.**

*World J Surg*, 38(6):1353-61.

Miller HC, Drymoussis P, Flora R, Goldin R, Spalding D, Frilling A. 2014.

**BACKGROUND:** Neuroendocrine neoplasias (NEN) of the gastroenteropancreatic (GEP) system frequently present with metastatic deposits. The proliferation marker Ki-67 is used for diagnosis and to assess the prognosis of disease. The aim of our study was to evaluate the usefulness of Ki-67 % in the assessment of NEN patients with regard to their disease stage in clinical practice. Additionally, a comparative analysis of Ki-67 levels among different sites of disease was performed. **METHODS:** This retrospective study included patients with

GEP NEN referred to our center from 2010 to 2012. The NEN diagnosis was confirmed by standard histopathology. Ki-67 immunohistochemistry was done on paraffin-embedded sections using an automated Leica immunohistochemistry machine. NEN grading was carried out according to European Neuroendocrine Tumor Society recommendations (low grade [G1] to intermediate grade [G2], well to moderately differentiated neuroendocrine neoplasms; high-grade [G3], moderately to poorly differentiated neuroendocrine neoplasms). Results of tumor staging and grading were correlated. In a subgroup of cases, comparative analysis of Ki-67 levels in different sites of disease was carried out. RESULTS: One hundred sixty-one GEP NEN patients were included in the study. Metastatic disease was seen in 46.1 % (53/115) of G1 tumors, 77.8 % (28/36) of G2 tumors, and 100 % of (10/10) G3 tumors ( $p = 0.0002$ ). When stratified according to primary tumor site, metastatic disease was documented in 42.9 % (36/84) of patients with pancreatic NEN and in 91.9 % (34/37) of those with small intestinal primary. Stage IV metastatic disease was present in 27.8 % (32/115) and 72.2 % (26/36) of the G1 and G2 tumors, respectively, and in 90 % (9/10) of the G3 tumors. Assessment of the Ki-67 index for a subset of cases at metastatic sites as well as the primary tumor site showed discrepancies in 35.3 % cases. In 7/9 (77.8 %) patients with liver metastases, Ki-67 % was higher in the liver lesions than in the primary tumor. CONCLUSIONS: Patients with GEP NEN exhibiting a high Ki-67 proliferation index present with metastatic disease in the vast majority of cases. Depending upon the primary tumor site, metastases are to be expected also in tumors with low Ki-67 %, although they are considered less aggressive. Different disease sites may express heterogeneous Ki-67 levels.

PubMed-ID: [24493070](https://pubmed.ncbi.nlm.nih.gov/24493070/)

<http://dx.doi.org/10.1007/s00268-014-2451-0>

### **Detection of Metastatic Insulinoma by Positron Emission Tomography With [(68)Ga]Exendin-4-a Case Report.**

*J Clin Endocrinol Metab*, 99(5):1519-24.

Eriksson O, Velikyan I, Selvaraju RK, Kandeel F, Johansson L, Antoni G, Eriksson B, Sorensen J, Korsgren O. 2014.

CONTEXT: Insulinomas are the most common cause of endogenous hyperinsulinemic hypoglycemia in nondiabetic adult patients. They are usually benign, and curative surgery is the "gold standard" treatment if they can be localized. Malignant insulinomas are seen in less than 10% of patients, and their prognosis is poor. The glucagon like peptide-1 receptor (GLP-1R) is markedly up-regulated in insulinomas-especially benign lesions, which are difficult to localize with current imaging techniques. OBJECTIVE: The aim of the study was to assess the possibility of the detection of primary and metastatic insulinoma by positron emission tomography (PET) using [(68)Ga]Ga-DO3A-VS-Cys(40)-Exendin-4 ([[(68)Ga]Exendin-4) in a patient with severe hypoglycemia. DESIGN AND SETTING: Dynamic and static PET/computed tomography (CT) examination of a patient was performed using [(68)Ga]Exendin-4 at Uppsala University Hospital, Uppsala, Sweden. PATIENTS: A patient presented with hypoglycemia requiring continuous iv glucose infusions. A pancreatic insulinoma was suspected, and an exploratory laparotomy was urgently performed. At surgery, a tumor in the pancreatic tail with an adjacent metastasis was found, and a distal pancreatic resection (plus splenectomy) and removal of lymph node were performed. Histopathology showed a World Health Organization classification grade II insulinoma. Postoperatively, hypoglycemia persisted, but a PET/CT examination using the neuroendocrine marker [(11)C]-5-hydroxy-L-tryptophan was negative. INTERVENTIONS: The patient was administered [(68)Ga]Exendin-4 and was examined by dynamic PET over the liver and pancreas. RESULTS: The stable GLP-1 analog Exendin-4 was labeled with (68)Ga for PET imaging of GLP-1R-expressing tumors. The patient was examined by [(68)Ga]Exendin-4-PET/CT, which confirmed several small GLP-1R-positive lesions in the liver and a lymph node that could not be conclusively identified by other imaging techniques. The results obtained from the [(68)Ga]Exendin-4-PET/CT examination provided the basis for continued systemic treatment. CONCLUSION: The results of the [(68)Ga]Exendin-4-PET/CT examination governed the treatment strategy of this particular patient and demonstrated the potential of this technique for future management of patients with this rare but potentially fatal disease.

PubMed-ID: [24512490](https://pubmed.ncbi.nlm.nih.gov/24512490/)

<http://dx.doi.org/10.1210/jc.2013-3541>

### **Resection of the Primary Pancreatic Neuroendocrine Tumor in Patients With Unresectable Liver Metastases: Possible Indications for a Multimodal Approach.**

*Surgery*, 155(4):607-14.

Bertani E, Fazio N, Botteri E, Chiappa A, Falconi M, Grana C, Bodei L, Papis D, Spada F, Bazolli B, Andreoni B. 2014.

BACKGROUND: Pancreatic neuroendocrine tumors (PNETs) present in more than 50% of cases with liver metastases as the only systemic localization. Liver metastases are unresectable in 80% of cases at diagnosis. In

the context of a metastatic disease, the benefit of primary tumor removal in terms of survival is controversial. METHODS: A single-center series of patients with PNETs presenting with synchronous unresectable hepatic metastases and treated within a framework of a multidisciplinary team was analyzed retrospectively to assess the prognostic factors and the potential benefit of primary tumor resection on long-term survival. RESULTS: At the time of diagnosis, 12 of 43 patients (28%) underwent primary tumor resection. After a median follow-up of 5 years (range, 0.6-14 years), 22 disease-related deaths were observed. The corresponding 5-year survival and median disease-specific duration of survival were 58% and 77 months, respectively. In the operated and nonoperated patients the 5-year disease-specific survival was 82% and 50%, respectively (P = .027). At multivariate analysis, patients with primary tumor removed had an improved survival compared with patients who did not (hazard ratio 0.18; 95% CI 0.05-0.66; P = .010). Other important factors associated with improved survival at multivariate analysis were lesser age, lesser Ki-67 index, and 25% less liver tumor burden. CONCLUSION: In the present series of patients with PNETs and unresectable liver metastases, resection of the primary tumor was associated with an improved survival. This observation suggests that resection of the primary tumor should be part of a global therapeutic strategy and its indication and timing should be discussed within a multidisciplinary team.

PubMed-ID: [24582492](https://pubmed.ncbi.nlm.nih.gov/24582492/)

<http://dx.doi.org/10.1016/j.surg.2013.12.024>

### **Altered Islet Function and Insulin Clearance Cause Hyperinsulinemia in Gastric Bypass Patients With Symptoms of Postprandial Hypoglycemia.**

*J Clin Endocrinol Metab*, 99(6):2008-17.

Salehi M, Gastaldelli A, D'Alessio DA. 2014.

CONTEXT: Postprandial hypoglycemia, a late complication of gastric bypass (GB) surgery, is associated with an exaggerated insulin response to meal ingestion. OBJECTIVE: The purpose of this study was to characterize insulin secretion and other glucoregulatory hormone responses to meal ingestion after GB based on hypoglycemia and clinical symptoms. METHODS: We conducted a cross-sectional analysis of insulin secretion rate and islet and gastrointestinal hormone responses to liquid mixed meal ingestion in 65 subjects with GB and 11 body mass index-matched controls without surgery. The GB subjects were stratified by clinical history for analysis of their responses to the test meal. RESULTS: The glucose and insulin responses to meal ingestion were shifted upward and to the left after GB, with the largest early insulin response and the lowest nadir glucose levels in patients with a history of hypoglycemia, particularly those with neuroglycopenic symptoms. Hypoglycemic GB subjects had lower postprandial insulin clearance rates and higher insulin secretion rates during the glucose decline after the test meal. Meal-induced glucagon was enhanced in all GB subjects but did not differ between subjects who did and did not develop hypoglycemia. Plasma gastric inhibitory polypeptide and glucagon-like peptide-1 concentrations did not differ between asymptomatic and neuroglycopenic GB subjects. CONCLUSION: Among GB subjects with a clinical history of hypoglycemia, hyperinsulinemia is the result of inappropriate insulin secretion and reduced insulin clearance. In subjects with symptoms of postprandial hypoglycemia, insulin secretion is higher in the latter stages of meal glucose clearance, and despite elevated meal-induced glucagon, there is no further response to hypoglycemia. These abnormalities in islet function are most pronounced in subjects who report neuroglycopenic symptoms.

PubMed-ID: [24617664](https://pubmed.ncbi.nlm.nih.gov/24617664/)

<http://dx.doi.org/10.1210/jc.2013-2686>

### **Prospective Evaluation of the Clinical Utility of 18-Fluorodeoxyglucose PET CT Scanning in Patients With Von Hippel-Lindau-Associated Pancreatic Lesions.**

*J Am Coll Surg*, 218(5):997-1003.

Sadowski SM, Weisbrod AB, Ellis R, Patel D, Alimchandani M, Quezado M, Millo C, Venzon DJ, Nilubol N, Linehan WM, Kebebew E. 2014.

BACKGROUND: The natural history of pancreatic neuroendocrine neoplasms (PNETs) in patients with Von Hippel-Lindau (VHL) disease is poorly defined. Management of patients with PNETs is challenging because there are no reliable preoperative criteria to detect malignant lesions, and the majority of resected tumors are found to be benign. The aim of this study was to determine whether 18-fluorodeoxyglucose-positron emission tomography ((18)FDG-PET) uptake predicts growth and detects malignant VHL-associated PNETs. STUDY DESIGN: We performed a prospective study of 197 patients with VHL-associated pancreatic lesions. Clinical and imaging characteristics were analyzed to study the associations between FDG-PET uptake, tumor growth, and the development of metastatic disease. RESULTS: One hundred nine of 197 patients had solid pancreatic lesions and underwent both CT and (18)FDG-PET scanning, which identified 165 and 144 lesions, respectively. Metastatic disease was detected by (18)FDG-PET in 3 patients in whom it was not detected by CT scan and suggested non-neoplastic disease in 3 patients. Maximum standardized uptake values (SUV) on (18)FDG-PET

correlated with tumor size on CT ( $r = 0.47$ ,  $p < 0.0001$ ), and an increase in SUVmax was associated with tumor growth ( $r = 0.36$ ,  $p = 0.0062$ ). No association was seen between (18)FDG-PET uptake and age, VHL genotype, or serum chromogranin A levels. **CONCLUSIONS:** Scanning with FDG-PET identifies metastatic disease not detected by CT scan and avoids resection of non-PNEN lesions that have no malignant potential in patients with VHL-associated PNENs. It should be considered as a valuable functional imaging modality in the clinical management of patients with VHL-associated PNENs.

PubMed-ID: [24661849](https://pubmed.ncbi.nlm.nih.gov/24661849/)

<http://dx.doi.org/10.1016/j.jamcollsurg.2014.01.004>

### **GEP-NETS Update: Functional Localisation and Scintigraphy in Neuroendocrine Tumours of the Gastrointestinal Tract and Pancreas (GEP-NETs).**

*Eur J Endocrinol*, 170(5):R173-R183.

de Herder WW. 2014.

For patients with neuroendocrine tumours (NETs) of the gastrointestinal tract and pancreas (GEP) (GEP-NETs), excellent care should ideally be provided by a multidisciplinary team of skilled health care professionals. In these patients, a combination of nuclear medicine imaging and conventional radiological imaging techniques is usually mandatory for primary tumour visualisation, tumour staging and evaluation of treatment. In specific cases, as in patients with occult insulinomas, sampling procedures can provide a clue as to where to localise the insulin-hypersecreting pancreatic NETs. Recent developments in these fields have led to an increase in the detection rate of primary GEP-NETs and their metastatic deposits. Radiopharmaceuticals targeted at specific tumour cell properties and processes can be used to provide sensitive and specific whole-body imaging. Functional imaging also allows for patient selection for receptor-based therapies and prediction of the efficacy of such therapies.

Positron emission tomography/computed tomography (CT) and single-photon emission CT/CT are used to map functional images with anatomical localisations. As a result, tumour imaging and tumour follow-up strategies can be optimised for every individual GEP-NET patient. In some cases, functional imaging might give indications with regard to future tumour behaviour and prognosis.

PubMed-ID: [24723670](https://pubmed.ncbi.nlm.nih.gov/24723670/)

<http://dx.doi.org/10.1530/EJE-14-0077>

### **The Clinical Phenotype of SDHC-Associated Hereditary Paraganglioma Syndrome (PGL3).**

*J Clin Endocrinol Metab*, 99(8):E1482-E1486.

Else T, Marvin ML, Everett JN, Gruber SB, Arts HA, Stoffel EM, Auchus RJ, Raymond VM. 2014.

**CONTEXT:** Mutations in the genes encoding subunits of the succinate dehydrogenase complex cause hereditary paraganglioma syndromes. Although the phenotypes associated with the more commonly mutated genes, SDHB and SDHD, are well described, less is known about SDHC-associated paragangliomas.

**OBJECTIVE:** To describe functionality, penetrance, number of primary tumors, biological behavior, and location of paragangliomas associated with SDHC mutations. **DESIGN:** Families with an SDHC mutation were identified through a large cancer genetics registry. A retrospective chart review was conducted with a focus on patient and tumor characteristics. In addition, clinical reports on SDHC-related paragangliomas were identified in the medical literature to further define the phenotype and compare findings. **SETTING:** A cancer genetics clinic and registry at a tertiary referral center. **PATIENTS:** Eight index patients with SDHC-related paraganglioma were identified.

**RESULTS:** Three of the eight index patients had mediastinal paraganglioma and four of the eight patients had more than one paraganglioma. Interestingly, the index patients were the only affected individuals in all families. When combining these index cases with reported cases in the medical literature, the mediastinum is the second most common location for SDHC-related paraganglioma (10% of all tumors), occurring in up to 13% of patients.

**CONCLUSIONS:** Our findings suggest that thoracic paragangliomas are common in patients with SDHC mutations, and imaging of this area should be included in surveillance of mutation carriers. In addition, the absence of paragangliomas among at-risk relatives of SDHC mutation carriers suggests a less penetrant phenotype as compared to SDHB and SDHD mutations.

PubMed-ID: [24758179](https://pubmed.ncbi.nlm.nih.gov/24758179/)

<http://dx.doi.org/10.1210/jc.2013-3853>

### **[The Relevance of PET/CT for the Surgical Management of Neuroendocrine Neoplasms]**

#### **Bedeutung Der PET/CT Fur Die Chirurgie Neuroendokriner Neoplasien.**

*Chirurg*, 85(6):500-4.

Hommann M, Kaemmerer D, Horsch D, Kulkarni HR, Robiller F, Baum RP. 2014.

Neuroendocrine neoplasms (NEN) are rare malignancies with a wide spectrum of metastatic potential which originate from the endocrine cells of the body and express somatostatin receptors. The (68)gallium somatostatin receptor positron emission tomography-computed tomography (PET/CT) technique is the most sensitive method

of assessment of well-differentiated NENs and for the detection of cancer of unknown primary (CUP syndrome) NENs. Imaging with 18F-fluorodeoxyglucose (18F-FDG PET/CT) is indicated in poorly differentiated neuroendocrine carcinomas. The receptor-dependent imaging of NENs has a decisive impact on further management.

PubMed-ID: [24844432](#)

<http://dx.doi.org/10.1007/s00104-013-2671-0>

**[Endoscopic Submucosal Resection of Small Neuroendocrine Rectal Tumors]  
Endoskopische Submukosaresektion Kleiner Neuroendokriner Tumoren Des Rektums.**

*Chirurg*, 85(7):639.

Dralle H, Satiroglu I. 2014.

PubMed-ID: [24938681](#)

<http://dx.doi.org/10.1007/s00104-014-2792-0>

**[Gastroenteropancreatic Neuroendocrine Tumors : Targeted Diagnostics and Therapy]  
Gastroenteropankreatische Neuroendokrine Tumoren : Zielgerichtete Diagnostik Und Therapie.**

*Chirurg*, 85(8):731-44.

Holzer K. 2014.

Gastroenteropancreatic neuroendocrine tumors (GEP-NET) are rare but an increase in incidence has been recognized worldwide. Approximately 70 % of NETs are localized in the gastrointestinal tract and in the pancreas, other locations are in the lungs (25 %) and rarely in the skin, urogenital tract and ovaries. Depending on the size, localization, grading (G1-G3) and production of hormones, the symptoms of patients can greatly vary. Outcome and survival of patients depend on the biological behavior and grading of the NET. Patients with a well differentiated G1 grade NET have a slow, sometimes also benign course over decades even with metastases in contrast to patients with G3 grade NETs. These tumors exhibit an aggressive behavior and patient survival is short. Liver and lymph node metastases are common (about 50 %) in GEP-NETs even at the initial diagnosis. The 5-year and 10-year survival of patients with GEP-NETs is increasing (currently approximately 80 % and 60 %, respectively), especially when a multidisciplinary team (e.g. surgery, endocrinology, oncology, nuclear medicine and gastroenterology) manages GEP-NET patients.

PubMed-ID: [25103842](#)

<http://dx.doi.org/10.1007/s00104-013-2679-5>

## **General**

### Meta-Analyses

- None -

### Randomized controlled trials

- None -

### Consensus Statements/Guidelines

- None -

### Other Articles