



ESES Review of Recently Published Literature

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

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Journals covered

Journal	IF2020	Journal	IF2020
Acta Cytol	2.319	J Bone Miner Res	6.741
Am J Kidney Dis	8.860	J Clin Endocrinol Metab	5.958
Am J Nephrol	3.754	J Clin Oncol	44.544
Am J Surg	2.565	J Endocrinol	4.286
Am Surgeon	0.688	J Endocrinol Invest	4.256
Ann Surg	12.969	J Nephrol	3.902
Ann Surg Oncol	5.344	J Nucl Med	10.057
ANZ J Surg	1.872	J Surg Oncol	3.454
Br J Surg	6.939	Lancet	79.321
Cancer	6.860	Langenbecks Arch Surg	3.445
Chirurg	0.955	Laryngoscope	3.325
Clin Endocrinol Oxf	3.478	N Engl J Med	91.245
Clin Nucl Med	7.794	Nat Rev Endocrinol (prev: Nat Clin Pract Endocrinol Metab)	43.330
Curr Opin Oncol	3.645	Nat Rev Clin Oncol (prev: Nat Clin Pract Oncol)	66.675
Endocr Relat Cancer	5.678	Nephrol Dial Transplant	5.992
Endocr Rev	19.871	Neuroendocrinology	4.914
Eur Arch Otorhinolaryngol	2.503	Oncologist	5.550
Eur J Endocrinol	6.664	Otolaryngol Head Neck Surg	3.497
Eur J Surg Oncol	4.424	Surg Clin North Am	2.741
Gland Surg	2.953	Surg Endosc	4.584
Head Neck	3.147	Surg Laparosc Endosc Percutan Tech	1.719
Horm Metab Res	2.936	Surg Oncol	3.279
JAMA Otolaryngol Head Neck Surg (prev: Arch Oto)	6.223	Surg Oncol Clin N Am	3.495
JAMA Surg (prev: Arch Surg)	14.766	Surgery	3.982
Int J Cancer	7.396	Thyroid	6.568
J Am Coll Surg	6.113	Updates In Surgery	2.797
J Am Soc Nephrol	10.121	World J Surg	3.352
J Bone Miner Metab	2.626		

Journal names are links to the journal's homepage!, IF2020: [Impact factor 2020](#)

Thyroid

Meta-Analyses

Antithyroid drug therapy in pregnancy and risk of congenital anomalies: Systematic review and meta-analysis.

Clin Endocrinol (Oxf), 96(6):857-68.

M. Agrawal, S. Lewis, L. Premawardhana, C. M. Dayan, P. N. Taylor and O. E. Okosieme. 2022.

OBJECTIVES: The risk of congenital anomalies following in utero exposure to thionamide antithyroid drugs (ATDs) is unresolved. Observational studies are contradictory and existing meta-analyses predate and preclude more recent studies. We undertook an updated meta-analysis of congenital anomaly risk in women exposed to carbimazole or methimazole (CMZ/MMI), propylthiouracil (PTU), or untreated hyperthyroidism in pregnancy. **METHODS:** We searched Medline, Embase, and the Cochrane database for articles published up till August 2021. We pooled separate crude and adjusted risk estimates using random effects models and subgroup analyses to address heterogeneity. **RESULTS:** We identified 16 cohort studies comprising 5957, 15,785, and 15,666 exposures to CMZ/MMI, PTU, and untreated hyperthyroidism, respectively. Compared to nondisease controls, adjusted risk ratio (RR) and 95% confidence intervals (95% CIs) for congenital anomalies was increased for CMZ/MMI (RR, 1.28; 95% CI, 1.06-1.54) and PTU (RR, 1.16; 95% CI, 1.08-1.25). Crude risk for CMZ/MMI was increased relative to PTU (RR, 1.20; 95% CI, 1.01-1.43). Increased risk was also seen with exposure to both CMZ/MMI and PTU, that is, women who switched ATDs in pregnancy (RR, 1.51; 95% CI, 1.14-1.99). However, the timing of ATD switch was highly variable and included prepregnancy switches in some studies. The excess number of anomalies per 1000 live births was 17.2 for patients exposed to CMZ/MMI, 9.8, for PTU exposure, and 31.4 for exposure to both CMZ/MMI and PTU. Risk in the untreated group did not differ from control or ATD groups. The untreated group was however highly heterogeneous in terms of thyroid status. Subgroup analysis showed more positive associations in studies with >500 exposures and up to 1-year follow-up. **CONCLUSIONS:** ATD therapy carries a small risk of congenital anomalies which is higher for CMZ/MMI than for PTU and does not appear to be reduced by switching ATDs in pregnancy. Due to key limitations in the available data, further studies will be required to clarify the risks associated with untreated hyperthyroidism and with switching ATDs in pregnancy.

PubMed-ID: [34845757](https://pubmed.ncbi.nlm.nih.gov/34845757/)

<http://dx.doi.org/10.1111/cen.14646>

Prophylactic Central Neck Dissection for Clinically Node-Negative Papillary Thyroid Carcinoma.

Laryngoscope, 132(6):1320-8.

K. M. Alsubaie, H. M. Alsubaie, F. R. Alzahrani, M. A. Alessa, S. K. Abdulmonem, M. A. Merdad, T. Al-Khatib, H. Z. Marzouki, M. A. Algarni and A. Z. Alherabi. 2022.

OBJECTIVE: We performed a systematic review and meta-analysis of randomized controlled trials (RCTs) that scrutinized the oncological benefits and postsurgical complications of total thyroidectomy (TT) plus prophylactic central neck dissection (pCND) versus TT alone among clinically node-negative (cN0) papillary thyroid cancer (PTC) patients. **METHODS:** We screened five databases from inception to September 4, 2021 and evaluated the risk of bias of the eligible studies. We pooled dichotomous outcomes using the risk ratio (RR) with 95% confidence interval (CI). **RESULTS:** Overall, we included 5 RCTs with low risk of bias comprising 795 patients (TT plus pCND = 410 and TT alone = 385). With regard to efficacy endpoint, the rate of structural loco-regional recurrence did not significantly differ between both groups (n = 4 RCTs, RR = 0.49, 95% CI [0.19, 1.27], P = .14). With regard to safety endpoints, the rates of hypoparathyroidism (n = 5 RCTs, RR = 1.48, 95% CI [0.73, 2.97], P = .27), recurrent laryngeal nerve injury (n = 5 RCTs, RR = 1.34, 95% CI [0.59, 3.03], P = .48), and bleeding (n = 3 RCTs, RR = 1.75, 95% CI [0.42, 7.26], P = .44) did not significantly differ between both groups. **CONCLUSION:** For cN0 PTC patients, there was no significant difference between TT plus pCND and TT alone with regard to the rate of structural loco-regional recurrence or frequency of postsurgical complications. Adaptation of pCND in cN0 PTC patients should be contemplated by taking into consideration the clinical oncological benefits and rate of postsurgical adverse events. **LEVEL OF EVIDENCE:** 1 *Laryngoscope*, 132:1320-1328, 2022.

PubMed-ID: [34708877](https://pubmed.ncbi.nlm.nih.gov/34708877/)

<http://dx.doi.org/10.1002/lary.29912>

Quality of Life in Patients with Benign Non-Toxic Goiter After Surgical Intervention: A Systematic Review and Meta-Analysis.

World J Surg, 46(5):1093-104.

N. Chaves, M. J. Rodriguez, J. M. Broekhuis, H. W. Chen, P. A. Bain and B. C. James. 2022.

BACKGROUND: Prior studies evaluating health-related quality of life (HR-QoL) outcomes in patients undergoing surgery for benign non-toxic goiter have used different instruments and time points, leading to conflicting results. We sought to systematically review the differences in HR-QoL among patients with BNTG at baseline and 6 months after surgery, using exclusively the ThyPRO questionnaire. **METHODS:** A systematic search was performed using PubMed, Embase, Web of Science, Cochrane Central, CINAHL, and PsycINFO for papers reporting the assessment of HR-QoL utilizing ThyPRO. Data were meta-analyzed using a random-effects model, and pooled estimates were calculated using weighted mean differences (WMD) between baseline and 6 months after surgery. We assessed the quality and risk of bias of the studies using the Robins-I tool and previously published minimally important change (MIC) values to assess clinical significance. **RESULTS:** Six papers met the predefined inclusion criteria, describing a total of 496 patients. Meta-analysis demonstrated improved QoL in all thirteen domains of ThyPRO six months post-surgical intervention compared to baseline. Specifically, the largest improvement in QoL was seen in the domains of overall QoL, WMD -25.84 (95% CI -29.70, -21.98, $p < 0.001$, $I(2) = 23\%$), goiter symptoms, 23.96 (95% CI -30.29, -17.64, $p < 0.001$, $I(2) = 91\%$), and tiredness, -16.20 (95% CI -19.23, -13.16, $p < 0.001$, $I(2) = 3\%$). The differences in scores 9 of 13 domains were clinically significant based on MIC. **CONCLUSIONS:** Disease-specific HR-QoL improved in all ThyPRO domains after surgery in patients with BNTG. Future studies of QoL in thyroid surgery patients will benefit from a standard questionnaire and improved reporting of covariates including complications to ensure comparability across studies.

PubMed-ID: [35075521](https://pubmed.ncbi.nlm.nih.gov/35075521/)

<http://dx.doi.org/10.1007/s00268-022-06452-w>

Serum Thyroglobulin Measurement Following Surgery Without Radioactive Iodine for Differentiated Thyroid Cancer: A Systematic Review.

Thyroid, 32(6):613-39.

R. Chou, T. Dana, G. A. Brent, W. Goldner, M. Haymart, A. M. Leung, M. D. Ringel and J. A. Sosa. 2022.

Background: The utility of serum thyroglobulin (Tg) measurement following partial thyroidectomy or total/near-total thyroidectomy without radioactive iodine (RAI) for differentiated thyroid cancer is unclear. This systematic review examines the diagnostic accuracy of serum Tg measurement for persistent, recurrent, and/or metastatic cancer in these situations. **Methods:** Ovid MEDLINE, Embase, and Cochrane Central were searched in October 2021 for studies on Tg measurement following partial thyroidectomy or total/near-total thyroidectomy without or before RAI. Quality assessment was performed, and evidence was synthesized qualitatively. **Results:** Thirty-seven studies met inclusion criteria. Four studies (N = 561) evaluated serum Tg measurement following partial thyroidectomy, five studies (N = 751) evaluated Tg measurement following total/near-total thyroidectomy without RAI, and 28 studies (N = 7618) evaluated Tg measurement following total or near-total thyroidectomy before RAI administration. Following partial thyroidectomy, Tg measurement was not accurate for diagnosing recurrence or metastasis, or estimates were imprecise. Following total/near-total thyroidectomy without RAI, evidence was limited due to few studies with very low rates of recurrence or metastasis, but indicated that Tg levels were usually stable and low. For Tg measurements before RAI administration, diagnostic accuracy for metastatic disease or persistence varied, although sensitivity appeared high (but specificity low) at a cutoff of >1 to 2.5 ng/mL. However, applicability to patients who do not undergo RAI is uncertain because patients selected for RAI are likely to represent a higher risk group. The evidence was very low quality for all scenarios. All studies had methodological limitations, and there was variability in the Tg thresholds evaluated, patient populations, outcomes assessed, and other factors. **Conclusions:** Very limited evidence suggests low utility of Tg measurement for identifying recurrent or metastatic disease following partial thyroidectomy. Following total/near-total thyroidectomy, Tg levels using a cutoff of 1-2.5 ng/mL might identify patients at low risk for persistent or metastatic disease. Additional research is needed to clarify the role of Tg measurement in these settings, determine optimal Tg thresholds, and determine appropriate measurement intervals.

PubMed-ID: [35412871](https://pubmed.ncbi.nlm.nih.gov/35412871/)

<http://dx.doi.org/10.1089/thy.2021.0666>

Quality of Life in Patients with Benign Non-toxic Goiter after Surgical Intervention: A Systematic Review and Meta-Analysis.

World J Surg, 46(5):1105-6.

C. Ihre-Lundgren. 2022.

PubMed-ID: [35190874](https://pubmed.ncbi.nlm.nih.gov/35190874/)

<http://dx.doi.org/10.1007/s00268-022-06489-x>

Prophylactic Central Neck Lymph Node Dissection in Low-risk Thyroid Carcinoma Patients Does Not Decrease the Incidence of Locoregional Recurrence: A Meta-analysis of Randomized Trials.

Ann Surg, 276(1):66-73.

A. Sanabria, C. Betancourt-Agüero, J. G. Sánchez-Delgado and C. García-Lozano. 2022.

OBJECTIVE: To evaluate the effectiveness of T + prophylactic CND (T+CND) compared to T alone on locoregional recurrence in patients with PTC. SUMMARY BACKGROUND DATA: Few RCTs have assessed the risks and benefits of prophylactic CND in patients with PTC. Most recommendations are still based on meta-analyses that include observational studies, which are prone to selection bias. METHODS: We included RCTs involving adult patients with clinically negative neck (cN0) PTC that compared T versus T+CND. The main outcomes assessed were structural and biochemical recurrence and complications. For methodological quality assessment, we used the Revised Cochrane risk-of-bias tool for randomized trials instrument, and for robustness, we used the fragility index. RESULTS: Five RCTs with 763 patients were included (354 in the T group and 409 in the T+CND group). Most studies were classified as having a low risk of bias. Publication bias was not found. Structural recurrence occurred in 11/409 (2.7%) patients in the T+CND group and 9/354 (2.5%) patients in the T group, with a risk difference (RD) =0% [95% confidence interval (CI) -2% to 2%]. For biochemical recurrence, the RD was 0% (95% CI -5% to 4%). The number needed to treat was 500. The rate of permanent hypoparathyroidism was higher in the T+CND group than in the T group [RD 3% (95% CI 0%-6%)]. CONCLUSIONS: We did not find a beneficial effect of prophylactic CND associated with T on locoregional or biochemical recurrence but did confirm a higher risk of permanent hypoparathyroidism associated with this procedure.

PubMed-ID: [35129470](https://pubmed.ncbi.nlm.nih.gov/35129470/)

<http://dx.doi.org/10.1097/SLA.0000000000005388>

Randomized controlled trials

- None -

Consensus Statements/Guidelines

- None -

Other Articles

The prevalence and significance of nonuniform thyroid radio-isotope uptake in patients with Graves' disease.

Clin Endocrinol (Oxf), 97(1):100-5.

A. Abdalaziz, R. Vanka, P. Bartholomew, N. Vennart, J. Vernazza, K. Stewart, V. Tsalidis, K. Narayanan, J. U. Weaver and S. Razvi. 2022.

OBJECTIVE: To evaluate the prevalence and clinical significance of nonuniform technetium (^{99m}Tc) uptake among patients with Graves' disease (GD). DESIGN, PATIENTS AND MEASUREMENTS: Patients with GD, referred between July 2005 and March 2018, had Tc(^{99m}) - uptake scans and TSH-receptor antibody (TRAb) measured before antithyroid drug (ATD) therapy. Risk of relapse after ATD cessation was monitored until June 2021 and compared between GD patients based on uptake patterns. RESULTS: Of the 276 GD patients (mean age, 49.8 years; 84% female), 25 (9.0%) had nonuniform Tc(^{99m}) uptake. At diagnosis, individuals with nonuniform uptake were older (mean age of 61.8 vs. 48.5 years, $p < .001$), had lower mean thyroid hormone levels (free thyroxine: 36.3 vs. 45.4 pmol/L, $p = .04$ and free triiodothyronine: 10.0 vs. 17.8 pmol/L, $p < .001$) and median TRAb levels (4.2 vs. 6.6 U/L, $p = .04$) compared with those with a uniform uptake. Older age was a significant predictor for the presence of nonuniform uptake in GD patients; odds ratio (95% confidence intervals) of 1.07 (1.03 - 1.10). The risk of relapse was similar in both groups after a median (IQR) follow-up of 41 (13-74) months after ATD cessation (56.0% vs. 46.3%, respectively); hazard ratio (95% confidence intervals) of 1.74 (0.96-3.15). CONCLUSIONS: Nonuniform radio-isotope uptake is seen in 1 in 11 patients with GD which could be

misdiagnosed as toxic multinodular goitre if TRAb levels are not measured. Treatment of GD patients with nonuniform radio-isotope uptake with ATD therapy as first-line appears to be equally effective as compared with those with uniform uptake. TRAb testing should be the main diagnostic test for patients with suspected GD with radio-labelled uptake scans being reserved for those who are TRAb negative.

PubMed-ID: [35244288](https://pubmed.ncbi.nlm.nih.gov/35244288/)

<http://dx.doi.org/10.1111/cen.14709>

Resident self-assessment of common endocrine procedures.

Am J Surg, 223(6):1094-9.

P. J. Abraham, J. Fazendin, R. Xie, H. Chen and B. Lindeman. 2022.

BACKGROUND: General surgery residency graduates are expected to be proficient in straightforward endocrine operations. This study aimed to elucidate residents' self-assessment of their ability to perform common endocrine procedures. METHODS: A fourteen-question survey was emailed to general surgery residents from seven U.S. residency programs regarding their self-assessed ability to perform each step of a straightforward thyroidectomy and parathyroidectomy. Demographics and perceived ability to perform the various procedures were collected. RESULTS: A minority of respondents (17, 27.9%) agreed they could complete a straightforward thyroidectomy for benign disease, with only 11.7% (n = 7) agreeing they could complete a straightforward thyroidectomy for malignant disease. 26.2% (n = 16) of respondents agreed they could complete a straightforward parathyroidectomy. Completed number of cases was significantly associated with greater self-assessed ability to perform the endocrine operations (p = 0.02). CONCLUSIONS: Most general surgery residents surveyed did not feel capable of performing common, straightforward endocrine procedures. Although confidence in operative ability increased with PGY-level and number of cases completed, the majority of PGY-5 residents still did not feel able to perform a thyroidectomy for malignant disease unassisted.

PubMed-ID: [34689978](https://pubmed.ncbi.nlm.nih.gov/34689978/)

<http://dx.doi.org/10.1016/j.amjsurg.2021.10.025>

Metastatic medullary thyroid carcinoma: a new way forward.

Endocr Relat Cancer, 29(7):R85-R103.

A. Angelousi, A. R. Hayes, E. Chatzellis, G. A. Kaltsas and A. B. Grossman. 2022.

Medullary thyroid carcinoma (MTC) is a rare malignancy comprising 1-2% of all thyroid cancers in the United States. Approximately 20% of cases are familial, secondary to a germline RET mutation, while the remaining 80% are sporadic and also harbour a somatic RET mutation in more than half of all cases. Up to 15-20% of patients will present with distant metastatic disease, and retrospective series report a 10-year survival of 10-40% from time of first metastasis. Historically, systemic therapies for metastatic MTC have been limited, and cytotoxic chemotherapy has demonstrated poor objective response rates. However, in the last decade, targeted therapies, particularly multitargeted tyrosine kinase inhibitors (TKIs), have demonstrated prolonged progression-free survival in advanced and progressive MTC. Both cabozantinib and vandetanib have been approved as first-line treatment options in many countries; nevertheless, their use is limited by high toxicity rates and dose reductions are often necessary. New generation TKIs, such as selpercatinib or pralsetinib, that exhibit selective activity against RET, have recently been approved as a second-line treatment option, and they exhibit a more favourable side-effect profile. Peptide receptor radionuclide therapy or immune checkpoint inhibitors may also constitute potential therapeutic options in specific clinical settings. In this review, we aim to present all current therapeutic options available for patients with progressive MTC, as well as new or as yet experimental treatments.

PubMed-ID: [35521769](https://pubmed.ncbi.nlm.nih.gov/35521769/)

<http://dx.doi.org/10.1530/ERC-21-0368>

Impact of thyroidectomy on quality of life in benign goitres: results from a prospective cohort study.

Langenbecks Arch Surg, 407(3):1193-9.

S. Azaria, A. J. Cherian, M. Gowri, S. Thomas, P. Gaikwad, P. Mj and D. T. Abraham. 2022.

PURPOSE: Benign thyroid diseases encompass a large spectrum of conditions that are chronic and subtle in nature. A majority of patients choose non-surgical management and continue living their daily lives with subconscious impairment of optimal functioning. We studied the effect of thyroidectomy on the quality of life (QoL) in patients with benign goitres. METHODS: A prospective study was conducted on 50 patients between January 2017 and August 2018 using the ThyPRO 39 questionnaire. This is a disease-specific health-related questionnaire administered the day before surgery and 6 months following surgery. Data analysis was performed using EpiData Manager and EpiData Entry Client (v 3.1). RESULTS: The mean age of the cohort was 43.30 years \pm 11.61, with a female preponderance (34:16). The most common indications for surgery were suspicion of malignancy and compressive symptoms in 34% and 30%, respectively. The most common

histopathology reported was nodular/adenomatous hyperplasia (56%). Prior to surgery, the most common domains affected were emotional susceptibility and tiredness. Following surgery, a significant improvement in all domains of the ThyPRO 39 questionnaire were seen except for psychological well-being ($p=0.126$). In addition, the composite scores significantly improved ($p<0.001$). Younger age, female gender, and longer duration of goitre were the factors that significantly affected the outcomes in various domains. CONCLUSION: Patients with benign goitres have subtle impairment of QoL which showed significant improvement following thyroidectomy.

PubMed-ID: [34988642](https://pubmed.ncbi.nlm.nih.gov/34988642/)

<http://dx.doi.org/10.1007/s00423-021-02391-7>

Papillary thyroid cancer: the value of bilateral diagnostic lymphadenectomy.

Langenbecks Arch Surg, 407(5):2059-66.

J. S. Bhangu, C. Bichler, J. Altmeier, L. Hargitai, A. Selberherr, P. Mazal, J. Brugger, C. Scheuba, P. Riss and B. Niederle. 2022. PURPOSE: Papillary thyroid carcinoma (PTC) spreads early to lymph nodes (LN). However, prophylactic central (CND) and lateral neck dissection (LND) is controversially discussed in patients with clinically negative nodes (cN0). The preoperative prediction of LN metastasis is desirable as re-operation is associated with higher morbidity and poor prognosis. The study aims to analyse possible benefits of a systemic bilateral diagnostic lateral lymphadenectomy (DLL) for intraoperative LN staging. METHODS: Preoperative prediction of LN metastasis by conventional ultrasound (US) was correlated with the results of DLL and intra-/postoperative complications in 118 consecutive patients with PTC (cN0) undergoing initial thyroidectomy and bilateral CND and DLL. RESULTS: Lateral LNs (pN1b) were positive in 43/118 (36.4%) patients, including skip lesions ($n = 6$; 14.0%). Preoperative US and intraoperative DLL suspected lateral LN metastasis in 19/236 (TP: 8.1%) and 54/236 (TP: 22.9%) sides at risk, which were confirmed by histology. Sixty-seven out of 236 (FN: 28.4%) and 32/236 (FN: 13.6%) sides at risk with negative preoperative US and intraoperative DLL lateral LN metastasis were documented. DLL was significantly superior compared to US regarding sensitivity (62.8% vs 22.1%; $p < 0.002$), positive predictive value (100% vs 76.0%), negative predictive value (82.4% vs 68.2%), and accuracy (86.4% vs 69.1%), but not specificity (100% vs 96.0%; $p = 0.039$). DLL-related complications (haematoma) occurred in 6/236 [2.5%] sides at risk, including chylous fistula in 2/118 [1.7%] patients. CONCLUSION: DLL can be recommended for LN staging during initial surgery in patients with PTC to detect occult lateral LN metastasis not suspected by US in order to plan lateral LN dissection.

PubMed-ID: [35301585](https://pubmed.ncbi.nlm.nih.gov/35301585/)

<http://dx.doi.org/10.1007/s00423-022-02493-w>

Empiric radioiodine for hyperthyroidism: Outcomes, prescribing patterns, and its place in the modern era of theranostics.

Clin Endocrinol (Oxf), 97(1):124-9.

E. Boehm, Y. H. Kao, J. Lai, P. R. Wraight and D. A. Sivaratnam. 2022.

BACKGROUND: The modern era of radioiodine (I-131) theranostics for metastatic differentiated thyroid cancer requires us to rationalize the role of traditional empiric prescription in nonmalignant thyroid disease. We currently practice empiric I-131 prescription for treatment of hyperthyroidism. This study aims to assess outcomes after treatment of hyperthyroidism by empiric I-131 prescription at our centre, evaluate factors that impact on outcomes and prescribing practice, and gain insight into whether there is a place for theranostically-guided prescription in hyperthyroidism. PATIENTS AND METHODS: A retrospective review was undertaken of all patients with Graves' disease, toxic multinodular goitre (MNG) and toxic adenoma treated with I-131 between 2016 and 2021. Associations between clinical or scintigraphic variables and remission (euthyroid or hypothyroid) or persistence of hyperthyroidism at follow-up were performed using standard t test as well as Pearson's product correlation. RESULTS: Of 146 patients with a mean follow-up of 13.6 months, 80.8% achieved remission of hyperthyroidism. This was highest in toxic nodules (90.1%), compared with Graves' disease (73.8%) and toxic MNG (75.5%). In patients with Graves' disease, higher administered activity was associated with remission ($p = .035$). There was a weak inverse correlation between the Tc-99m pertechnetate uptake vs prescribed activity in Graves' disease ($r = -0.33$; $p = .009$). Only one patient (0.7%) had an I-131 induced flare of thyrotoxicosis. CONCLUSION: Traditional empiric I-131 prescription is a safe and effective treatment of hyperthyroidism and suitable for most patients. However, there may be a role for personalized I-131 prescription by theranostic guidance in selected patients with high thyroid hyperactivity.

PubMed-ID: [35508893](https://pubmed.ncbi.nlm.nih.gov/35508893/)

<http://dx.doi.org/10.1111/cen.14753>

Clinical Outcomes of Diffuse Sclerosing Variant Papillary Thyroid Carcinoma in Pediatric Patients.

Laryngoscope, 132(5):1132-8.

C. Brady, S. C. Manning, E. Rudzinski, V. Paulson, X. Wang, Y. J. Liu, S. R. Parikh, J. Bonilla-Velez, D. S. Hawkins and J. Dahl. 2022.

OBJECTIVES/HYPOTHESIS: The diffuse sclerosing variant of papillary thyroid carcinoma (DSV) may be more aggressive than conventional well-differentiated non-DSV related papillary thyroid carcinomas (N-PTC). **STUDY DESIGN:** Retrospective chart review. **METHODS:** Retrospective review of clinical outcomes for patients 21 years of age or younger who underwent initial surgery for PTC at a single institution from January 1, 2005 to April 1, 2020. Genomic analysis was performed using targeted next-generation sequencing. Data were analyzed using Fischer's exact test and Kaplan-Meier curve log-rank test. **RESULTS:** Our cohort consisted of 72 patients, nine with DSV and 63 with N-PTC. Age at diagnosis was comparable (15.4 vs. 16.2 years, respectively, $P = .46$). DSV were more likely to be in the high-risk American Thyroid Academy pediatric risk group (100% vs. 41.3%, $P = .004$), to present with regional cervical lymph node metastases (100% vs. 60.3%, $P = .036$), and to present with distant metastases (67% vs. 22%, $P = .005$). No mortality seen in either group over 27.5 (interquartile range 14.8, 46.00) months average follow-up. Throughout the follow-up period, DSV were more likely to experience progression than N-PTC (hazard ratio = 5.7 [95% confidence interval 1.7-20.0; $P = .0056$]). In a subset of 19 patients with aggressive disease who had molecular testing as part of clinical care we detected RET fusions in nearly all DSV compared to a minority of N-PTC (83% vs. 15.4%, $P = .0095$). **CONCLUSIONS:** Pediatric patients with DSV have more advanced disease at diagnosis and are more likely to experience progression of disease compared to patients with N-PTC. The prevalence of RET fusions in our cohort recapitulates the frequency of this alteration described in prior studies. **LEVEL OF EVIDENCE:** 4 *Laryngoscope*, 132:1132-1138, 2022.

PubMed-ID: [34713899](https://pubmed.ncbi.nlm.nih.gov/34713899/)

<http://dx.doi.org/10.1002/lary.29926>

Role of Thyroidectomy in Recurrent Laryngeal Carcinoma.

Otolaryngol Head Neck Surg, 166(5):894-900.

A. Brunet, C. Tornari, A. Ezebuoro, R. Kennedy, S. E. J. Connor, R. Oakley, J. P. Jeannon, A. Arora, A. Rovira and R. Simo. 2022.

OBJECTIVE: Management of recurrent laryngeal cancer presents a major challenge, and salvage laryngectomy is complicated by previous oncologic treatments. Thyroidectomy as part of salvage laryngectomy adds a nonnegligible degree of morbidity. The purpose of this study is to assess the rate of thyroid gland invasion in patients undergoing salvage laryngectomy to determine relevant predictive factors. **STUDY DESIGN:** Case series with chart review. **SETTING:** Department of Otorhinolaryngology, Head and Neck Surgery, Guy's Hospital, London, United Kingdom. **METHODS:** A retrospective review of patients undergoing salvage laryngectomy between 2009 and 2019 was undertaken. Preoperative cross-sectional imaging and histopathological analysis were performed to define evidence and predictors of thyroid gland invasion (TGI). **RESULTS:** Fifty-one patients had salvage laryngectomy. Histological evidence of TGI was found in 4 patients (7.8%). No significant relationship was found between histological TGI and subsite of primary carcinoma, degree of differentiation, T staging, or radiological TGI. Preoperative computed tomography had a high negative predictive value for TGI. **CONCLUSION:** Thyroidectomy should be carefully considered in patients undergoing salvage laryngectomy, and its extent should be defined on an individual basis. Total thyroidectomy should not routinely be performed in salvage laryngectomy or pharyngolaryngectomy in patients with no preoperative radiological evidence of TGI on cross-sectional imaging, unless there is intraoperative evidence of TGI.

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Safety and Feasibility of Robotic Transaxillary Thyroidectomy for Graves' Disease: A Retrospective Cohort Study.

World J Surg, 46(5):1107-13.

M. S. Bu Bshait, J. K. Kim, C. R. Lee, S. W. Kang, J. J. Jeong, K. H. Nam and W. Y. Chung. 2022.

BACKGROUND: Despite the increase in experience and understanding of robotic thyroidectomy, its application for Graves' disease (GD) remains controversial. This study aimed to assess the safety and feasibility of robotic transaxillary thyroidectomy (RTT) for GD in comparison with the conventional open thyroidectomy (open group: OG) approach. **METHODS:** A total of 192 patients who underwent surgical resection for GD were retrospectively reviewed. Among them, 51 patients underwent RTT and the remaining 141 patients were in the conventional OG. **RESULTS:** All robotic operations were performed successfully without open conversion. Patients who underwent RTT were significantly younger ($P < 0.001$) and predominantly of the female sex. Operative time was longer for RTT than for the OG (182.5 ± 58.1 vs. 112.0 ± 29.5 ; $P < 0.001$). The mean intraoperative blood loss was not statistically different between RTT and the OG (113.3 ± 161.6 vs. 95.3

± 209.1, P = 0.223). The mean weight of the resected thyroid was reduced in those who underwent RTT compared with open thyroidectomy (P = 0.033). The overall complication rate for RTT and open thyroidectomy was not significantly different (33.3% vs. 22.7%, P = 0.135). In RTT, the most common complication was transient hypocalcemia (21%). Permanent hypocalcemia and recurrent laryngeal nerve injury occurred in only one patient in each group. The weight of the resected thyroid was not related to the incidence of complications in patients receiving RTT. CONCLUSIONS: Considering excellent cosmesis, findings of this study support the safety and feasibility of RTT. Nevertheless, it should be performed by expert surgeons with extensive robotic surgery experience.

PubMed-ID: [35015120](https://pubmed.ncbi.nlm.nih.gov/35015120/)

<http://dx.doi.org/10.1007/s00268-021-06430-8>

Prognostic value of LODDS in medullary thyroid carcinoma based on competing risk model and propensity score matching analysis.

Updates Surg, 74(5):1551-62.

Z. X. Cao, X. Weng, J. S. Huang and X. Long. 2022.

Log odds of positive lymph nodes (LODDS) is an independent prognostic factor for patients with medullary thyroid carcinoma (MTC). However, the optimal cutoff value for LODDS needs to be further confirmed, and previous studies have ignored the prevalent competing events of non-cancer deaths among patients with MTC, thus possibly overestimating the risk of death from cancer. The information of patients with MTC who underwent total thyroidectomy was collected from SEER database. Restricted cubic splines (RCS) were used to determine the optimal cutoff for LODDS. Moreover, patients' overall survival (OS) and disease-specific survival (DSS) were determined using Kaplan-Meier and Cox proportional-hazards model. The competing risk models (CRM) were used to reduce the effect of competing events, and propensity score matching was performed to balance the confounding factors between groups. The cutoff value of LODDS determined by RCS was - 1.004, and a total of 2314 patients with MTC were recruited. In the CRM after PSM, factors such as age over 55 years at diagnosis, being male, treatment with chemotherapy or radiotherapy, unknown tumor size, and LODDS > - 1.004 were significantly associated with poor prognosis of patients both in univariate and multivariate analyses, while the presence of multifocal tumor indicated better prognosis. Patients with MTC who were over 55 years old at diagnosis, were male, received chemotherapy or radiation, had an unclear initial tumor size, and had LODDS > - 1.004 had a worse prognosis than patients with multifocal tumor.

PubMed-ID: [35821560](https://pubmed.ncbi.nlm.nih.gov/35821560/)

<http://dx.doi.org/10.1007/s13304-022-01320-7>

Histopathological Characteristics of N1b Papillary Thyroid Carcinoma are Associated with Risk of Recurrence.

World J Surg, 46(8):1917-25.

N. N. Carmel Neiderman, I. Duek, B. Kuzmenko, B. Ringel, A. Warshavsky, N. Muhanna, G. Horowitz and D. M. Fliss. 2022.

BACKGROUND: The presence of cervical lymph node (LN) metastasis at the initial presentation of papillary thyroid carcinoma (PTC) constitutes an independent risk factor for disease recurrence, increases the risk for mortality, and impacts overall outcome. The 2016 American Joint Committee on Cancer raised the age cutoff for PTC staging from 45 to 55 years for better prediction of overall survival. Age > 55 years is considered a significant risk factor for a more aggressive and advanced disease with worse outcomes. We identified histopathological factors for disease recurrence in PTC patients younger and older than 55 years of age. METHODS: Data on all patients who underwent thyroid surgery due to PTC between 2006 and 2018 in the Tel Aviv Sourasky Medical Center were retrieved for this retrospective cohort study. Patients with lymph node (LN) metastases were further investigated for preoperative presentation, pathological characteristics, and recurrence. A multivariate analysis was used to detect predictors for recurrence and patient outcome for each age-group. RESULTS: Twenty-two of the 183 patients (12%) with PTC who met the inclusion criteria and had sufficient follow-up period sustained recurrence. The predictors of recurrence varied between the two age-groups. The size of thyroid lesions (p = 0.003) was identified as a risk factor in the older group, while the number of metastatic cervical LNs (p = 0.001) and the ratio of metastatic-to-total dissected cervical LNs (p = 0.027) were the main predictors of recurrence for the younger group. CONCLUSION: The histopathological factors predictive for disease recurrence differed among PTC patients younger and older than 55 years of age.

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<http://dx.doi.org/10.1007/s00268-022-06581-2>

Modified Larssen solution (MLS)-fixed cadaver model for transoral endoscopic thyroidectomy vestibular approach (TOETVA) education: a feasibility study.

Surg Endosc, 36(7):5518-30.

S. Celik, O. Bilge, M. Ozdemir, G. Dionigi, A. Anuwong and O. Makay. 2022.

BACKGROUND: Training formats for transoral endoscopic thyroidectomy vestibular approach (TOETVA) are limited. Our aim was to create and investigate a TOETVA training model for general and ENT surgeons. **METHODS:** A total of 15 modified Larssen solution (MLS) human cadavers were used in the study. A day duration TOETVA human cadaver workshops were offered in two years consecutive. Post-training verbal and online questionnaires were applied to all trainers to evaluate course structure and program, organoleptic characteristics of MLS-fixed human cadavers, and TOETVA training effectiveness. Cost assessment is included in the study. **RESULTS:** Ninety-eight participants, i.e., 14 trainers and 84 hands-on (HO) and observer (OB) trainees, attended the workshops, completed the tasks assigned, and fulfilled the questionnaires. Implementation of all steps of TOETVA was approved positively by 89.8% of all participants, 94.4% of HO, and 83.3% of OB trainees. Regarding human cadaver and teaching quality, 10.8 ± 0.8 (10-12) human cadavers were "practical" by 13.2 (94.5%) of the trainers, and by 33.3 (92.5%) of the trainees for all steps of TOETVA. The cadavers were stored for 4.53 years and used 6.27 times repeatedly for endoscopic workshops and research studies. TOETVA workshop cost with repeatable use of MLS-fixed human cadaver is half of other performed TOETVA workshops. **CONCLUSIONS:** A TOETVA human cadaver workshop model has not been reported yet. Our findings suggest the feasibility of MLS-fixed human cadaver model for training of TOETVA, preserve the organoleptic properties necessary for the implementation of surgical steps, and reduce the cost.

PubMed-ID: [35471255](https://pubmed.ncbi.nlm.nih.gov/35471255/)

<http://dx.doi.org/10.1007/s00464-022-09224-8>

Concerns Over Thyroid Cancer Surgeries and Quality of Life-Reply.

JAMA Surg, 157(8):740.

W. Chen, J. Li and W. Lv. 2022.

PubMed-ID: [35476013](https://pubmed.ncbi.nlm.nih.gov/35476013/)

<http://dx.doi.org/10.1001/jamasurg.2022.0814>

The Impact of Hospital Surgical Volume on Healthcare Utilization Outcomes After Pediatric Thyroidectomy.

World J Surg, 46(5):1082-92.

A. D. Chesover, A. Eskander, R. Griffiths, J. D. Pasternak, J. D. Pole, N. E. Wolter and J. D. Wasserman. 2022.

BACKGROUND: A positive relationship between an individual surgeon's operative volume and clinical outcomes after pediatric and adult thyroidectomy is well-established. The impact of a hospital's pediatric operative volume on surgical outcomes and healthcare utilization, however, are infrequently reported. We investigated associations between hospital volume and healthcare utilization outcomes following pediatric thyroidectomy in Canada's largest province, Ontario. **METHODS:** Retrospective analysis of administrative and health-related population-level data from 1993 to 2017. A cohort of 1908 pediatric (<18 years) index thyroidectomies was established. Hospital volume was defined per-case as thyroidectomies performed in the preceding year. Healthcare utilization outcomes: length of stay (LOS), same day surgery (SDS), readmission, and emergency department (ED) visits were measured. Multivariate analysis adjusted for patient-level, disease and hospital-level co-variables. **RESULTS:** Hospitals with the lowest volume of pediatric thyroidectomies, accounted for 30% of thyroidectomies province-wide and performed 0-1 thyroidectomies/year. The highest-volume hospitals performed 19-60 cases/year. LOS was 0.64 days longer in the highest, versus the lowest quartile. SDS was 83% less likely at the highest, versus the lowest quartile. Hospital volume was not associated with rate of readmission or ED visits. Increased ED visits were, however, associated with male sex, increased material deprivation, and rurality. **CONCLUSIONS:** Increased hospital pediatric surgical volume was associated with increased LOS and lower likelihood of SDS. This may reflect patient complexity at such centers. In this cohort, low-volume hospitals were not associated with poorer healthcare utilization outcomes. Further study of groups disproportionately accessing the ED post-operatively may help direct resources to these populations.

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<http://dx.doi.org/10.1007/s00268-022-06456-6>

Effects of dabrafenib and erlotinib combination treatment on anaplastic thyroid carcinoma.

Endocr Relat Cancer, 29(6):307-19.

Y. S. Choi, H. Kwon, M. H. You, T. Y. Kim, W. B. Kim, Y. K. Shong, M. J. Jeon and W. G. Kim. 2022.

Dabrafenib is a BRAF kinase inhibitor approved for treatment of BRAF-mutated anaplastic thyroid carcinoma (ATC) in combination with trametinib. Erlotinib is a tyrosine kinase inhibitor of EGF receptor (EGFR). We evaluated effects of dabrafenib and erlotinib combination treatment on ATC cells in vitro and in vivo. Cell proliferation, colony formation, apoptosis, and migration of ATC cells harboring a BRAF mutation (BHT101, 8505C, and SW1736) were evaluated after treatment with dabrafenib in combination with erlotinib or trametinib. The changes in activation of mitogen extracellular kinase (MEK) and extracellular signal-related kinase (ERK) signaling were also evaluated by Western blot analysis. Effects of these combinations were also evaluated using an in vivo xenograft model. First, we detected EGFR activation in dabrafenib-resistant SW1736 cells using a phospho-receptor tyrosine kinase array. A dabrafenib and erlotinib combination synergistically inhibited cell proliferation, colony formation, and migration, with an induction of apoptotic cell death in all three ATC cells, compared with dabrafenib or erlotinib alone. This synergistic effect was comparable with a dabrafenib and trametinib combination. The dabrafenib and erlotinib combination effectively inhibited phosphorylated (p)-MEK, p-ERK, and p-EGFR expressions compared with dabrafenib or erlotinib alone, while the dabrafenib and trametinib combination only inhibited p-MEK and p-ERK expressions. The dabrafenib with erlotinib or trametinib combinations also significantly suppressed tumor growth and induced apoptosis in a BHT101 xenograft model. The dabrafenib and erlotinib combination could be a potential novel treatment regimen to overcome drug resistance to dabrafenib alone in patients with BRAF-mutated ATC.

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<http://dx.doi.org/10.1530/ERC-22-0022>

Pre- and Post-operative Circulating Tumoral DNA in Patients With Medullary Thyroid Carcinoma.

J Clin Endocrinol Metab, 107(8):e3420-e7.

R. Ciampi, C. Romei, T. Ramone, A. Matrone, A. Prete, C. Gambale, G. Materazzi, L. De Napoli, L. Torregrossa, F. Basolo, M. G. Castagna, L. Brilli, E. Ferretti and R. Elisei. 2022.

CONTEXT: Measurement of driver mutations in circulating tumoral DNA (ctDNA) obtained by liquid biopsy has been shown to be a sensitive biomarker in several human tumors. OBJECTIVE: The aim of this study was to evaluate the clinical relevance of pre- and post-operative ctDNA in sporadic medullary thyroid cancer (sMTC). METHODS: We studied pre- and post-operative ctDNA in 26 and 23 sMTC patients, respectively. ctDNA results were correlated to serum calcitonin (Ct), carcinoembryonic antigen (CEA), and other clinical/pathological features. RESULTS: Twenty-six of 29 (89.7%) sMTCs were mutated either for RET or RAS and 3/29 (10.3%) were negative. Four of 26 (15.4%) cases showed positive pre-operative ctDNA with a significantly higher presence of RET M918T mutation ($P = 0.0468$). Patients with positive pre-operative ctDNA showed a higher variation allele frequency value of the somatic driver mutation ($P = 0.0434$) and a higher frequency of persistent disease ($P = 0.0221$). Post-operative ctDNA was positive only in 3/23 (13%) sMTCs and no one was positive for pre-operative ctDNA. Higher values of both Ct ($P = 0.0307$) and CEA ($P = 0.0013$) were found in positive ctDNA cases. Finally, the 7 cases harboring either pre- or post-operative positive ctDNA had a persistent disease ($P = 0.0005$) showing a higher post-operative serum Ct when compared with cases with negative ctDNA ($P = 0.0092$). CONCLUSIONS: Pre-operative ctDNA in medullary thyroid cancer is not useful for diagnostic purposes, but it can be useful for predicting the outcome of the disease. In our series, post-operative ctDNA showed a potential for monitoring the response to therapies, but further studies are required to confirm our results.

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Revisiting the role of surgery in the treatment of Graves' disease.

Clin Endocrinol (Oxf), 96(6):747-57.

O. Cohen, O. Ronen, A. Khafif, J. P. Rodrigo, R. Simo, P. Pace-Asciak, G. Randolph, L. H. Mikkelsen, L. P. Kowalski, K. D. Olsen, A. Sanabria, R. P. Tufano, S. Babighian, A. R. Shaha, M. Zafereo and A. Ferlito. 2022.

Graves' disease (GD) can be managed by antithyroid drugs (ATD), radioactive iodine (RAI) and surgery. Thyroidectomy offers the highest success rates for both primary and persistent disease, yet it is the least recommended or utilized option reaching <1% for primary disease and <25% for persistent disease. Several surveys have found surgery to be the least recommended by endocrinologists worldwide. With the development of remote access thyroidectomies and intraoperative nerve monitoring of the recurrent laryngeal nerve, combined with current knowledge of possible risks associated with RAI or failure of ATDs, reevaluation of the benefit to harm ratio of surgery in the treatment of GD is warranted. The aim of this review is to discuss possible reasons for the low proportion of surgery in the treatment of GD,

emphasizing an evidence-based approach to the clinicians' preferences for surgical referrals, surgical indications and confronting traditional reasons and concerns relating to the low referral rate with up-to-date data.

PubMed-ID: [34954838](https://pubmed.ncbi.nlm.nih.gov/34954838/)

<http://dx.doi.org/10.1111/cen.14653>

Is there a role for diagnostic scans in the management of intermediate-risk thyroid cancer?

Endocr Relat Cancer, 29(8):475-83.

D. L. S. Danilovic, G. B. Coura-Filho, G. M. Recchia, L. A. Castroneves, S. Marui, C. A. Buchpiguel, A. O. Hoff and P. Kopp. 2022.

Radioiodine (RAI) is selectively recommended for intermediate-risk differentiated thyroid carcinomas (DTC). The information gleaned from pretherapy stimulated thyroglobulin levels (sTg) and diagnostic 131I whole-body scans (DxWBS) to guide therapy remains controversial. The present study aimed at evaluating the impact of preablation sTg and DxWBS in the management of intermediate-risk DTC. A retrospective analysis of 301 intermediate-risk DTC patients submitted to total thyroidectomy and RAI therapy was performed. Pretherapy sTg and DxWBS and post-therapy WBS (RxWBS) findings were analyzed and compared to outcomes. Fifty-two patients (17.3%) had metastases diagnosed by DxWBS and/or RxWBS. The DxWBS identified 10.6% of patients with functioning metastases, including unexpected distant metastases. If combined with SPECT-CT, DxWBS detected RAI-avid metastases more frequently, particularly lymph node metastases (13.1% vs 4.2% planar WBS, $P = 0.015$). The DxWBS findings modified patient management in 8.3%. A pretherapy sTg <1 ng/mL was associated with a low false-negative rate for the presence of metastases (5.2%), and its performance in excluding metastasis was improved by a negative DxWBS (2.7% of patients with both negative exams had metastases in RxWBS). A sTg <1 ng/mL predicted statistically significant lower rates of recurrent/persistent disease and biochemical/structural incomplete responses. In conclusion, preablation sTg and DxWBS contribute to the detection of unknown or persistent metastatic disease in intermediate-risk DTC patients. A sTg <1 ng/mL in combination with a negative DxWBS is highly suggestive of the absence of remaining malignant disease, and one may consider deferring RAI ablation if both exams are negative. A stunning effect is rarely observed and it does not impair proper treatment of metastases.

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<http://dx.doi.org/10.1530/ERC-22-0038>

Flexible single port access in transoral endoscopic thyroidectomy vestibular approach.

Gland Surg, 11(5):778-87.

M. de Cillia, C. Obrist, C. Mittermair, E. Karakas and H. Weiss. 2022.

BACKGROUND: Transoral endoscopic thyroidectomy vestibular approach (TOETVA) is regarded the only no-scar technique which combines minimized surgical trauma with all advantages of endoscopy such as enhanced view, fluorescent parathyroid imaging (FPI) and optimum cosmesis. Addressing TOETVA specific local risk profiles like mental nerve injury, the potential of skin lesions or difficult specimen retrieval we modified the three trocar based TOETVA towards a soft single port platform. **METHODS:** Single port-TOETVA (SP-TOETVA) was established and retrospectively analysed in five patients using a soft handmade single port housing multiple trocar valves. Standard laparoscopic instruments, one articulating instrument and a vessel-sealing device were utilized. CO₂ insufflation was maintained at 6-8 mmHg. **RESULTS:** In all patients SP-TOETVA was completed successfully. Hemigland and total thyroid volumes ranged from 5-40 and 55 mL, respectively. Neither additional trocars nor conversion to open was required. Operation time yielded 102-214 min. Neuromonitoring and FPI were applied. The soft wound protection foil served for convenient specimen harvest. No intra- or postoperative complication occurred. In particular, no functional impairment on mental nerve was seen. **CONCLUSIONS:** SP-TOETVA with the soft and flexible handmade single port system is feasible and ensures wound protection. It allows for easy instrument application and benefits of minimally invasive surgery without the specific risk of lateral vestibular incisions.

PubMed-ID: [35694100](https://pubmed.ncbi.nlm.nih.gov/35694100/)

<http://dx.doi.org/10.21037/gs-21-818>

Which Is the Best Endoscopic Procedure for Thyroid Gland?

Ann Surg Oncol, 29(5):3093-4.

G. Dionigi, L. Boni, L. Fugazzola, H. Y. Kim and P. Miccoli. 2022.

PubMed-ID: [35275328](https://pubmed.ncbi.nlm.nih.gov/35275328/)

<http://dx.doi.org/10.1245/s10434-022-11604-2>

Nerve monitoring decreases recurrent laryngeal nerve injury risk for neoplasm-related thyroidectomy.

Am J Surg, 223(5):918-22.

W. Duong, A. Grigorian, C. Farzaneh, D. Elfenbein, M. Yamamoto, K. Rosenbaum, M. Lekawa and J. Nahmias. 2022.

OBJECTIVE: Conflicting reports exist regarding the benefit of intraoperative neuromonitoring (INM) for patients undergoing thyroidectomy. We hypothesized that in a national sample, the risk of mild and severe RLNi is decreased for patients undergoing neoplasm-related disease (NRD) thyroidectomy with INM compared to patients without INM.

METHODS: The database was queried for patients that underwent total thyroidectomy for NRD with and without INM. A multivariable logistic regression model was used to determine the associated odds of RLNi. **RESULTS:** From 6942 patients, 4269 (61.5%) had INM during thyroidectomy. Patients with INM had a similar rate of overall RLNi compared to patients without INM (5.7% vs. 6.6%, $p = 0.118$). After adjusting for covariates, INM was associated with decreased odds of severe-RLNi (OR 0.23, $p = 0.036$) but not mild-RLNi ($p = 0.16$). **CONCLUSION:** INM is associated with a nearly 80% decreased associated odds of severe RLNi during thyroidectomy for NRD. Future prospective confirmation is needed, and if confirmed, patients undergoing thyroidectomy for NRD should have INM to reduce the risk of RLNi and its associated morbidity.

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<http://dx.doi.org/10.1016/j.amjsurg.2021.10.013>

A prospective comparison of ACR-TIRADS and EU-TIRADS in thyroid nodule assessment for FNA-US.

Clin Endocrinol (Oxf),

L. B. Eidt, C. Nunes de Oliveira, Y. B. B. Lagos, G. L. M. Solera, R. Izquierdo, E. L. S. Meyer, V. S. Mattevi and L. Golbert. 2022.

OBJECTIVE: Prospective data on the accuracy of ultrasound (US) classification systems in thyroid nodules are still scarce. The aim of this study is to compare the accuracy of the American College of Radiology Thyroid Imaging Reporting and Data System (ACR-TIRADS) and European (EU)-TIRADS classification systems. **DESIGN AND PATIENTS:** Consecutive patients with one or more thyroid nodule(s) who underwent fine-needle aspiration (FNA) under ultrasonographic guidance (FNA-US) were prospectively evaluated. **MEASUREMENTS:** Clinical evaluation and US data were collected. The reference standard used for this study was FNA-US cytology and histopathological diagnosis. **RESULTS:** A total of 186 thyroid nodules in 166 patients were evaluated, resulting in 168 nodules from 149 patients with conclusive benign or malignant results. Sensitivity, specificity, negative predictive value (NPV) and false negative (FN) were 100.0%, 28.7%, 100.0% and 0.0%, respectively, for ACR-TIRADS; and 90.0%, 19.1%, 96.8% and 9.1% ($n = 1$), respectively, for EU-TIRADS. The number of unnecessary FNA-US indicated by ACR-TIRADS was lower than EU-TIRADS (71.3% vs. 80.9%, $p = .017$), and the number of possibly avoided FNA-US was higher (26.7% vs. 17.8%). Using the same threshold of ACR-TIRADS to indicate FNA-US in EU-TIRADS 3 nodules (2.5 cm), there was an improvement in specificity (30.6%) and avoided FNA-US (28.6%). The best performance of both systems was demonstrated when FNA-US would be indicated only in highly suspicious nodules and/or in the presence of lymphadenopathy, with 85.7% and 89.3% of possibly avoided FNA-US for ACR-TIRADS and EU-TIRADS, respectively, without increasing FN. **CONCLUSION:** Both systems presented high sensitivity, but low specificity in selecting nodules for FNA-US. The use of nodular size for FNA-US selection is questioned.

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<http://dx.doi.org/10.1111/cen.14799>

Mortality after benign thyroid surgery in patients aged 80 years or older.

Langenbecks Arch Surg, 407(4):1659-65.

S. A. Farhad, B. Anders, N. Erik, N. Martin and A. Martin. 2022.

INTRODUCTION: A recent report from the United Nations showed that aged people are increasing worldwide. Few data exist on overall survival for patients 80 years or older undergoing benign thyroid surgery. Short- and long-term survival and risk factors for death in patients undergoing thyroid surgery for benign disease were evaluated, using a nationwide, population-based quality register. **METHODS:** Patients operated for benign thyroid disease, 2004 to 2017, were collected from the national quality register for thyroid surgery. Mortality data were retrieved from the Swedish National Board of Health and Welfare. Mortality at 30 days, 90 days, and 1 year after surgery, for patients 80 years or older, was calculated. Overall survival was calculated using the Kaplan-Meier estimate. Risk factors for mortality were assessed with Cox's multiple regression analysis. The standardized mortality ratio was calculated. **RESULTS:** There were 17,969 patients. Among them, 483 patients were 80 years or older, and of these, 397 (82.2%) were women. The mortality rate at 0-30 days, 31-90 days, and at 91-365 days after surgery was 0.4%, 0.2%, and 2.5%, respectively. The median (IQR) follow-up time was 4.5 (2.9-7.2) and the median (IQR) survival time was 8.0 (4.1-12.5) years. Apart from age, there was no other risk factor for death. The standardized mortality ratio (SMR) was 0.67 (0.49-0.91) for men and 0.76 (0.65-0.89) for women.

CONCLUSION: Mortality after surgery for benign thyroid disease in patients 80 years or older was lower than the general population with no specific risk factors for death except for age.

PubMed-ID: [35286467](https://pubmed.ncbi.nlm.nih.gov/35286467/)

<http://dx.doi.org/10.1007/s00423-022-02463-2>

Best Left to the Experts: Proficiency and Experience are Key for Safety in Remote-Access Thyroidectomy for Graves' Disease.

World J Surg, 46(5):1114-5.

C. E. Graves and M. J. Campbell. 2022.

PubMed-ID: [35230507](https://pubmed.ncbi.nlm.nih.gov/35230507/)

<http://dx.doi.org/10.1007/s00268-022-06496-y>

Effects of Social Determinants of Health Care on Pediatric Thyroid Cancer Outcomes in the United States.

Otolaryngol Head Neck Surg, 166(6):1045-54.

N. R. Gruszczynski, C. M. Low, G. Choby, K. D. Meister, B. H. Smith and K. Balakrishnan. 2022.

OBJECTIVE: To identify social determinants of health care that are associated with poorer pediatric well-differentiated thyroid cancer (WDTC) outcomes and increased stage at presentation. STUDY DESIGN: Using the SEER database (Surveillance, Epidemiology, and End Results), we retrospectively gathered data on pediatric WDTC across the United States between 1973 and 2015. SETTING: All patients between 0 and 19 years old with a diagnosis of WDTC were included. METHODS: Patient variables were analyzed for relationships to AJCC stage at presentation (American Joint Committee on Cancer), overall survival, and disease-specific survival. RESULTS: Among 3913 patients with pediatric thyroid cancer, 3185 were female (81.4%), 3366 had papillary thyroid cancer (85.3%), and 367 had follicular thyroid cancer (9.4%). Two- and 5-year overall and disease-specific survival approached 100%. However, when outcomes were analyzed by specific populations, male sex, non-Caucasian race, poverty, and language isolation were linked to worse overall survival. Male sex and poverty were associated with poorer disease-specific survival. Regarding overall AJCC stage at presentation, male sex and Black race were related to higher overall presenting AJCC stage. Later AJCC T stage at presentation was seen in male, Hispanic, Asian, and Black patients. There were no variables significantly related to following through with recommended surgery. CONCLUSION: Pediatric WDTC continues to carry an excellent prognosis in the United States. However, when we consider specific populations, the social determinants of health care affect survival and disease burden at presentation: male sex, poverty, language isolation, and race affected survival and/or AJCC stage at presentation in pediatric WDTC.

PubMed-ID: [34311618](https://pubmed.ncbi.nlm.nih.gov/34311618/)

<http://dx.doi.org/10.1177/01945998211032901>

Assessing the influence of (99m)Tc-Sesta-MIBI-positive thyroid nodules on preoperative localisation studies in patients with primary hyperparathyroidism.

Langenbecks Arch Surg, 407(3):1183-91.

L. Hargitai, M. Schefner, T. Traub-Weidinger, A. Haug, M. Arian, C. Scheuba and P. Riss. 2022.

PURPOSE: Curative treatment for primary hyperparathyroidism (PHPT) is parathyroidectomy (PTX) with removal of the hyperfunctioning gland(s). In an endemic goitre region, 35-78% of PHPT patients show concomitant thyroid disease. This study aimed to evaluate if (99m)Tc-sestamibi (MIBI)-positive thyroid nodules decrease sensitivity in regard to localising the hyperfunctioning parathyroid gland(s) in PHPT patients. METHODS: Within 5 years, 497 consecutive patients with biochemically proven PHPT were included in this study. The data was analysed retrospectively. RESULTS: In total, 198 patients underwent PTX with thyroid surgery and 299 patients underwent sole PTX. Sensitivity of MIBI scan for PTX with and without thyroid surgery was 72.1% and 73.6%, respectively. A statistically significant difference in sensitivity of ultrasound for PTX with and without thyroid surgery (57.0% and 70.9%, respectively) was observed ($p = 0.029$). Thyroid nodule histology did not have a significant effect on the MIBI scan. Unilateral neck exploration (UNE) was performed in 110 patients and bilateral neck exploration (BNE) in 177 patients. The probability of surgical conversion from UNE to BNE due to incorrect localisation was 1.733 times higher in patients with thyroid nodules. CONCLUSIONS: Concomitant benign thyroid nodules did not influence MIBI sensitivity. No correlation between thyroid carcinoma and MIBI uptake was determined. However, MIBI detection of thyroid malignancy is important in patients initially being considered for minimal invasive parathyroidectomy. Sensitivity and positive predictive value of ultrasound were significantly lower in patients with thyroid nodules. The probability of conversion from UNE to BNE due to incorrect localisation was 1.733 times higher in patients with thyroid nodules.

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<http://dx.doi.org/10.1007/s00423-022-02442-7>

Extranodal extension is an independent predictor of extensive nodal metastasis in T1 papillary thyroid cancer.

Langenbecks Arch Surg, 407(4):1647-52.

H. Hei, Y. Li, Z. Luo, X. Chai, H. Zhang, C. Zheng, B. Zhou, W. Gong and J. Qin. 2022.

PURPOSE: Extensive lymph node metastasis (ELM) can occur in some patients with T1 papillary thyroid cancer (PTC). However, the risk factors for ELM in patients with T1 PTC have not been fully explored. In this study, we aimed to examine the association between extranodal extension (ENE) and ELM in patients with T1 PTC. PATIENTS AND METHODS: We identified 645 consecutive patients who had T1 PTC initially resected at our centre. Clinical and pathological data were reviewed. Univariate and multivariate logistic regression analyses were performed to identify the risk factors for ELM. RESULTS: ELM was identified in 3.9% of T1 PTC patients, and ENE was identified in 8.1% of patients. ENE was associated with male sex, large tumour size, more positive nodes, and comprehensive surgical treatment. In multivariate analysis, three variables were independently associated with ELM, including ENE (odds ratio [OR], 11.15; 95% confidence interval [CI], 4.54 to 27.30; P < 0.001), age (OR, 0.96; 95% CI, 0.93 to 0.99; P = 0.022), and tumour size (OR, 1.18; 95% CI, 1.06 to 1.31; P = 0.002). Bilateral multifocality and sex were not independently associated with ELM. CONCLUSION: ENE is a strong independent predictor of ELM in patients with T1 PTC. Patients with ENE-positive nodes might need extensive neck dissection.

PubMed-ID: [35146548](https://pubmed.ncbi.nlm.nih.gov/35146548/)

<http://dx.doi.org/10.1007/s00423-021-02425-0>

Effects of treatment with methimazole on circulating CD4⁺ and CD8⁺ T cells positive for programmed cell death protein-1 and on subsets of CD4⁺ T cells in untreated hyperthyroid patients with Graves' disease.

Clin Endocrinol (Oxf), 97(6):841-8.

N. Hirao, T. Iijima, D. Tanuma, E. Ohira, H. Kurai, T. Shinzawa, M. Kase, S. Sakurai, T. Tomaru, T. Jojima, I. Usui and Y. Aso. 2022.

OBJECTIVE: We investigated longitudinal changes in circulating CD4⁺ and CD8⁺ T cells positive for programmed cell death protein-1 (PD-1) and in other subsets of CD4⁺ T cells in untreated hyperthyroid patients with Graves' disease after treatment with methimazole (MMI). DESIGN AND PATIENTS: The study included 18 untreated hyperthyroid patients with Graves' disease and 18 age-matched controls. Before and after 12-week treatment with MMI, we used flow cytometry to measure circulating PD-1⁺ CD4⁺ and PD-1⁺ CD8⁺ T cells and subsets of CD4⁺ T cells in peripheral blood, as well as serum levels of chemokines related to T-helper type 1 (Th-1) and Th-2 cells. RESULTS: At baseline, the percentage of CD4⁺ and CD8⁺ T cells expressing PD-1 was significantly higher in patients than in age-matched controls. Serum levels of chemokines related to Th-1 and Th-2 also were higher in patients. Twelve weeks after initiation of MMI, the percentage of CD4⁺ T cells expressing PD-1 was significantly lower than at baseline, but no such change was seen in CD8⁺ T cells. Furthermore, the percentage of Th-1 cells among CD4⁺ T cells and the serum levels of soluble CD26/dipeptidyl peptidase-4, a surface marker of Th-1 cells, also were significantly lower than at baseline. CONCLUSIONS: The expression of PD-1 on circulating CD4⁺ and CD8⁺ T cells is increased in hyperthyroid patients with active Graves' disease. MMI significantly decreases levels of circulating PD-1⁺ CD4⁺ T cells, suggesting that PD-1⁺ T lymphocytes may be associated with the pathogenesis of Graves' disease.

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<http://dx.doi.org/10.1111/cen.14788>

The Effect Modification of Ultrasound Risk Classification on Molecular Testing in Predicting the Risk of Malignancy in Cytologically Indeterminate Thyroid Nodules.

Thyroid, 32(8):905-16.

T. X. Hu, D. T. Nguyen, M. Patel, K. Beckett, M. Douek, R. Masamed, J. Rhyu, J. Kim, C. H. Tseng, M. W. Yeh and M. J. Livhits. 2022.

Background: Thyroid nodules with indeterminate cytology are increasingly subjected to molecular testing. We evaluated the diagnostic performances of Afirma Genomic Sequencing Classifier (GSC) and ThyroSeq v3 in thyroid nodules with high versus low/intermediate suspicion ultrasound classification. Methods: In this prospective cohort study, we analyzed all Bethesda III and IV thyroid nodules that underwent fine-needle aspiration biopsies in the University of California Los Angeles Health System from July 2017 to April 2020. All patients underwent molecular testing with Afirma GSC or ThyroSeq v3 as part of an institutional randomized trial (NCT02681328). Nodules were categorized according to the American Thyroid Association (ATA) ultrasound risk classification. The benign call rate and the positive predictive value of

molecular testing were compared between ATA high suspicion versus all other categories. Results: A total of 343 patients with 375 indeterminate thyroid nodules were included. The malignancy rate in ATA high suspicion nodules was not significantly increased by a suspicious Afirma GSC result (77.8% for all ATA high suspicion nodules vs. 87.5% for nodules with ATA high suspicion and suspicious Afirma GSC results, positive likelihood ratio [LR] = 2.0, 95% confidence interval [CI 0.5-8.0], $p = 1.0$) or by a positive ThyroSeq v3 result (80.0% vs. 80.0%, positive LR = 1.0 [CI 1.0-1.0], $p = 1.0$). The rate of malignancy in ATA low/intermediate suspicion nodules increased from 21.0% to 56.3% with a suspicious Afirma GSC result (positive LR = 4.8 [CI 3.4-6.9], $p < 0.0001$) and decreased to 3.8% with a benign Afirma GSC result (negative LR = 0.1 [CI 0.07-0.3], $p < 0.0001$). Similarly, the rate of malignancy in ATA low/intermediate suspicion nodules increased from 24.3% to 66.7% with a positive ThyroSeq v3 result (positive LR = 6.2 [CI 4.0-9.7], $p < 0.0001$) and decreased to 2.1% with a negative ThyroSeq v3 result (negative LR = 0.07 [CI 0.02-0.3], $p < 0.0001$). Conclusions: Afirma GSC and ThyroSeq v3 performed well in ruling out malignancy in sonographically low/intermediate suspicion thyroid nodules but has limited diagnostic value in sonographically high suspicion nodules. Molecular testing can prognosticate more aggressive thyroid cancers, which can inform treatment decisions.

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<http://dx.doi.org/10.1089/thy.2021.0659>

Age increased the cancer-specific mortality risk of thyroid cancer with lung metastasis.

Clin Endocrinol (Oxf), 96(5):719-27.

X. Huang, Q. Xia, Y. Huang, A. Peng and J. Yang. 2022.

OBJECTIVE: To investigate the relationship between age and cancer-specific mortality in thyroid cancer (TC) with lung-metastasis. **PATIENTS AND METHODS:** A total of 1418 patients with initial distant metastases from Surveillance, Epidemiology, and End Results databases were investigated. Patients with a median follow-up time of 8 months (interquartile range [IQR]: 2-27] and a median age of 66 years (IQR: 55-76) were divided into five groups by age and the association between age and TC-specific mortality was analysed. **RESULTS:** The TC-specific mortality rates were 32.78% (118/360), 46.71% (156/334), 53.93% (199/369), 58.96% (158/268) and 82.76% (72/87) in patients aged =55 years, >55 but =65 years, >65 but =75 years, >75 but =85 years and >85 years. Kaplan-Meier curves showed that TC-specific mortality rate was associated with increased age ($p < .001$). Compared with patients =55 years, patients aged >55 but =65 years, >65 but =75 years, >75 but =85 years and >85 years had significantly higher hazard ratios (HRs) of 1.69 (1.26-2.26), 1.97 (1.47-2.64), 2.18 (1.59-2.99) and 3.24 (2.08-5.06) after adjustments for sex, tumour size and radiation therapy (all $p < .001$). In TC with initial lung-metastasis, compared with patients =55 years, patients aged >55 but =65 years, >65 but =75 years, >75 but =85 years and >85 years had significantly higher adjusted HRs of 1.68 (1.20-2.36; $p = .003$), 2.18 (1.57-3.02), 2.16 (1.51-3.08) and 2.91 (1.79-4.75; $p < .001$). Similar results were obtained in papillary TC. **CONCLUSIONS:** The TC-specific mortality was increased with age in TC patients with initial lung-metastasis, indicating that further risk stratification based on age was necessary for TC over 55 years with lung-metastasis. Individual treatment strategies maybe recommended for such patients.

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Prognosis of Patients with 1-4 cm Papillary Thyroid Cancer Who Underwent Lobectomy: Focus on Gross Extrathyroidal Extension Invading Only the Strap Muscles.

Ann Surg Oncol, 29(12):7835-42.

A. Jang, M. Jin, W. W. Kim, M. J. Jeon, T. Y. Sung, D. E. Song, T. Y. Kim, K. W. Chung, W. B. Kim, Y. K. Shong, Y. M. Lee and W. G. Kim. 2022.

BACKGROUND: This study was designed to evaluate the prognostic implication of gross extrathyroidal extension (ETE) invading the strap muscles after thyroid lobectomy in patients with 1-4 cm papillary thyroid cancer (PTC). **METHODS:** This retrospective cohort study included patients with 1-4 cm PTC who underwent thyroid lobectomy from 2005 to 2012. Overall, 595 patients were enrolled after excluding patients with aggressive variants of PTC, gross ETE into a major neck structure, and lateral cervical lymph node (LN) metastasis. We evaluated the risk factors for structural recurrence after lobectomy in 1-4 cm PTC. **RESULTS:** Seventy-eight patients (13.1%) had gross ETE invading only the strap muscles. During the median follow-up period of 7.7 years, structural recurrence was confirmed in 35 patients (5.9%). The presence of gross ETE was an independent risk factor for structural recurrence (hazard ratio 2.54, 95% confidence interval 1.19-5.44; $p = 0.016$). Subgroup analysis of patients with gross ETE showed that 11 and 47 patients had low- and intermediate-risk LN metastasis, respectively. A significant difference in recurrence-free survival was observed according to the degree of cervical LN metastasis ($p = 0.03$). Those without LN metastasis or low-risk LNs had a 75% lower risk of recurrence when compared with those with both gross ETE and intermediate-risk LNs. **CONCLUSION:** Gross ETE and intermediate-risk

cervical LN metastasis were associated with a significantly high risk of recurrence after lobectomy in patients with 1-4 cm PTC. Completion thyroidectomy would be considered in this subgroup of patients but not in all patients with gross ETE invading only the strap muscles.

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<http://dx.doi.org/10.1245/s10434-022-12155-2>

Optimal cutoff values of primary tumour size to better predict long-term outcomes in patients with papillary thyroid carcinoma undergoing total thyroidectomy: A preliminary study using restricted cubic spline analysis.

Clin Endocrinol (Oxf), 96(6):888-95.

S. W. Jang, J. H. Park, H. J. Kwon and J. H. Yoon. 2022.

OBJECTIVE: Primary tumour size (PTS) is known to be a significant prognostic factor in patients with papillary thyroid carcinoma (PTC) undergoing thyroidectomy. Although cutoff values of 2 and 4 cm are widely used in surgical extent decision and long-term outcomes predictions, the effectiveness of arbitrary cutoff values in stratifying patients for target outcomes is questionable. This study aimed to determine new optimal cutoffs of PTS. DESIGN, PATIENT AND MEASUREMENTS: Patients (n = 529) with PTC who underwent total thyroidectomy were retrospectively reviewed. After risk factor analysis for structural recurrence, the optimal cutoffs of PTS were automatically calculated using restricted cubic spline analysis and X-tile software. Subgroups were classified based on the newly determined cutoff values. Both the recurrence-free survival (RFS) and the proportion of patients in each response-to-therapy category, using the dynamic risk stratification system (DRS), were compared between the subgroups. RESULTS: PTS was confirmed as an independent risk factor for structural recurrence. The optimal cutoff values were calculated as 1.4 and 3.0 cm. The subgroups stratified using these newly determined cutoffs showed significantly different RFS and DRS based on the response to initial therapy, but the subgroups classified using the cutoffs of 2 and 4 cm did not. CONCLUSIONS: The newly determined cutoff values of PTS may be useful in better stratifying patients with PTC undergoing thyroidectomy for target outcomes and can be considered as a new definition in staging and risk stratification systems.

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Clinicopathological features and outcomes of thyroid nodules with EIF1AX mutations.

Endocr Relat Cancer, 29(8):467-73.

E. Karlioglu French, A. V. Nikitski, L. Yip, M. N. Nikiforova, Y. E. Nikiforov and S. E. Carty. 2022.

EIF1AX gene mutations are reported in both benign and malignant thyroid tumors, with unclear outcomes when detected preoperatively. The aim of this study was to determine the features and outcomes of thyroid nodules with various types of mutation identified in cytologic (fine-needle aspiration) samples on preoperative ThyroSeq testing and with surgical outcomes. In this single-institution retrospective study of 31 consecutive patients, 77% were female and nodule size ranged from 1.5 to 9.4 cm with widely varying cytologic and TI-RADS ultrasound categorizations. Among two main mutational hotspots, 55% were located in exon 2 and 45% at the intron 5/exon 6 splice site. On histology, 45% of -positive nodules were cancer/noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) including 19% encapsulated follicular variant papillary thyroid carcinoma, 10% follicular carcinoma, 10% anaplastic carcinoma (ATC), and 7% NIFTP. Almost half (48%) of patients had one or more coexisting mutations, most frequently RAS. The prevalence of cancer/NIFTP was 80% for mutation with coexisting molecular alteration vs 13% with an isolated mutation (P = 0.0002). Cancer probability was associated with mutation type and was 64% for splice-site mutation and 29% for non-splice mutation (P = 0.075). All 3 nodules with EIF1AX+RAS+TERT+TP53 mutations were ATC. In summary, in this study, all nodules with an isolated non-splice mutation were benign, one-third of those with an isolated splice mutation were cancer, and most nodules with coexisting with RAS or other alterations were malignant. These findings suggest that clinical management decisions for patients with EIF1AX-mutant nodules should consider both the type of mutation and its co-occurrence with other genetic alterations.

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UK national chronic hypoparathyroidism audit.

Clin Endocrinol (Oxf), 97(5):562-7.

J. S. Kiam, V. Sharma, L. Glenister, W. D. Fraser and J. J. O. Turner. 2022.

OBJECTIVES: Individuals with chronic hypoparathyroidism may experience suboptimal medical care with high frequency of unplanned hospitalisation and iatrogenic harm. In 2015 the European Society for Endocrinology published consensus guidelines on the management of chronic hypoparathyroidism. We set out to audit compliance with these guidelines.

METHODS: Using these recommendations as audit standards we worked with the Society for Endocrinology and Parathyroid UK to conduct a national audit of management of chronic hypoparathyroidism in the United Kingdom. Endocrine leads in 117 endocrine departments were invited to participate in the survey by completing a data collection tool on up to 5 sequential cases of chronic hypoparathyroidism seen in their outpatient clinics in the preceding 12 months. Data were collected on 4 treatment standards and 9 monitoring standards. Data on hospitalisations and Quality of Life monitoring were also collected. **RESULTS:** Responses were received from 22 departments giving a response rate of 19%, concerning 80 individual cases. The mean age of subjects was 48.4 years. The main findings were that the commonest cause of hypoparathyroidism was post surgical (66.3%). Treatments taken by the group included activated vitamin D analogues (96.3%), oral calcium salts (66.3%), vitamin D supplements (17.5%), thiazide diuretics (5%) and rhPTH₁₋₃₄ (1.3%). Compliance with the audit standards varied between 98.8% and 60% for the treatment standards and between 91.3% and 20% for the monitoring standards. Some of the areas of weakness revealed include low rates of 24 h urinary calcium excretion monitoring, serum magnesium monitoring and low rates of renal imaging where indicated. In addition and importantly, 16.3% of subjects had experienced at least one hospital admission in the preceding 12 months. **CONCLUSION:** We conclude that further improvements in the UK national standard of management of chronic hypoparathyroidism should be made and that this will benefit both quality of life, morbidity and potentially mortality in this group of patients.

PubMed-ID: [35792134](https://pubmed.ncbi.nlm.nih.gov/35792134/)

<http://dx.doi.org/10.1111/cen.14798>

Perioperative transcutaneous laryngeal ultrasonography to assess vocal cord function in thyroid surgery.

Am J Surg, 223(5):893-9.

D. H. Kim, J. Lee, Y. Seo, S. W. Kim and S. H. Hwang. 2022.

BACKGROUND: Early diagnosis of vocal cord iatrogenic injury is crucial, as is perioperative vocal cord evaluation.

METHODS: Vocal cord mobility detected via transcutaneous laryngeal ultrasonography was compared with that detected via laryngoscopy (the reference). The vocal cord visualization rate of ultrasonography for evaluation of mobility was explored.

RESULTS: The diagnostic odds ratio of transcutaneous laryngeal ultrasonography was 303.2212 (95% CI, [86.7944; 1059.3198]). The area under the summary receiver operating characteristic curve was 0.944. The sensitivity, specificity, and negative predictive value were 0.9154 [0.8471; 0.9548], 0.9771 [0.9541; 0.9887], and 0.9915 [0.9868; 0.9946], respectively. The vocal cord visualization of ultrasonography used to evaluate vocal cord mobility was high (0.9572 [0.9091; 0.9804]).

CONCLUSIONS: Since transcutaneous laryngeal ultrasonography has the advantage in vocal cord visualization, it can be considered when laryngoscopy is unavailable or patients refuse laryngoscopy. Also, it is diagnostically accurate regardless of the used landmarks, VCP definition, and timing for application.

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<http://dx.doi.org/10.1016/j.amjsurg.2021.08.019>

Medullary thyroid cancer with ectopic Cushing's syndrome: A multicentre case series.

Clin Endocrinol (Oxf), 96(6):847-56.

V. F. Koehler, C. T. Fuss, C. M. Berr, K. Frank-Raue, F. Raue, E. Hoster, M. Hepprich, E. Christ, T. Pusl, M. Reincke, C. Spitzweg and M. Kroiss. 2022.

OBJECTIVE: Ectopic Cushing's syndrome (ECS) induced by medullary thyroid cancer (MTC) is rare, and data on clinical characteristics, treatment and outcome are limited. **DESIGN:** Retrospective cohort study in three German and one Swiss referral centres. **PATIENTS:** Eleven patients with MTC and occurrence of ECS and 22 matched MTC patients without ECS were included. **MEASUREMENTS:** The primary endpoint of this study was the overall survival (OS) in MTC patients with ECS versus 1:2 matched MTC patients without ECS. **RESULTS:** The median age at diagnosis of ECS was 59 years (range: 35-81) and the median time between initial diagnosis of MTC and diagnosis of ECS was 29 months (range: 0-193). Median serum morning cortisol was 49 µg/dl (range: 17-141, normal range: 6.2-18). Eight (73%) patients received treatment for ECS. Treatment of ECS consisted of bilateral adrenalectomy (BADX) in four (36%) patients and adrenostatic treatment in eight (73%) patients. One patient received treatment with multityrosine kinase inhibitor (MKI) to control hypercortisolism. All patients experienced complete resolution of symptoms of Cushing's syndrome and biochemical control of hypercortisolism. Patients with ECS showed a shorter median OS of 87 months (95% confidence interval [95% CI]: 64-111) than matched controls (190 months, 95% CI: 95-285). Of the nine deaths, four were related to progressive disease (PD). Four patients showed PD as well as complications and comorbidities of hypercortisolism before death. **CONCLUSION:** This study shows that ECS occurs in advanced stage MTC and is associated with a poor prognosis. Adrenostatic treatment and BADX were effective systemic treatment options in patients with MTC and ECS to control their hypercortisolism. MKI treatment achieved complete remission of hypercortisolism and sustained tumour control in one treated case.

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<http://dx.doi.org/10.1111/cen.14617>

Safety and Efficacy of Single-Session Radiofrequency Ablation Treatment for Benign Non-toxic Multinodular Goiter.

World J Surg, 46(7):1704-10.

B. H. H. Lang and M. M. H. Fung. 2022.

BACKGROUND: Radiofrequency ablation (RFA) is an effective treatment for benign thyroid nodules. However, it remains unclear if ablating multiple nodules in single-session offers comparable safety and efficacy to ablating single nodule. Our study compared early complication rate and 6-month nodule shrinkage between multiple-nodules ablation and single-nodule ablation by RFA. METHODS: Among the 174 eligible patients undergoing RFA of one or more benign thyroid nodules, 85 (48.8%) had single-nodule ablation (group I) while 89 (51.1%) had two or three nodules ablation (group II). The 6-month nodule shrinkage of each nodule (by volume reduction ratio) (VRR) was calculated by $(\text{Baseline volume} - \text{volume at 6-month}) / (\text{Baseline volume}) * 100$ and compared between two groups. To determine independent predictors for VRR, a multivariate analysis was done by logistic regression analysis. RESULTS: Patients in group II reported significantly higher pain scores during and 2-h after treatment than group I (42.31 vs. 29.66, $p = 0.029$ and 38.21 vs. 26.18, $p = 0.037$, respectively). Two vocal cord paresis occurred in each group. 3- and 6-month VRR of the largest nodule were comparable between two groups (67.39% vs. 63.89%, $p = 0.248$ and 77.29% vs. 73.38%, $p = 0.182$). Similar 3- and 6-month VRR were observed for 2 and 3 largest nodules in group II. In multivariate analysis, total energy given per nodule volume (OR = 1.007, 95% CI = 1.001-1.012, $p = 0.036$) was the only independent predictor for 6-month VRR. CONCLUSION: In the presence of multinodular goiter, ablating two or more nodules by RFA within one session appears to offer a comparable level of safety and efficacy to ablating single nodule.

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<http://dx.doi.org/10.1007/s00268-022-06527-8>

Evolution of transoral endoscopic thyroidectomy vestibular approach according to the IDEAL framework.

Br J Surg, 109(6):497-502.

S. H. Lee, R. Moorthy and S. Nagala. 2022.

BACKGROUND: The IDEAL Framework is a scheme for safe implementation and assessment of surgical innovation. The transoral endoscopic thyroidectomy vestibular approach (TOETVA) is a new innovation in thyroid surgery that eliminates the need for a cervical incision. Despite considerable interest and adoption worldwide, significant scepticism remains regarding the outcomes and cost-effectiveness for healthcare systems. The aim of this narrative review was to appraise the available literature and examine whether TOETVA has progressed in line with the IDEAL Framework. METHODS: A literature review of PubMed with a focus on historical and landmark studies was undertaken to classify the evidence according to the different stages of the IDEAL Framework. RESULTS: Several different transoral approaches were developed by a small number of surgeon-innovators on animals and cadavers, and subsequently in first-in-human studies. The trivestibular approach emerged as the safest technique, with further refinements of this technique culminating in TOETVA. The basic steps and indications for this technique have been standardized and it is now being replicated by early adopters in many centres worldwide. The development of TOETVA has closely aligned with the IDEAL Framework, and is currently at stage 2B (Exploration). CONCLUSION: There is need for multi-institutional collaborations and international registry studies to plan high-quality randomized trials comparing TOETVA with other remote-access approaches and collect long-term follow-up data. In countries where TOETVA has yet to be adopted, the IDEAL Framework will be a useful roadmap for government regulators and professional societies to evaluate, regulate, and provide best practice recommendations for the adoption of this technique.

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<http://dx.doi.org/10.1093/bjs/znac072>

Preoperative prediction of central lymph node metastasis in cN0T1/T2 papillary thyroid carcinoma: A nomogram based on clinical and ultrasound characteristics.

Eur J Surg Oncol, 48(6):1272-9.

J. Li, P. Sun, T. Huang, L. Li, S. He, X. Ai, H. Xiao and G. Xue. 2022.

BACKGROUND: Preoperative status of central lymph nodes is a key determinant of the initial surgical extent for papillary thyroid carcinoma (PTC). We aimed to develop and validate a nomogram based on preoperative clinical characteristics and ultrasound features to predict central lymph node status in patients with clinically lymph node-negative (cN0) T1/T2 PTC. METHODS: This retrospective study included 729 patients with cN0T1/T2 PTC who were treated between January 2015 and March 2020. Based on the ratio of 6:4, 431 patients who underwent surgeries relatively earlier comprised the training

set to develop the nomogram, while the other 298 who underwent surgeries relatively later comprised validation set to validate the performance of nomogram. Least absolute shrinkage and selection operator (LASSO) regression and multivariate logistic regression were used to identify predictors of central lymph node metastasis (CLNM). These variables were used to construct a nomogram for predicting the risk of CLNM. The predictive performance, discriminative ability, calibration, and clinical utility of the nomogram model were evaluated in both sets. RESULTS: A total of 313 (42.9%) PTC patients were identified with CLNM. On multivariate logistic regression analyses, male gender, younger age, larger maximum diameter, multifocality, capsular invasion, infiltrative margins, intra-nodular vascularity, and aspect ratio >1 were independent risk factors for CLNM. Nomogram integrating these 8 factors showed excellent discrimination in the training [area under the curve (AUC): 0.788] and validation (AUC: 0.829) sets, and obtained well-fitted calibration curves. The cut-off value of this nomogram was 0.410 (~245 points). Decision curve analysis confirmed the clinical utility of the nomogram. CONCLUSION: The CLNM-predicting nomogram can facilitate stratification of cN0T1/T2 PTC patients. Prophylactic central neck lymph node dissection can be considered for those with high nomogram scores.

PubMed-ID: [35414404](https://pubmed.ncbi.nlm.nih.gov/35414404/)

<http://dx.doi.org/10.1016/j.ejso.2022.04.001>

Postoperative Complications After Total Thyroidectomy for Patients With Graves' Disease.

Otolaryngol Head Neck Surg:1945998221108050.

J. J. Liang, R. Irizarry, L. S. Victor, L. A. Hoepner and N. Chernichenko. 2022.

OBJECTIVE: To identify the rates and types of postoperative complications in patients with and without Graves' disease undergoing total thyroidectomy using the National Surgical Quality Improvement Program (NSQIP) database. STUDY DESIGN: Retrospective cohort study. SETTING: All hospitals participating in NSQIP from 2007 to 2017. METHODS: Thyroidectomy data were abstracted from the NSQIP database from 2007 to 2017 using related Current Procedural Terminology codes. Exclusion criteria included diagnosis of malignancy and partial thyroidectomy. Patients with a diagnosis of Graves' disease were compared against the control group, which consisted of other nononcologic diagnoses. Statistical analysis including matched pair analysis was performed. RESULTS: Unmatched data demonstrated that patients with Graves' disease who underwent total thyroidectomy (n = 5495) had a higher rate of readmission (odds ratio [OR], 1.41; 95% CI, 1.16-1.73) and rate of reoperation (OR, 2.29; 95% CI, 1.88-2.79) in comparison to control patients (n = 24,213). They also had a higher rate of postoperative complication (OR, 1.54; 95% CI, 1.23-1.93) especially for wound-related outcomes (OR, 1.88; 95% CI, 1.32-2.69), readmission for postoperative hypocalcemia (OR, 2.12; 95% CI, 1.54-2.92), and reoperation for hematoma or hemorrhage (OR, 1.88; 95% CI, 1.32-2.69). A matched-pair analysis of the data also demonstrated similar significant results. CONCLUSION: Patients with Graves' disease undergoing total thyroidectomy are at higher risk of complications in comparison to those who do not have Graves' disease, likely due to sequelae of the disease. However, overall rates were low, suggesting that the procedure remains relatively low risk and should continue to be offered to select patients who meet criteria for surgery.

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A Closer Look at "Taller-Than-Wide" Thyroid Nodules: Examining Dimension Ratio to Predict Malignancy.

Otolaryngol Head Neck Surg, 167(2):236-41.

A. S. Mattingly, J. E. Noel and L. A. Orloff. 2022.

OBJECTIVE: To evaluate nodule height-to-width ratio as a continuous variable predicting likelihood of thyroid malignancy. STUDY DESIGN: Retrospective cohort study. SETTING: All study information was collected from a single academic tertiary care hospital. METHODS: Subjects included adult patients with thyroid nodules who underwent thyroid surgery between 2010 and 2020. The following variables were collected: patient demographics, nodule dimensions via ultrasound, fine-needle aspiration biopsy results, and surgical pathology results. Statistical analysis included logistic regression modeling malignancy with variables of interest. We used a receiver operating characteristic curve to assess the discriminatory value of variables. RESULTS: Height-to-width ratio, as a continuous variable, was associated with malignancy (with each 0.1 increase in ratio; odds ratio [OR], 1.25; 95% CI, 1.14-1.37). The same relationship was true for height-to-length ratio (OR, 1.36; 95% CI, 1.24-1.56). The area under the receiver operating characteristic curve for height-to-width ratio was 63.7%. In line with current emphasis on the transverse ultrasound view, we determined 4 different height-to-width ratio intervals: <0.8, 0.8 to <1.0, 1.0 to <1.5, and =1.5. Likelihood ratios of malignancy for each interval were 0.6, 1.0, 2.3, and 4.9, respectively. CONCLUSION: Our results support the association between greater height-to-width ratio and malignancy but suggest that a multilevel rather than binary variable improves prediction. The likelihood ratios at different intervals give a more nuanced view of how height-to-width ratio predicts malignancy. With continuing review of guidelines for thyroid nodule biopsy, it is important to consider these data for any point total attributed to shape.

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Mutation based approaches to the treatment of anaplastic thyroid cancer.

Clin Endocrinol (Oxf), 96(5):734-42.

H. C. McCrary, J. Aoki, Y. Huang, B. Chadwick, K. Kerrigan, B. Witt, J. P. Hunt and D. Abraham. 2022.

OBJECTIVE: The treatment of anaplastic thyroid cancer (ATC) has continued to rapidly evolve over time. Increased utilization of novel, personalized therapies based upon the tumour's somatic mutation status has recently been integrated. The aim of this case series is to describe a series of patients that underwent rapid genomic testing upon their diagnosis of ATC, allowing for the early integration of novel therapies. **DESIGN:** A fast track pathway for genomic tumour analysis of patients with ATC was implemented at a single academic cancer hospital in January of 2020. **PATIENTS:** All patients were evaluated by head and neck surgery, endocrinology, and medical oncology upon diagnosis of ATC. **MEASUREMENTS:** Genetic work-up was completed, which prompted a recommendation for dual BRAF/MEK inhibition with dabrafenib and trametinib for tumours with BRAF V600E mutation. For patients whose tumours were BRAF V600E wild-type, pembrolizumab with lenvatinib was offered. **RESULTS:** A total of four patients were included in this series. Two patients (50%) had tumours that were BRAF V600E positive. Among patients that were BRAF V600E positive, both patients initiated urgent dabrafenib and trametinib dual tyrosine kinase inhibitor (TKI) therapy; with one patient demonstrating near-complete clinical response allowing for posttreatment surgery, while the other demonstrated decreased tumour burden. Among patients who were BRAF V600E wild-type, lenvatinib and pembrolizumab were recommended off-label; one patient demonstrated decreased tumour burden, but developed severe pure red cell aplasia, while the other patient is demonstrating an early clinical response. **CONCLUSIONS:** The integration of early genomic analysis and personalized neoadjuvant TKI therapy into the treatment of ATC can greatly benefit patient care outcomes and optimize tumour control.

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<http://dx.doi.org/10.1111/cen.14679>

Recurrent Laryngeal Nerve Paralysis Following Thyroidectomy: Analysis of Factors Affecting Nerve Recovery.

Laryngoscope, 132(8):1692-6.

R. Mohammad, G. Huh, W. Cha and W. J. Jeong. 2022.

OBJECTIVES: Paralysis of the recurrent laryngeal nerves (RLNs), albeit decreased over the years, leaves the surgeon helpless as there is not much that can be done once it occurs. Nimodipine has been suggested as a remedy that could accelerate the recovery of the nerve. Our study aimed to examine the factors that affect the recovery rate (RR) and time to recovery (TTR) of post-thyroidectomy RLN paralysis, with an emphasis on the use of nimodipine. **METHODS:** A total of 197 patients who had undergone thyroid and parathyroid surgeries were retrospectively reviewed from October 2016 to August 2019. Patients who had RLN paralysis following surgery were assessed. The medical records were retrospectively analyzed to look for possible factors that may influence RLN recovery. **RESULTS:** A total of 289 nerves were at risk. Temporary RLN paralysis rate was 7.9% while 1.7% was permanent. Age (odds ratio [OR] = 4.8) and intra-operative extra-thyroid extension (OR = 9.0) were independent risk factors for RLN paralysis. The rate of recovery was 82.1%. Loss of signal (LOS; P = .066) was a factor trending for an impact on RR but not nimodipine (P > .05). The mean TTR was 32 days. LOS, nimodipine, and steroid use, among others, were factors trending for an impact on the TTR. **CONCLUSION:** Although not reaching statistical significance, nimodipine and steroids might influence TTR but not the RR. Larger studies are warranted to address the effect of nimodipine on the outcome of RLN paralysis. **LEVEL OF EVIDENCE:** 4 *Laryngoscope*, 132:1692-1696, 2022.

PubMed-ID: [35043983](https://pubmed.ncbi.nlm.nih.gov/35043983/)
<http://dx.doi.org/10.1002/lary.30024>

Thyroid Cancer Incidence, Clinical Presentation, and Survival Among Native Hawaiian and Other Pacific Islanders.

Otolaryngol Head Neck Surg:1945998221118538.

P. K. Moon, T. Chakoma, Y. Ma and U. C. Megwalu. 2022.

OBJECTIVE: To assess the incidence, clinical presentation, and survival in Native Hawaiian and other Pacific Islander (NHPI) patients with well-differentiated thyroid cancer. **STUDY DESIGN:** This population-based incidence analysis and retrospective cohort study utilized data from the Surveillance, Epidemiology, and End Results database. **SETTING:** Incidence analysis included patients diagnosed between 1990 and 2014, while the cohort to study clinical presentation and survival comprised patients diagnosed between 2004 and 2015. **METHODS:** Incidence rates and trends were compared among NHPI, Asian, and non-Hispanic White (NHW) populations. Clinical presentation was assessed via

multivariable logistic regression. Survival was assessed per Cox regression. RESULTS: Recent incidence trends (2009-2014) show that the rate of increase remained consistent among NHPI patients (annual percentage change, 3.67%; 95% CI, 2.66%-4.69%), while it slowed in the NHW population and plateaued among Asians as compared with previous years. NHPI patients were more likely to present with distant metastasis than NHW patients (odds ratio, 3.37; 95% CI, 1.97-5.36) and Asian patients (odds ratio, 1.82; 95% CI, 1.05-2.97). NHPI race was also associated with advanced T stage and nodal metastasis as compared with the NHW race. Survival outcomes were similar among NHPI, NHW, and Asian patients. CONCLUSION: Well-differentiated thyroid cancer incidence has increased at a higher rate for the NHPI population as opposed to the NHW and Asian populations in recent years. NHPI patients are more likely to present with advanced disease when compared with NHW and Asian patients. These results highlight the importance of disaggregating the often-combined Asian/Pacific Islander group in epidemiologic studies.

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<http://dx.doi.org/10.1177/01945998221118538>

Clinicopathological indicators for TERT promoter mutation in papillary thyroid carcinoma.

Clin Endocrinol (Oxf), 97(1):106-15.

H. Y. Na, H. W. Yu, W. Kim, J. H. Moon, C. H. Ahn, S. I. Choi, Y. K. Kim, J. Y. Choi and S. Y. Park. 2022.

OBJECTIVE: Mutations in the telomerase reverse transcriptase (TERT) promoter have been reported as a convincing prognostic factor in papillary thyroid carcinomas (PTCs). We aimed to investigate the frequency of TERT promoter mutations in patients with thyroid cancer and identify the clinicopathological factors associated with them in PTCs. DESIGN: A total of 1086 consecutive cases of thyroid cancer composed of mostly PTCs were included in this study. TERT promoter and BRAF mutations were detected by pyrosequencing and their associations with clinicopathological features of tumour were analyzed. RESULTS: TERT promoter mutations were observed in 1.9% of PTCs, 6.7% of follicular thyroid carcinomas, 8.3% of Hurthle cell carcinomas and 25.0% of poorly differentiated thyroid carcinomas and in a single case of anaplastic thyroid carcinoma. In PTCs, aggressive clinicopathological features, higher stage and BRAF V600E mutation were all found to be associated with TERT promoter mutations. Distant metastasis and disease recurrence were more frequent in TERT promoter-mutated PTCs. In multivariate analysis, age \geq 55 years, tall cell variant, mitoses \geq 3/10 high-power fields, tumour necrosis, and gross extrathyroidal extension (ETE) were identified as independent factors associated with TERT promoter mutations in PTCs. CONCLUSIONS: This study revealed a relatively low frequency of TERT promoter mutations in Korean patients with PTC. Certain clinicopathological features including old age, tall cell variant, increased mitoses, tumour necrosis and gross ETE were found to be indicative of TERT promoter mutations in PTCs, suggesting that mutational analysis in a particular group of PTCs can be effective in regions with low mutation rates.

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<http://dx.doi.org/10.1111/cen.14728>

Clinicopathologic features of thyroid nodules with PTEN mutations on preoperative testing.

Endocr Relat Cancer, 29(9):513-20.

J. A. Quaytman, Y. E. Nikiforov, M. N. Nikiforova and E. Morariu. 2022.

The incidence of cancer in thyroid nodules carrying germline or somatic phosphatase and tensin homolog (PTEN) mutations is not well-defined. This study characterizes the clinical and histopathologic features of thyroid nodules with preoperatively detected PTEN mutations and their impact on management. Thyroid nodules with PTEN mutations on molecular testing of fine-needle aspiration (FNA) specimens from November 2017 to July 2020 at our institution were included. Demographic and clinicopathologic data were obtained through retrospective chart review. We identified 49 PTEN mutation-positive nodules from 48 patients. Surveillance was pursued for 28 patients and surgery for 20 patients. There were 14 follicular adenomas (FA), 4 oncocytic adenomas, 1 oncocytic hyperplastic nodule, and 1 encapsulated follicular variant papillary thyroid carcinoma (EFVPTC). The EFVPTC had two somatic PTEN mutations, an NRAS mutation, and was a low-risk tumor with capsular but no angiolymphatic invasion. Four patients, all with multiple nodules, had PTEN hamartoma syndrome (PHTS) with germline mutations or a clinical diagnosis of Cowden syndrome (CS); two had surgery finding FAs, and one previously had follicular carcinoma removed. Among surveillance patients, 1/20 had a significant increase in the size of the thyroid nodule and underwent repeat FNA, and no thyroid malignancy was found with a mean of 1.77 years of follow-up (range 1.00-2.78). Thyroid nodules with isolated somatic PTEN mutations are primarily benign and unlikely to grow at a high rate, at least on short-term follow-up. About 8% of patients with PTEN mutations may have PHTS or CS, which should be suspected in younger patients with multiple thyroid nodules.

PubMed-ID: [35723418](https://pubmed.ncbi.nlm.nih.gov/35723418/)

<http://dx.doi.org/10.1530/ERC-22-0061>

Can COVID-19 immunisation cause subacute thyroiditis?

Clin Endocrinol (Oxf), 97(1):140-1.

G. M. Ratnayake, D. Dworakowska and A. B. Grossman. 2022.

PubMed-ID: [34272751](https://pubmed.ncbi.nlm.nih.gov/34272751/)

<http://dx.doi.org/10.1111/cen.14555>

The risk of chronic kidney disease development in adult patients with chronic hypoparathyroidism treated with rhPTH(1-84): A retrospective cohort study.

Clin Endocrinol (Oxf),

L. Rejnmark, O. Ayodele, A. Lax, F. Mu, E. Swallow and E. O. Gosmanova. 2022.

OBJECTIVE: This study assessed the risk of developing chronic kidney disease (CKD) and decline in estimated glomerular filtration rate (eGFR) over a period of up to 5 years in adult patients with chronic hypoparathyroidism treated with recombinant human parathyroid hormone (1-84) (rhPTH[1-84]) compared with a historical control cohort of patients not treated with rhPTH(1-84). DESIGN: Retrospective cohort study of patients with chronic hypoparathyroidism treated with rhPTH(1-84) derived from the REPLACE (NCT00732615), RELAY (NCT01268098), RACE (NCT01297309) and HEXT (NCT01199614, and its continuation study NCT02910466) clinical trials and a historical control cohort who did not receive PTH selected from an electronic medical record database. PATIENTS: One hundred and eighteen patients treated with rhPTH(1-84) and 497 patient controls. MEASUREMENTS: Incident CKD was defined as ≥ 2 eGFR measurements < 60 ml/min/1.73 m² ≥ 3 months apart during the study and a sustained eGFR decline of $\geq 30\%$ from baseline. RESULTS: Over the 5-year period, Kaplan-Meier analyses showed that rhPTH(1-84)-treated patients had a significantly lower risk of developing CKD (log-rank $p = .002$) and a lower risk for a sustained eGFR decline $\geq 30\%$ from baseline (log-rank $p < .001$) compared with patients in the control cohort. In adjusted analyses, patients in the rhPTH(1-84)-treated cohort had a 53% lower risk of developing CKD (hazard ratio [HR], 0.47; 95% confidence interval [CI], 0.25-0.87) and a 65% lower risk for sustained eGFR decline $\geq 30\%$ from baseline (HR, 0.35; 95% CI, 0.13-0.89) compared with controls. CONCLUSIONS: Patients with chronic hypoparathyroidism treated with rhPTH(1-84) in long-term clinical trials had a significantly lower risk of developing CKD compared with patients in a historical control cohort not treated with rhPTH(1-84).

PubMed-ID: [35974422](https://pubmed.ncbi.nlm.nih.gov/35974422/)

<http://dx.doi.org/10.1111/cen.14813>

Predictive value of postoperative day 1 parathyroid hormone levels for early and late hypocalcaemia after thyroidectomy.

Langenbecks Arch Surg, 407(4):1653-8.

F. Riordan, C. Brophy, M. S. Murphy and P. Sheahan. 2022.

PURPOSE: Early parathyroid hormone (PTH) levels after total thyroidectomy can predict patients at low risk of hypocalcaemia who can be discharged early without calcium supplementation. For centres without facility to perform early PTH levels, PTH levels sent on the first postoperative day (POD1) may be an alternative. However, there is less data regarding optimal cut-off PTH levels for POD1 discharge. METHODS: Retrospective review of prospective database of thyroid operations between September 2009 and February 2020 at tertiary referral centre. Main outcome measure was symptomatic hypocalcaemia. RESULTS: Five hundred seventy patients undergoing total (521) or completion thyroidectomy with POD1 PTH levels available were included. Among patients with POD1 PTH levels ≥ 20 pg/ml and POD1 calcium $= 2.0$ mmol/l, the incidence of symptomatic hypocalcaemia was 1% (3/300), and need for intravenous calcium 0.3% (1/300). For POD1 PTH levels 15-19 pg/ml and POD1 calcium $= 2.0$ mmol/l, the incidence of symptomatic hypocalcaemia and need for intravenous calcium was 5.4% (3/55). For PTH levels 10-14 pg/ml and calcium $= 2.0$ mmol/l, the incidence of symptomatic hypocalcaemia and need for intravenous calcium was 11.7% (7/60). The risk of permanent hypoparathyroidism was $< 1\%$ for POD1 PTH levels $= 15$ pg/ml; 5.4% for levels 10-14 pg/ml; and 19.8% for levels < 10 pg/ml. CONCLUSIONS: POD1 PTH levels $= 15$ pg/ml along with calcium $= 2.0$ mmol/l are associated with low risk of symptomatic hypocalcaemia, and represent a safe criterion for discharge of most patients without calcium supplementation. For certain patient groups, a higher threshold of 20 pg/ml could be considered.

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<http://dx.doi.org/10.1007/s00423-022-02480-1>

Symptoms of thyrotoxicosis, bone metabolism, and occult atrial fibrillation in older women with mild endogenous subclinical hyperthyroidism: A reassessment after 5 years.

Clin Endocrinol (Oxf), 96(6):914-5.

P. W. Rosario. 2022.

PubMed-ID: [34369606](https://pubmed.ncbi.nlm.nih.gov/34369606/)

<http://dx.doi.org/10.1111/cen.14579>

Post-thyroidectomy hypocalcemia: Is a routine preferable over a selective supplementation?

Am J Surg, 223(6):1126-31.

L. Sessa, C. De Crea, F. Zotta, M. Pia Cerviere, P. Gallucci, F. Pennestri, P. Princi, L. Revelli, G. Arcuri, R. Bellantone and M. Raffaelli. 2022.

BACKGROUND: Comparative studies among protocols for the management of post-total thyroidectomy (TT) hypocalcemia are lacking. We compared the effectiveness of PTH-driven selective supplementation (PD-SS) and routine calcium and calcitriol supplementation with preoperative calcitriol administration in preventing symptomatic hypocalcemia (SH) and readmission. **METHODS:** Three-hundred consecutive patients undergoing TT were assigned to 3 groups: the PD-SS group, the high-dose routine supplementation (HD-RS) group and the low-dose routine supplementation (LD-RS) group. **RESULTS:** Mean post-operative stay was shorter in HD-RS patients when compared to PD-SS and LD-RS ($p < 0.001$). Significantly more patients in the PD-SS group experienced SH ($p = 0.042$). The rate of post-operative hypocalcemia was not significantly different among the groups ($p = 0.063$). No readmission for SH or hypercalcemia occurred. **CONCLUSIONS:** HD-RS emerged as the most effective treatment to prevent SH, without increasing the risk of readmission for calcitriol-related hypercalcemia. Basing on the present results, HD-RS should be recommended as the preferable protocol.

PubMed-ID: [34711410](https://pubmed.ncbi.nlm.nih.gov/34711410/)

<http://dx.doi.org/10.1016/j.amjsurg.2021.10.015>

Indications of Superselective Neck Dissection in Patients With Lateral Node Metastasis of Papillary Thyroid Carcinoma.

Otolaryngol Head Neck Surg, 166(5):832-9.

Y. Song, G. Xu, T. Wang, Y. Zhang and B. Zhang. 2022.

OBJECTIVE: The extent of neck dissection in papillary thyroid carcinoma (PTC) patients with lateral neck metastasis is controversial. This work aims to screen the patients suitable for superselective neck dissections including only levels III-IV. **STUDY DESIGN:** Prospective observational cohort study. **SETTING:** The study was conducted in a high-volume tertiary care setting. **METHODS:** A total of 134 consecutive previously untreated PTC patients with lateral neck metastases and subjected to 154 therapeutic lateral neck dissections (including levels II, III, IV, and VB) between June 2018 and March 2021 were enrolled. Fine-needle aspiration was performed preoperatively at each suspicious neck level. Clinical predictors were analyzed for occult lymph node metastases at levels II and VB. **RESULTS:** As a result, 44.8% and 5.8% of neck specimens exhibited metastatic lymph nodes at levels II and VB. In addition, univariate and multivariate analyses showed that the primary tumor in the ipsilateral thyroid upper lobe ($P = .016$, odds ratio = 3.528) and clinically multiple metastatic lymph nodes in level III-IV ($P = .005$, odds ratio = 6.414) were independent predictive factors for occult level II metastases. All 3 (1.9%) occult metastases at level VB were found in necks with preoperative multiple lymph node metastases. **CONCLUSIONS:** A superselective lateral neck dissection including levels III to IV may be considered in patients with PTC when the preoperative evaluation identifies a single lymph node metastasis located at levels III to IV and the primary tumor is not in the upper lobe of the ipsilateral thyroid.

PubMed-ID: [34488520](https://pubmed.ncbi.nlm.nih.gov/34488520/)

<http://dx.doi.org/10.1177/01945998211038318>

Concerns Over Thyroid Cancer Surgeries and Quality of Life.

JAMA Surg, 157(8):739-40.

P. Sun, H. Yang and W. Niu. 2022.

PubMed-ID: [35476014](https://pubmed.ncbi.nlm.nih.gov/35476014/)

<http://dx.doi.org/10.1001/jamasurg.2022.0813>

Comparative Study of ACR TI-RADS and ATA 2015 for Ultrasound Risk Stratification of Thyroid Nodules.

Otolaryngol Head Neck Surg, 167(1):35-40.

W. Thedinger, E. Raman and J. K. Dhingra. 2022.

OBJECTIVE: To study the adoption rate of the American College of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS) scoring system over a 3-year period in a community setting and compare its performance with that of the American Thyroid Association 2015 (ATA 2015) ultrasound risk scoring system. **STUDY DESIGN:** Case series with prospective data collection and retrospective chart review. **SETTING:** Large community-based practice with multiple satellite offices and a dedicated thyroid ultrasound clinic. **METHODS:** All patients referred to the thyroid clinic between January 2018 and December 2020 for ultrasound-guided fine-needle biopsy were assigned an ATA 2015 risk score in a

prospective manner immediately prior to biopsy. ACR TI-RADS scores were recorded through retrospective chart review of the radiologist report. Performance of the 2 systems was compared with cytology as the gold standard. RESULTS: A total of 949 nodules underwent biopsy, of which 236 had available data for both scoring systems. There was a 33.8% increase in adoption of the ACR TI-RADS over the 3-year study period. The ATA 2015 guidelines yielded sensitivity and specificity of 81.6% and 54.5%, respectively, as opposed to 73.7% and 27.0% for the ACR TI-RADS. CONCLUSION: In our community, there has been a gradual increase in adoption of the ACR TI-RADS, although the ATA 2015 risk scoring system has performed better.

PubMed-ID: [34905442](https://pubmed.ncbi.nlm.nih.gov/34905442/)

<http://dx.doi.org/10.1177/01945998211064607>

The outcome of treatment in differentiated thyroid cancer according to recommendations in current Dutch and American guidelines.

Clin Endocrinol (Oxf), 98(1):123-30.

D. van Dijk, A. H. Groen, B. A. C. van Dijk, T. L. van Veen, W. J. Sluiter, T. P. Links and J. Plukker. 2022.

OBJECTIVE: Assessment of treatment outcome in current de-escalation for differentiated thyroid cancer (DTC) according to the 2015 Dutch thyroid cancer guidelines (NL-15) and American Thyroid Association guidelines (ATA-15). DESIGN: Retrospectively, the recommendations of the NL-15 and ATA-15 guidelines were evaluated to estimate potentially adequate, under- and overtreatment of DTC in patients treated in the University Medical Center Groningen between 2007 and 2017. PATIENTS: A total of 240 patients with a cT1-T3aN0-1aM0 DTC fulfilled the inclusion criteria. MEASUREMENTS: After actual treatment was given, patients were again categorized according to both guidelines into low, intermediate, or high-risk based on tumour status. Next, they were categorized into a congruent low-risk (n = 60), congruent high-risk (n = 73), or incongruent risk group (n = 107). Follow-up data were used to estimate the proportion of potentially adequate, under-, and overtreatment according to both guidelines. RESULTS: Comparing treatment recommended by NL-15 and ATA-15 showed significantly more over- and adequate treatment when following NL-15 recommendations, and more undertreatment following ATA-15 (all: $p < .001$). Subanalysis of the congruent low-risk group showed overtreatment in 64% when following NL-15 guidelines ($p < .001$). No treatment differences were found in the congruent high-risk group. Undertreatment was most often seen in the incongruent risk group when following ATA-15 ($p < .001$). CONCLUSIONS: Low-risk patients were treated too aggressively when following NL-15 recommendations, where the less aggressive ATA-15 approach seemed more adequate. Treatment of intermediate risk DTC patients varies greatly, with a relative higher rate of undertreatment according to the recommendations of the ATA-15, advocating further refining of the risk classification in this patient group.

PubMed-ID: [35781313](https://pubmed.ncbi.nlm.nih.gov/35781313/)

<http://dx.doi.org/10.1111/cen.14795>

Regarding the Impact of Truncal vs Branch Ligation of the Inferior Thyroid Artery on Postoperative Hypoparathyroidism.

Otolaryngol Head Neck Surg, 167(2):412-3.

A. B. S. Vardag. 2022.

PubMed-ID: [35913810](https://pubmed.ncbi.nlm.nih.gov/35913810/)

<http://dx.doi.org/10.1177/01945998211054016>

Effects of Regional and General Anesthesia on the Therapeutic Outcome of Benign Thyroid Nodules Treated with High Intensity Focused Ultrasound (HIFU).

World J Surg, 46(5):1076-81.

C. Vorländer, A. Fischer and H. Korkusuz. 2022.

BACKGROUND: The study investigated whether anesthesia performed during high-intensity-focused-ultrasound treatment (HIFU) of benign thyroid nodules influenced the therapy outcome, based on volume reduction and the amount of energy delivered. METHODS: Thirty patients with benign thyroid nodules were treated with HIFU under general or regional anesthesia at two centers from 2014 to 2019. During HIFU, a therapeutic ultrasound probe, EchoPulse (Teraclion, Malakoff, France), heats the focus to 80-90 degrees Celsius. Nodal volumes were measured by ultrasound before and 3 months after therapy. For statistical analysis, the total population was divided into two groups according to the anesthesia performed. In a retrospective long-term multicenter study, volume reduction and the energy delivered were analyzed using the Wilcoxon signed-rank test and the Mann-Whitney test. RESULTS: At three months follow-up, the total study population had an average volume reduction of 39.26% (range 4.03-91.16%, $p < 0.001$, $n = 30$), the general anesthesia group of 47.46% (range 13.64-91.16%, $p = 0.001$, $n = 15$) and the regional anesthesia group of 31.06% (range 4.03-68.63%, $p = 0.001$, $n = 15$). Under regional anesthesia a median energy of 3.16 kJ/cm³ (range: 0.96 - 8.2 kJ/cm³) and under

general anesthesia a median energy of 0.88 kJ/cm(3) (range: 0.18 - 1.63 kJ/cm(3)) were delivered. All results were significant with $p < 0.05$. The complication rate was 6.67%. CONCLUSION: HIFU is an effective method to treat benign thyroid nodules. Comparing anesthesia methods, volume reduction is higher in patients treated under general anesthesia and less energy has to be delivered under general anesthesia. TRIAL REGISTRATION NUMBER: 2020-1728-evBO. AGENCY: Ethik-Kommission bei der Landes%oztekammer Hessen.

PubMed-ID: [35072745](https://pubmed.ncbi.nlm.nih.gov/35072745/)

<http://dx.doi.org/10.1007/s00268-022-06447-7>

Differential diagnosis of thyroid nodules by the Demetics ultrasound-assisted diagnosis system and contrast-enhanced ultrasound combined with thyroid image reporting and data systems.

Clin Endocrinol (Oxf), 97(1):116-23.

G. Wang, F. Nie, Y. Wang, D. Yang, T. Dong, T. Liu and P. Wang. 2022.

BACKGROUND: More and more new ultrasound techniques with their own characteristics are applied in the differential diagnosis of thyroid nodules. This study aimed to assess and compare the diagnostic value of the Demetics ultrasound-assisted diagnosis system and contrast-enhanced ultrasound (CEUS) combined with the Thyroid Image Reporting and Data Systems (TI-RADS) for thyroid nodules. DESIGN AND PATIENTS: A total of 600 thyroid nodules with pathological findings were retrospectively analysed. Demetics and CEUS were performed for all nodules. The diagnostic efficacy of Demetics and CEUS for nodules of different sizes was evaluated and compared in terms of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR-). The characteristics of nodules diagnosed and misdiagnosed by Demetics were compared to analyse the factors affecting the diagnostic accuracy of Demetics. The necessity of CEUS for nodules that are prone to misdiagnosis in Demetics was assessed. RESULTS: Both Demetics and CEUS can be used for the differential diagnosis of benign and malignant thyroid nodules of different sizes. The diagnostic agreement between Demetics and CEUS for thyroid nodules of different sizes was moderate, substantial and fair, respectively. The sensitivity and NPV of Demetics were higher than those of CEUS, and the specificity, PPV and LR+ of CEUS were higher than that of Demetics. The LR- of Demetics was lower than those of CEUS. There were significant differences in age, calcification and margin in analysing the factors affecting Demetics. CEUS correctly diagnosed 50 of the 101 nodules misdiagnosed by Demetics. CONCLUSIONS: Demetics showed high sensitivity in diagnosing thyroid nodules, while CEUS showed high specificity. In clinical practice, CEUS can further improve the diagnostic accuracy for nodules that are easily misdiagnosed by Demetics.

PubMed-ID: [35441715](https://pubmed.ncbi.nlm.nih.gov/35441715/)

<http://dx.doi.org/10.1111/cen.14741>

Response to "Regarding the Impact of Truncal vs Branch Ligation of the Inferior Thyroid Artery on Postoperative Hypoparathyroidism".

Otolaryngol Head Neck Surg, 167(2):413-4.

T. Waseem. 2022.

PubMed-ID: [35913809](https://pubmed.ncbi.nlm.nih.gov/35913809/)

<http://dx.doi.org/10.1177/01945998211054017>

The Prognosis of Skip Metastasis in Papillary Thyroid Microcarcinoma Is Better Than That of Continuous Metastasis.

J Clin Endocrinol Metab, 107(6):1589-98.

H. Y. Weng, T. Yan, W. W. Qiu, Y. B. Fan and Z. L. Yang. 2022.

CONTEXT: A few papillary thyroid microcarcinomas (PTMCs) may have skip metastasis (SLNM), but the risk factors remain controversial and the prognosis is unclear. OBJECTIVES: To investigate the incidence, lymph node metastasis (LNM) patterns, risk factors, and prognosis of SLNM in PTMCs. METHODS: We reviewed the medical records of PTMC patients who underwent thyroid surgery in our institution. Analyses of risk factors were performed for SLNM. Recurrence-free survival (RFS) of SLNM, central lymph node metastasis (CLNM), and continuous metastasis (CLNM and lateral lymph node metastasis [CLNM + LLNM]) were compared after propensity score matching (PSM). RESULTS: SLNM was detected in 1.7% (50/3923) and frequently involved level III (66.7%). Compared with CLNM + LLNM, SLNM had more LNM at a single level ($P < 0.01$) and less LNM at 2 levels ($P < 0.05$). A tumor size of 0.5 to 1 cm (odds ratio [OR], 2.26; 95% CI, 1.27-4.00) and location in the upper pole (OR, 3.30; 95% CI, 2.02-5.40) were independent risk factors for SLNM. A total of 910 (23.2%) PTMCs with LNM were included in the prognostic analysis. At a median follow-up of 60 months, the RFS of SLNM did not differ from that of CLNM ($P = 0.10$) but was significantly higher than that of CLNM + LLNM ($P < 0.01$) after using PSM. CONCLUSIONS: When the tumor size is 0.5 to 1 cm or its location is in the upper pole, we must remain vigilant to SLNM in PTMC. Because its prognosis is comparable to that of only CLNM and better than that of CLNM + LLNM, less intensive

treatment should be considered.

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<http://dx.doi.org/10.1210/clinem/dgac107>

I-PET score: Combining whole body iodine and (18) F-FDG PET/CT imaging to predict progression in structurally or biochemically incomplete thyroid cancer.

Clin Endocrinol (Oxf),

A. Wijewardene, J. Hoang, A. M. Maw, M. Gild, L. Tacon, P. Roach, G. Schembri, D. Chan and R. Clifton-Bligh. 2022.

OBJECTIVE: We propose a new scoring system (I-PET) combining whole body scan (WBS) and FDG findings to identify patients who have or are likely to become refractory to radioactive iodine. DESIGN: Retrospective analysis of 142 patients age >18 with differentiated thyroid cancer who had a F-18 labelled fluoro-2-deoxyglucose ((18) F-FDG) positron emission tomography (PET) and WBS within a 6-month period between 2010 and 2020. Pairs of (18) F-FDG PET and WBS were reviewed by three independent nuclear medicine physicians and an I-PET score was assigned: I-PET [0]: Iodine -ve/FDG -ve, I-PET [1]: Iodine +ve/FDG -ve, I-PET [2]: Iodine +ve/FDG +ve and I-PET [3]: Iodine -ve/FDG +ve. Patients with FDG +ve lesions (I-PET [2] and I-PET [3]) were further classified into groups A and B if SUVmax was =5 or >5, respectively. Follow-up data were obtained by chart review. Progression was defined as structural progression as per RECIST 1.1 or further surgical intervention; or biochemical progression as unstimulated thyroglobulin increasing >20% from baseline. RESULTS: Of 142 patients included in the study 121 patients had follow-up data available for review. At baseline, 49 patients were classified as I-PET [0], 10 as I-PET [1], 16 as I-PET [2] and 46 as I-PET [3]. Progression was seen in 11/49 (22%) of I-PET [0], 4/10 (40%) of I-PET [1], 10/16 (63%) of I-PET [2] and 34/46 (74%) of I-PET [3] ($p < 0.001$). I-PET [2B] and I-PET [3B] had a progression rate of 88% (7/8) and 78% (25/32), respectively. I-PET [3B] were 9.6 times more likely to commence multikinase inhibitor therapy ($p = 0.001$) and had 8 times greater mortality ($p = 0.003$) than patients in other I-PET groups combined. CONCLUSION: I-PET is a simple readily acquired imaging biomarker that potentially enhances the dynamic risk stratification and guide treatment in thyroid cancer.

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<http://dx.doi.org/10.1111/cen.14804>

Value of dissection of lymph nodes posterior to the right recurrent laryngeal nerve in patients with cN(0) papillary thyroid carcinoma.

Gland Surg, 11(7):1204-11.

X. Xiao, Y. Wu, L. Zou, Y. Chen and C. Zhang. 2022.

BACKGROUND: Tumor metastasis to lymph nodes posterior to the right recurrent laryngeal nerve (LN-prRLN) is a main cause of disease recurrence in patients with papillary thyroid carcinoma (PTC), which may increase the risk of recurrence and secondary surgery, and the disruption of normal anatomical relationships during secondary surgery increases the risk of laryngeal nerve injury and hypoparathyroidism. However, controversy remains as to whether the dissection of LN-prRLN is required in cN(0) PTC patients. The purpose of this study is to explore the factors associated with LN-prRLN metastasis in patients with cN(0) PTC and the need for LN-prRLN node dissection in patients with cN(0) PTC who undergo right central compartment dissection. METHODS: The clinical data of 290 patients with cN(0) PTC who received radical thyroid cancer surgery from December 2019 to March 2022 at our center were retrospectively analyzed. All the patients underwent thyroid lobectomy and right central lymph node dissection (CLND), along with other treatments. SPSS 26.0 statistical software was used for the analysis. The measurement data were compared using the rank-sum test, and the count data were compared using the chi-square test. RESULTS: LN-prRLN metastasis was detected in 65 (22.4%) of the 290 cN(0) PTC patients. The metastasis sites included level VIa (51.72%), the left central compartment (22.76%), and the prelaryngeal compartment (8.97%). The univariate analysis revealed that tumor multifocality, a tumor diameter >1 cm, capsular invasion, LN metastasis in the left central compartment, and level VIa positivity were influencing factors of LN-prRLN metastasis in PTC patients. The logistic regression analysis showed that a tumor diameter >1 cm (OR =2.897, 95% CI: 1.630-5.147, $P < 0.001$), LN metastasis in the left central compartment (OR =3.724, 95% CI: 2.039-6.801, $P < 0.001$), and level VIa (OR =3.405, 95% CI: 1.846-6.281, $P < 0.001$) positivity were independent risk factors of LN-prRLN metastasis in PTC patients. CONCLUSIONS: The high-risk factors of LN-prRLN metastasis in cN(0) PTC patients include a large tumor (a diameter >1 cm), lymph node metastasis in the left central compartment, and lymph node metastasis in level VIa. For patients with cN(0) PTC undergoing right CLND, with high-risk factors of LN-prRLN metastasis, LN-prRLN dissection is recommended. KEYWORDS: Papillary thyroid carcinoma (PTC); lymph nodes posterior to the right recurrent laryngeal nerve (LN-prRLN); central compartment lymph node dissection; risk factor.

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<http://dx.doi.org/10.21037/gs-22-337>

Assesment of attainment of recommended TSH levels and levothyroxine compliance in differentiated thyroid cancer patients.

Clin Endocrinol (Oxf), 97(6):833-40.

D. G. Yavuz, C. D. Yazan, Z. Hekimsoy, K. Aydin, N. Gokkaya, C. Ersoy, A. Akalin, O. Topaloglu, B. I. Aydogan, E. N. A. Dilekci, Z. Alphan Uc, G. B. Cansu, L. Ozsari, O. T. Iyidir, M. E. Olgun, L. Keskin, M. Mert, B. Can, K. Gungor, T. Galip, Z. Cant_rk, G. Elbuken, Z. Pekkolay, N. O. Kutbay, G. Yorulmaz, A. T. Kalkan, Y. A. Unsal, A. Yay, B. Karagun and E. Bozkur. 2022.

OBJECTIVE: Thyroid-stimulating hormone (TSH) suppression treatment can induce signs and symptoms of hyperthyroidism and hypothyroidism due to inappropriate treatment or poor compliance to the treatment. The current study aimed to investigate TSH levels, frequency of being on target TSH, adherence to levothyroxine (LT4) suppression treatment in differentiated thyroid cancer (DTC) patients after surgery in a multicentric setting. DESIGN AND PATIENTS: This multicentric cross-sectional study was conducted at 21 medical centres from 12 cities in Turkey. DTC patients followed at least one year in the same center included in the study. Clinical data, serum TSH, free thyroxine (FT4), thyroglobulin (Tg) and anti-Tg levels were recorded during the most recent visit. Body mass index, systolic and diastolic blood pressures, pulse rate were measured. LT4 doses were recorded and doses per kilogram of bodyweight were calculated. Pill ingestion habits recorded and adherence to the therapy were evaluated using the Morisky Medication Adherence Scale and categorized as good, moderate or poor compliant based on their scores. Risk stratification for predicting the disease persistence and/or recurrence was assessed using the American Joint Committee on Cancer-7th edition thyroid cancer staging calculator. TSH serum concentrations were classified as severe suppression (TSH < 0.01 mU/L), moderate suppression (TSH: 0.01-0.1 mU/L), mild suppression (TSHL 0.1-0.5 mU/L), euthyroid (TSH: 0.5-4 mU/L) and hypothyroid (TSH > 4 mU/L). TSH levels can also be classified as on being on target, under the target, or beyond over the target, according to the American Thyroid Association recommendations. RESULTS: A group of 1125 patients (F/M: 941/184, 50.7 ± 11.7 years) were included in the study. The mean LT4 daily dosage was 132.4 ± 39.6 mcg/day. TSH levels showed severe suppression in 99 (%8.8) patients, moderate suppression in 277 (%24.6) patients and mild suppression in 315 (%28) patients and euthyroid range in 332 (%29.5) patients and hypothyroid range in 97 (8.6%). TSH levels were in target in 29.2% of the patients 20.4% of the patients were undertreated, 50.4% overtreated. The daily LT4 dose and LT4 dose/kg were significantly higher in the severe suppression group (p < .001, p < .001). According to the Morisky scale, 564 patients (50.1%) were good compliant, 368 patients (32.7%) were moderate compliant, and 193 patients (17.1%) were noncompliant. Patients with poor compliance need a higher dose of LT4 compared to the good compliance group (p < .001). TSH levels of patients with good compliance were 0.67 ± 1.96 mU/L and TSH with poor compliance was 2.74 ± 7.47 mU/L (p < .001). TSH levels were similar in patients on fixed and alternating dosages. CONCLUSION: In 29.2% of the DTC patients, serum TSH levels were at target levels. Remaining of the study group have TSH levels under or over treatment range, exposing the patient to medication side effects. Majority of the study group 82.8% have good or moderate adherence to LT4 therapy. Reaching TSH targets requires simplified and applicable guidelines and following the guideline recommendations.

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Use of thyroid hormones in hypothyroid and euthyroid patients: A THESIS questionnaire survey of UK endocrinologists.

Clin Endocrinol (Oxf),

Y. R. Younes, P. Perros, L. Heged_s, E. Papini, E. V. Nagy, R. Attanasio, R. Negro and B. C. T. Field. 2022.

OBJECTIVE: Management of hypothyroidism is controversial because of medication cost pressures and scientific uncertainty on how to address treatment dissatisfaction experienced by some patients. The objective was to investigate the experience and preferences of UK endocrinologists in use of thyroid hormones. DESIGN: Web-based survey. PATIENTS: UK endocrinologists were invited to participate. MEASUREMENTS: Responses to questionnaire. RESULTS: The response rate was 21% (272/1295). While levothyroxine monotherapy is regarded as the treatment of choice for hypothyroidism, 51% of respondents stated that combined treatment with levothyroxine and liothyronine could be considered for levothyroxine-treated patients whose symptoms persist despite normalisation of serum thyroid stimulating hormone (TSH) concentration. However, only 40% are currently prescribing such treatment, and just 23% would consider taking it themselves. A small minority prescribe desiccated thyroid extract, and those most likely to do so are aged over 60 years. Most respondents stated that they have no influence over brand or formulation of levothyroxine dispensed to their patients and expect no major differences in efficacy between different formulations. A total of 9% would prescribe levothyroxine for euthyroid enlarging goitre, and 29% for euthyroid female infertility with high titre thyroid peroxidase antibodies, despite recent trials finding no benefit. CONCLUSIONS: UK endocrine practice in management of hypothyroidism is broadly in line with international guidance. However, a minority of respondents would consider thyroid

hormone supplementation in euthyroid individuals for female infertility, enlarging goitre, and other indications in which evidence of efficacy is lacking. Willingness to consider prescribing combined levothyroxine and liothyronine, for hypothyroid symptoms which persist despite normalised TSH, has increased in comparison to previous international surveys, despite inconsistent evidence of benefit.

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<http://dx.doi.org/10.1111/cen.14812>

Recurrent Laryngeal Nerve Injury in Thermal Ablation of Thyroid Nodules-Risk Factors and Cause Analysis.

J Clin Endocrinol Metab, 107(7):e2930-e7.

Z. L. Zhao, Y. Wei, L. L. Peng, Y. Li, N. C. Lu and M. A. Yu. 2022.

CONTEXT: Recurrent laryngeal nerve (RLN) injury is a complication of thermal thyroid nodule treatment. OBJECTIVE: We investigated the influencing factors of RLN injury in patients who underwent thermal ablation of thyroid nodules.

METHODS: The data of 1004 patients (252 male, 752 female; median age 44 years) who underwent thermal thyroid nodule ablation were retrospectively reviewed. Patients were divided into benign cystic, benign solid, and papillary thyroid cancer (PTC) groups. The parameters related to RLN injury were analyzed, including the largest diameter, location of the nodules, and shortest distance of the nodule to thyroid capsule and tracheoesophageal groove (TEG). Univariate and multivariate analyses were performed to select risk factors for RLN injury. RESULTS: The RLN injury rate was higher in PTC (6.3%) than in benign cystic (1.2%, $P = 0.019$) and solid nodules (2.9%, $P = 0.018$). PTC subgroup analysis showed that the RLN injury rate was higher in T1b (10.7%) and T2 (28.6%) PTC than in T1a PTC (5.0%, $P < 0.05$). In the PTC group, TEG distance, anterior capsule distance, median capsule distance, posterior capsule distance, and maximum nodule diameter were risk factors for RLN injury. The logistic regression fitting of the nomogram showed high prediction efficiency (C-Index 0.876). The main cause of RLN injury was insufficient medial isolating fluid (MIF). The safety thicknesses of MIF for benign cystic, benign solid, and PTC nodules were 3.1 mm, 3.7 mm, and 3.9 mm, respectively. CONCLUSION: Several risk factors for RLN injury should be considered before thermal ablation of thyroid nodules. The RLN injury rate could be predicted with the nomogram.

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<http://dx.doi.org/10.1210/clinem/dgac177>

Parathyroids

Meta-Analyses

- None -

Randomized controlled trials

- None -

Consensus Statements/Guidelines

The American Association of Endocrine Surgeons Guidelines for the Definitive Surgical Management of Secondary and Tertiary Renal Hyperparathyroidism.

Ann Surg, 276(3):e141-e76.

S. Dream, L. E. Kuo, J. H. Kuo, S. M. Sprague, F. E. Nwariaku, M. Wolf, J. A. Olson, Jr., S. M. Moe, B. Lindeman and H. Chen. 2022.

OBJECTIVE: To develop evidence-based recommendations for safe, effective, and appropriate treatment of secondary (SHPT) and tertiary (THPT) renal hyperparathyroidism. **BACKGROUND:** Hyperparathyroidism is common among patients with chronic kidney disease, end-stage kidney disease, and kidney transplant. The surgical management of SHPT and THPT is nuanced and requires a multidisciplinary approach. There are currently no clinical practice guidelines that address the surgical treatment of SHPT and THPT. **METHODS:** Medical literature was reviewed from January 1, 1985 to present January 1, 2021 by a panel of 10 experts in SHPT and THPT. Recommendations using the best available evidence was constructed. The American College of Physicians grading system was used to determine levels of evidence. Recommendations were discussed to consensus. The American Association of Endocrine Surgeons membership reviewed and commented on preliminary drafts of the content. **RESULTS:** These clinical guidelines present the epidemiology and pathophysiology of SHPT and THPT and provide recommendations for work-up and management of SHPT and THPT for all involved clinicians. It outlines the preoperative, intraoperative, and postoperative management of SHPT and THPT, as well as related definitions, operative techniques, morbidity, and outcomes. Specific topics include Pathogenesis and Epidemiology, Initial Evaluation, Imaging, Preoperative and Perioperative Care, Surgical Planning and Parathyroidectomy, Adjuncts and Approaches, Outcomes, and Reoperation. **CONCLUSIONS:** Evidence-based guidelines were created to assist clinicians in the optimal management of secondary and tertiary renal hyperparathyroidism.

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<http://dx.doi.org/10.1097/SLA.0000000000005522>

Other Articles

Intraoperative freehand SPECT as an alternative imaging technique for use in radioguided parathyroidectomy.

Updates Surg, 74(4):1429-34.

E. Alci, M. Ozdemir, A. Miftari, A. Oral, T. Gumus, G. Icoz and Makay. 2022.

Freehand single photon emission computed tomography (fhSPECT) is a technique that is used to monitor body's radioactivity intraoperatively. Accordingly, in this study, the feasibility of using fhSPECT for intraoperative 3D mapping in radioguided parathyroidectomy has been assessed. Patients, who were diagnosed with primary hyperparathyroidism consecutively, were scanned intraoperatively using fhSPECT to locate parathyroid adenomas before surgical procedure. The fhSPECT images were acquired intraoperatively using a declipse((r))SPECT device (SurgicEye(TM)). The fhSPECT protocol could not be completed due to the technical problems in one patient. Parathyroid adenoma was located in the first patient with no lateral deviation. Nevertheless, a deviation of 8 mm was detected in the depth of the parathyroid adenoma, which is the distance of parathyroid adenoma from the skin. A 20 mm lateral deviation and a 10 mm deviation in depth were detected in the second patient. In the third patient, as was the case in the first patient, parathyroid adenoma was located with no lateral deviation. However, there was a 15 mm deviation in the depth of the parathyroid adenoma. A 5 mm lateral deviation was detected in the fourth patient yet with no deviation in the depth of parathyroid adenoma. Finally, neither lateral nor vertical deviation was detected in fifth patient. Based on the findings of this study, it

was concluded that the fhSPECT technology can be helpful to a certain degree in locating the parathyroid adenoma. However, further studies are needed to support the findings of this preliminary study.

PubMed-ID: [35661121](https://pubmed.ncbi.nlm.nih.gov/35661121/)

<http://dx.doi.org/10.1007/s13304-022-01300-x>

Hypercalcaemia and hyperparathyroidism in surgical practice.

Br J Surg, 109(6):481-2.

K. Bateman and R. J. Egan. 2022.

PubMed-ID: [35576378](https://pubmed.ncbi.nlm.nih.gov/35576378/)

<http://dx.doi.org/10.1093/bjs/znac033>

Diagnostic Performance of Cervical Ultrasound, (99m)Tc-Sestamibi Scintigraphy, and Contrast-Enhanced (18)F-Fluorocholine PET in Primary Hyperparathyroidism.

J Nucl Med, 63(7):1081-6.

V. Boudousq, N. Guignard, O. Gilly, B. Chambert, A. Mamou, O. Moranne, M. Zemmour, H. Sharara and B. Lallemand. 2022.

Preoperative localization of pathologic parathyroids is crucial for minimally invasive treatment of primary hyperparathyroidism (PHPT). This study compared contrast-enhanced (18)F-fluorocholine PET/CT, cervical ultrasonography (CU), and conventional scintigraphic imaging modalities (MIBI scintigraphy, consisting of (99m)Tc-sestamibi/(123)I-sodium iodide SPECT/CT, (99m)Tc-sestamibi/(123)I-sodium iodide planar subtraction imaging, and (99m)Tc-sestamibi planar dual-phase imaging), combined and individually, for preoperative localization of hyperfunctional parathyroids in PHPT. The gold standard was histologic examination. Methods: Data from consecutive patients with clinically suspected PHPT were retrospectively collected. All 3 imaging modalities were systematically performed. The ability of (18)F-fluorocholine PET/CT, CU, and MIBI scintigraphy to identify a hyperfunctional parathyroid and specify the side or identify an ectopic location was noted. Patients underwent surgical exploration if at least 1 examination was positive. The findings of CU + MIBI scintigraphy combined were considered positive if CU and MIBI scintigraphy separately showed a hyperfunctional parathyroid gland on the same side or in the same ectopic location; any findings other than these were considered negative. The composite judgment criterion for pathologic parathyroid was a combination of histologic analysis and normalization of parathyroid hormone and calcium levels. Results: In total, 149 pathologic parathyroids were found in 143 of the 144 included patients. (18)F-fluorocholine PET/CT diagnosed 148 of 149 pathologic parathyroids. Only 4 false-positives and 1 false-negative were found. The (18)F-fluorocholine PET/CT sensitivity of 99.3% was superior to that of CU, at 75.2% ($P < 0.0001$); MIBI scintigraphy, at 65.1% ($P < 0.0001$); and CU + MIBI scintigraphy, at 89.9%, ($P = 0.0009$). Five of the 5 ectopic locations were diagnosed by (18)F-fluorocholine PET/CT, 2 of the 5 by MIBI scintigraphy, and none by CU. Accuracy was better for (18)F-fluorocholine PET/CT, at 98%, than for CU, at 84% ($P < 0.0001$); MIBI scintigraphy, at 81% ($P < 0.0001$); or CU + MIBI scintigraphy, at 91% ($P < 0.0001$). Among the 72 (50%) patients who had a negative CU + MIBI scintigraphy result, (18)F-fluorocholine PET/CT correctly identified hyperfunctional thyroids in 70 (97.2%). Average uptake in the (18)F-fluorocholine PET/CT hyperfunctional parathyroid was higher than that in the adjacent thyroid (SUV(max) adjusted for lean body mass, 6.45 vs. 2.15) ($P < 0.0001$). Conclusion: The accuracy of (18)F-fluorocholine PET/CT is higher than that of CU and MIBI scintigraphy for localization of hyperfunctional parathyroids, justifying the systematic use of (18)F-fluorocholine PET/CT as the first-line method for PHPT diagnosis.

PubMed-ID: [34857659](https://pubmed.ncbi.nlm.nih.gov/34857659/)

<http://dx.doi.org/10.2967/jnumed.121.261900>

Variation in parathyroid adenoma size in patients with sporadic, primary hyperparathyroidism: small gland size does not preclude single gland disease.

Langenbecks Arch Surg, 407(5):2067-73.

S. Dream, T. W. F. Yen, K. Doffek, D. B. Evans and T. S. Wang. 2022.

PURPOSE: Small, abnormal parathyroid glands are usually associated with multigland hyperplasia in patients with primary hyperparathyroidism (pHPT). The purpose of this study was to determine the association between parathyroid adenoma size and biochemical cure rates in patients undergoing single gland parathyroidectomy. METHODS: The study included patients with sporadic pHPT who underwent initial parathyroidectomy and met intraoperative PTH criteria for cure after resection of a single adenoma (SGD). Patients were divided into quartiles (Q1 = smallest) based on gland weight and maximum dimension; cure rates were compared across groups. RESULTS: A single parathyroid adenoma was removed in 517 patients, with a median gland weight of 500 mg (range 50-11890). Median maximum gland dimension was 15 mm (range 5-55). With median follow-up of 28 months (range 6-81), the biochemical cure rate was 97.1%. There was no difference in cure rate by gland weight (Q1 94.6%, Q2 96.9%, Q3 98.4%, Q4 98.5%, $p = 0.217$) or maximum gland

dimension (Q1 95.6%, Q2 97.6%, Q3 97.1%, Q4 98.2%, $p = 0.641$). When Q1 patients (by gland weight) were divided by quartile, there was no difference in cure rates (93.1% [50-140 mg]; 95.2% [150-190 mg]; 97.1% [200-230 mg]; 93.3% [240-280 mg]; $p = 0.665$). CONCLUSION: For patients with pHPT who underwent single gland parathyroidectomy, there was no difference in cure rates by gland weight or maximum dimension. These data suggest that the removal of parathyroid adenomas as small as 50 mg with an appropriate decline in ioPTH likely represent single gland disease and additional exploration may not be necessary.

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<http://dx.doi.org/10.1007/s00423-022-02539-z>

Minimally Invasive Parathyroidectomy: Can Intraoperative Parathyroid Hormone Monitoring be Omitted?

World J Surg, 46(8):1908-14.

S. Eligal, M. Mekel, J. M. Weinberger, M. Neymark, N. Hirshoren, I. Mizrahi, R. Eliashar and H. Mazeh. 2022.

BACKGROUND: Intraoperative PTH (ioPTH) monitoring has become widely accepted in the era of minimally invasive parathyroidectomy (MIP). The purpose of this study was to evaluate the need for ioPTH during parathyroidectomy in patients with positive preoperative imaging. METHODS: The charts of patients who underwent parathyroidectomy at three tertiary centers between the years 2012 and 2021 were retrospectively reviewed. Patients were defined as MIP candidates with either concordant preoperative imaging or a single positive imaging. Patients with negative or discordant imaging, concomitant thyroidectomy, or previous neck surgery were excluded. RESULTS: Of a total of 1013 patients who underwent parathyroidectomy, 535 (52.8%) were defined as MIP candidates and were included in the statistical analysis. Surgical success was achieved in all patients. A single adenoma that corresponded to the preoperative imaging was identified and resected in 517 (93.8%) patients. In only 18 (3.3%) patients, the ioPTH correctly changed the operative management where additional pathologic glands were identified and excised. Patients with additional lesions were significantly more likely to have decreased index adenoma size as indicated either by preoperative imaging or by intraoperative findings (15.5 ± 6.6 vs. 8.3 ± 2.5 mm, $p < 0.001$). None of the patients with an adenoma size greater than 13 mm had an additional pathologic gland. CONCLUSIONS: Our findings suggest that the routine use of ioPTH in MIP candidates may be omitted in patients with an index adenoma greater than 13 mm, even with only a single positive preoperative imaging study, without compromising surgical success.

PubMed-ID: [35403873](https://pubmed.ncbi.nlm.nih.gov/35403873/)

<http://dx.doi.org/10.1007/s00268-022-06537-6>

Volume-Outcome Associations for Parathyroid Surgery in England: Analysis of an Administrative Data Set for the Getting It Right First Time Program.

JAMA Surg, 157(7):581-8.

W. K. Gray, A. V. Navaratnam, J. Day, J. A. H. Wass, T. W. R. Briggs and M. Lansdown. 2022.

IMPORTANCE: Previous studies have suggested an association between surgical volume and patient outcomes for parathyroid surgery. However, most previous studies are relatively small and the literature is dominated by studies from the US, which might not be readily generalizable to other settings. OBJECTIVE: To investigate volume-outcome associations for parathyroid surgery in England. DESIGN, SETTING, AND PARTICIPANTS: Cohort study that included all National Health Service hospital trusts in England with secondary analysis of administrative data using International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10). Participants included all adult, elective hospital admissions for parathyroid surgery without a diagnosis of multiple endocrine neoplasia, parathyroid cancer, or kidney disease over a 5-year period (April 2014-March 2019 inclusive). EXPOSURES: The number of procedures conducted in the year prior to the index procedure by each surgeon and each hospital trust. MAIN OUTCOMES AND MEASURES: Repeat parathyroid surgery within 1 year of the index procedure. RESULTS: This study included data for 17,494 participants who underwent parathyroidectomies conducted across 125 hospital trusts. The median (IQR) age of patients was 62 (53-71) years, and 13,826 were female (79.0%). Across the period, the number of surgeons conducting parathyroid surgery changed little (280 in 2014-2015 and 2018-2019), although the number of procedures conducted rose from 3331 to 3848 per annum. Repeat parathyroid surgery at 1 year was significantly associated with surgeon volume (odds ratio [OR], 0.99; 95% CI, 0.98-0.99), but not trust volume, in the previous 12 months. Extended length of stay (OR, 0.98; 95% CI, 0.98-0.99), hypoparathyroidism/calcium disorder (OR, 1.0; 95% CI, 0.99-1.0), and postprocedural complications (OR, 0.99; 95% CI, 0.99-1.0) were also associated with lower surgeon volume. CONCLUSIONS AND RELEVANCE: In this cohort study, higher surgeon annual volume was associated with decreased rates of repeat parathyroid surgery. A minimum volume threshold of 20 procedures per annum should improve patient outcomes, although possible negative effects on access to services should be monitored.

PubMed-ID: [35507350](https://pubmed.ncbi.nlm.nih.gov/35507350/)

<http://dx.doi.org/10.1001/jamasurg.2022.1353>

The Diagnosis of Normocalcaemic Hyperparathyroidism is Strikingly Dissimilar Using Different Commercial Laboratory Assays.

Horm Metab Res, 54(7):429-34.

T. Kalaria, J. Fenn, A. Sanders, A. Yates, C. Duff, H. Ashby, P. Mohammed, C. Ford and R. Gama. 2022.

We assessed the impact of intact parathyroid hormone (iPTH) and adjusted calcium analyses on Abbott, Roche and Siemens analytical platforms in the diagnosis of normocalcaemic primary hyperparathyroidism (NCPHPT). These assays are used by over 85% of clinical laboratories in the UK. Over five months, consecutive serum samples from outpatients with NCPHPT in the laboratory with Abbott assays were identified, aliquoted and stored at -80°C . Frozen aliquots were transported monthly to the other two laboratories. After thawing, samples were mixed and analysed immediately for calcium, albumin and iPTH in the laboratories with Abbott, Roche and Siemens analytical platforms. Adjusted calcium was calculated using the equation used in the respective laboratory. Diagnostic concordance of iPTH and adjusted calcium were assessed using manufacturer-provided assay-specific reference intervals and the pathology harmony reference interval respectively. Fifty-five patients with NCPHPT were identified using Abbott assays. Of these, 16 (29.1%) and 11 (20.0%) had NCPHPT, 9 (16.4%) and 13 (23.6%) had hypercalcaemic primary hyperparathyroidism, and 30 (54.6%) and 31 (56.4%) patients had normal results when analysed in laboratories with Roche and Siemens assays, respectively. The diagnosis of NCPHPT was strikingly different depending on the commercial assay used. There is a pressing need for iPTH assay harmonisation and robust reference intervals. Reference intervals may become invalid if an assay drifts, as exemplified by adjusted calcium in this study.

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<http://dx.doi.org/10.1055/a-1856-4900>

Parathyroidectomy vs Cinacalcet Among Patients Undergoing Hemodialysis.

J Clin Endocrinol Metab, 107(7):2016-25.

H. Komaba, T. Hamano, N. Fujii, K. Moriwaki, A. Wada, I. Masakane, K. Nitta and M. Fukagawa. 2022.

CONTEXT: Parathyroidectomy (PTx) and cinacalcet are both effective treatments for secondary hyperparathyroidism in hemodialysis patients, but limited data exist comparing the long-term outcomes of these interventions. OBJECTIVE: We aimed to compare the risk of mortality among hemodialysis patients who underwent PTx and those who started treatment with cinacalcet. METHODS: In this prospective cohort study, comprising patients from the Japanese Society for Dialysis Therapy Renal Data Registry, patients who had intact parathyroid hormone (PTH) levels = 300 pg/mL in late 2007 and underwent PTx or started treatment with cinacalcet in 2008 to 2009 were matched by propensity score at 1:3. PTx and cinacalcet were compared for all-cause mortality within 6 years. RESULTS: Among eligible patients, 894 patients who underwent PTx were matched with 2682 patients who started treatment with cinacalcet. The median baseline intact PTH levels were 588 pg/mL and 566 pg/mL in the PTx and cinacalcet groups, respectively. PTx resulted in greater reductions in intact PTH, calcium, and phosphorus levels compared with cinacalcet. During the 6-year follow-up period, 201 patients (22.5%) in the PTx group and 736 patients (27.4%) in the cinacalcet group died. PTx was associated with a lower risk of mortality compared with cinacalcet (hazard ratio, 0.78 [95% CI, 0.67-0.91]; $P = 0.002$). This association was more pronounced in patients with intact PTH levels = 500 pg/mL and in patients with serum calcium levels = 10.0 mg/dL (both P for interaction < 0.001). CONCLUSION: PTx compared with cinacalcet is associated with a lower risk of mortality, particularly among patients with severe secondary hyperparathyroidism.

PubMed-ID: [35277957](https://pubmed.ncbi.nlm.nih.gov/35277957/)

<http://dx.doi.org/10.1210/clinem/dgac142>

Neuropsychiatric Comorbidity in Primary Hyperparathyroidism Before and After Parathyroidectomy: A Population Study.

World J Surg, 46(6):1420-30.

A. Koman, R. Brønström, Y. Pernow, R. Brønström, I. L. Nilsson and F. Granath. 2022.

BACKGROUND: Primary hyperparathyroidism (PHPT) is often accompanied by neuropsychiatric symptoms. This study aimed to map out psychiatric comorbidity as reflected by medical treatment for psychiatric symptoms. METHODS: A retrospective case-control analysis and a prospective cohort analysis of psychotropic drug utilization before and after PTX. A total of 8279 PHPT patients treated with parathyroidectomy in Sweden between July 1, 2008 and December 31, 2017 compared to a matched control cohort from the total population ($n = 82,790$). Information on filled prescriptions was collected from the Swedish Prescribed Drug Register (SDR). Socioeconomic data and diagnoses were added by linkage to

national patient and population registers. Regression analyses were used to calculate relative drug utilization (OR) within 3 years prior to PTX and relative incidence of drug treatment (RR) within 3 years postoperatively. RESULTS: Utilization of antidepressant, anxiolytic and sleep medication was more comprehensive in PHPT patients compared with the controls prior to PTX. The most common were benzodiazepines [OR 1.40 (95% CI: 1.31-1.50)] and selective serotonin reuptake inhibitors [SSRI; OR 1.38 (95% CI: 1.30-1.47)]. Postoperatively, the excess prescription rate for anxiolytic benzodiazepines decreased within three years from a 30 to 19% excess and for benzodiazepines for sleep from 31 to 14%. No corresponding decrease in excess prescription rate was observed for SSRI. CONCLUSION: PHPT is associated with increased utilization of antidepressive medications and benzodiazepines before PTX. This study implies that psychiatric symptoms should be considered in PHPT patients and continuous medication should be reevaluated after PTX.

PubMed-ID: [35246714](https://pubmed.ncbi.nlm.nih.gov/35246714/)

<http://dx.doi.org/10.1007/s00268-022-06485-1>

Normocalcemic primary hyperparathyroidism: 99mTc SestaMibi SPECT/CT results compare with hypercalcemic hyperparathyroidism.

Clin Endocrinol (Oxf), 96(6):831-6.

M. Musumeci, L. V. Pereira, L. San Miguel, C. Cianciarelli, E. C. Vazquez, A. M. Mollerach, I. J. Arma, I. Hume, A. M. Galich and C. Collaud. 2022.

CONTEXT: Normocalcemic primary hyperparathyroidism (nPHPT) is defined by an inappropriately increased serum PTH with normal serum calcium. Information about the diagnostic yield of parathyroid SPECT/CT scan and ultrasonography in nPHPT is limited and not conclusive. PURPOSE: To evaluate the positivity rate of (99m) Tc-Sestamibi SPECT/CT scan in nPHPT compared with classical hypercalcemic PHPT (cPHPT). MATERIALS AND METHODS: We retrospectively studied 125 patients with (99m) Tc-Sestamibi SPECT/CT scans. Subjects were divided into 2 groups: cPHPT (n = 93) and nPHPT (n = 32). RESULTS: The detection rate of (99m) Tc-Sestamibi SPECT/CT in cPHPT was 86.02% (80/93) and 59.37%, in nPHPT (19/32), $p = .003$. No significant differences were seen between the SPECT/CT scan and ultrasonography ($p = .28$) and the agreement was higher in cPHPT than in nPHPT, $p = .03$. Sensitivity of (99m) Tc-Sestamibi-SPECT/CT was 98% on a per-patient basis (PPV 96%) and 91% on a per-lesion basis (PPV 88%). Glandular size was smaller in nPHPT (mean value 6.8 mm) and it was related only with PTH value. CONCLUSION: Localization rate of parathyroid hyperfunctioning tissue with (99m) Tc-Sestamibi SPECT/CT is lower in nPHPT and it is related to a smaller glandular size. However, our study suggests that the positivity rate and sensitivity are nonnegligible by adding SPECT/CT. The reduction in the detection rate in nPHPT could benefit techniques with higher resolution such as (18) F-Choline PET/CT when the clinical context justifies it.

PubMed-ID: [34951035](https://pubmed.ncbi.nlm.nih.gov/34951035/)

<http://dx.doi.org/10.1111/cen.14667>

Removal of Thyroglossal Duct Cyst by a Submental Approach.

World J Surg, 46(6):1431-7.

J. L. Roh. 2022.

BACKGROUND: Thyroglossal duct cyst (TGDC) is the most common congenital cyst in the neck and is removed by the Sistrunk procedure. This surgery involves a horizontal skin incision over the cyst that may leave a noticeable scar on the front of the neck. Therefore, this study examined the clinical outcomes and cosmetic benefits of the Sistrunk procedure by an incision in the submental area that is not easily visible from the front. MATERIALS AND METHODS: This observational study was performed on 152 patients who underwent the Sistrunk procedure by a submental approach to remove TGDC at a university medical center. Intraoperative findings, postoperative complications, subjective pain levels, and satisfaction with incision scars and neck and facial deformities, and recurrence were prospectively evaluated. RESULTS: The length of the submental incision was about 3 cm and the median total operation time was 36 min. Postoperative complications were minimal. Hematoma occurred in two cases (1.3%), surgical site infection in 1 case (0.7%), and dysphagia for more than 1 week occurred in 1 case (0.7%). On a 0-10 visual analogue scale, the pain had a median value of 2 on the first day after surgery, and satisfaction with incision scars and neck and facial deformities showed median values of 8 and 10 at 6 months after surgery, respectively. Recurrence occurred in one patient (0.7%) during the median follow-up period of 68 months. CONCLUSIONS: The submental approach for TGDC excision may be a reliable new surgical method that is safe and has cosmetic advantages. This observational study evaluated the clinical outcomes and cosmetic benefits of the Sistrunk procedure by a submental incision for thyroglossal duct cyst in 152 patients. The surgical procedure showed no increased operation time, no need for wide flap elevation, easy suprahyoid dissection, and an invisible scar in a natural position of the neck.

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<http://dx.doi.org/10.1007/s00268-022-06493-1>

Kidney Stone Events Following Parathyroidectomy vs Nonoperative Management for Primary Hyperparathyroidism.

J Clin Endocrinol Metab, 107(7):e2801-e11.

C. D. Seib, C. Ganesan, K. D. Arnow, A. C. Pao, J. T. Leppert, N. B. Barreto, E. Kebebew and M. Kurella Tamura. 2022.

CONTEXT: Primary hyperparathyroidism (PHPT) is associated with an increased risk of kidney stones. Few studies account for PHPT severity or stone risk when comparing stone events after parathyroidectomy vs nonoperative management.

OBJECTIVE: Compare the incidence of kidney stone events in PHPT patients treated with parathyroidectomy vs nonoperative management. DESIGN: Longitudinal cohort study with propensity score inverse probability weighting and multivariable Cox proportional hazards regression. SETTING: Veterans Health Administration integrated health care system. PATIENTS: A total of 44 978 patients with > 2 years follow-up after PHPT diagnosis (2000-2018); 5244 patients (11.7%) were treated with parathyroidectomy. MAIN OUTCOMES MEASURE: Clinically significant kidney stone event.

RESULTS: The cohort had a mean age of 66.0 years, was 87.8% male, and 66.4% White. Patients treated with parathyroidectomy had higher mean serum calcium (11.2 vs 10.8mg/dL) and were more likely to have a history of kidney stone events. Among patients with baseline history of kidney stones, the unadjusted incidence of = 1 kidney stone event was 30.5% in patients managed with parathyroidectomy (mean follow-up, 5.6 years) compared with 18.0% in those managed nonoperatively (mean follow-up, 5.0 years). Patients treated with parathyroidectomy had a higher adjusted hazard of recurrent kidney stone events (hazard ratio [HR], 1.98; 95% CI, 1.56-2.51); however, this association declined over time (parathyroidectomy \times time: HR, 0.80; 95% CI, 0.73-0.87). CONCLUSION: In this predominantly male cohort with PHPT, patients treated with parathyroidectomy continued to be at higher risk of kidney stone events in the immediate years after treatment than patients managed nonoperatively, although the adjusted risk of stone events declined with time, suggesting a benefit to surgical treatment.

PubMed-ID: [35363858](https://pubmed.ncbi.nlm.nih.gov/35363858/)

<http://dx.doi.org/10.1210/clinem/dgac193>

Adverse Cardiovascular Outcomes Among Older Adults with Primary Hyperparathyroidism Treated with Parathyroidectomy vs. non-operative Management.

Ann Surg,

C. D. Seib, T. Meng, R. M. Cisco, I. Suh, D. T. Lin, A. H. S. Harris, A. W. Trickey, M. K. Tamura and E. Kebebew. 2022.

OBJECTIVE: We sought to compare the incidence of adverse cardiovascular events in older adults with primary hyperparathyroidism (PHPT) treated with parathyroidectomy versus non-operative management. SUMMARY OF BACKGROUND DATA: PHPT is a common endocrine disorder that is associated with increased cardiovascular mortality, but it is not known whether parathyroidectomy reduces the incidence of adverse cardiovascular events. METHODS: We conducted a population-based, longitudinal cohort study of Medicare beneficiaries diagnosed with PHPT (2006-2017). Multivariable, inverse probability weighted Cox proportional hazards regression was used to determine the associations of parathyroidectomy with major adverse cardiovascular events (MACE), cardiovascular disease-related hospitalization, and cardiovascular hospitalization-associated mortality. RESULTS: We identified 210,206 beneficiaries diagnosed with PHPT from 2006-2017. Among 63,136 (30.0%) treated with parathyroidectomy and 147,070 (70.0%) managed non-operatively within one year of diagnosis, the unadjusted incidence of MACE was 10.0% (mean follow-up 59.1 [SD 35.6] months) and 11.5% (mean follow-up 54.1 [SD 34.0] months), respectively. In multivariable analysis, parathyroidectomy was associated with a lower incidence of MACE (HR 0.92 [95%CI 0.90-0.94]), cardiovascular disease-related hospitalization (HR 0.89 [95%CI 0.87-0.91]), and cardiovascular hospitalization-associated mortality (HR 0.76 [95%CI 0.71-0.81]) compared to non-operative management. At 10 years, parathyroidectomy was associated with adjusted absolute risk reduction for MACE of 1.7% (95%CI 1.3%-2.1%), for cardiovascular disease-related hospitalization of 2.5% (95%CI 2.1%-2.9%), and for cardiovascular hospitalization-associated mortality of 1.4% (95%CI 1.2%-1.6%). CONCLUSIONS: In this large, population-based cohort study, parathyroidectomy was associated with a lower long-term incidence of adverse cardiovascular outcomes when compared with non-operative management for older adults with PHPT, which is relevant to surgical decision-making for patients with a long life expectancy.

PubMed-ID: [36005546](https://pubmed.ncbi.nlm.nih.gov/36005546/)

<http://dx.doi.org/10.1097/SLA.0000000000005691>

Is it Time to Obviate Intraoperative Parathyroid Hormone Monitoring in Localized Large Adenomas?

World J Surg, 46(8):1915-6.

S. A. Shah. 2022.

PubMed-ID: [35562541](https://pubmed.ncbi.nlm.nih.gov/35562541/)

<http://dx.doi.org/10.1007/s00268-022-06583-0>

PTH Spikes During Surgical Treatment for Secondary and Tertiary Hyperparathyroidism: A Prospective Observational Study.

World J Surg, 46(7):1693-701.

A. A. Silveira, M. D. G. Brescia, C. P. do Nascimento, F. F. Magnabosco, S. S. Arap and F. L. de Menezes Montenegro. 2022. BACKGROUND: The aim of the present study was to determine whether PTH spikes in renal hyperparathyroidism can interfere with the interpretation of intraoperative PTH monitoring and to determine its frequency and characteristics. METHODS: This was a prospective observational study of consecutive patients who underwent surgical treatment in a single tertiary institution. Patients were divided into two groups: spike and no spike. Patients with secondary and tertiary hyperparathyroidism were analyzed separately. Intraoperative PTH monitoring by venous serial samples: two samples were taken before the excision of the parathyroid gland, and two others were taken after resection. RESULTS: PTH spikes occurred in 23.5% (53 of 226), and their occurrence was similar between secondary and tertiary hyperparathyroidism patients ($p = 0.074$). The relative PTH spike intensity was higher in transplanted patients than in dialysis patients (55 vs. 20%, $p = 0.029$). A characteristic of the secondary hyperparathyroidism patients was the highest frequency of surgical failure (23 vs. 7.5%, $p = 0.016$) and the higher occurrence of supernumerary glands in the spike group (23 vs. 10.3%, $p = 0.035$). Supernumerary parathyroid was associated with surgical failure [19.1 (6.5-55.7) odds ratio [confidence interval], $p < 0.001$). In the studies evaluating the diagnostic test validity for patients on dialysis and experiencing spikes, the most significant impacts were in the sensitivity, accuracy, and negative predictive value of the method. CONCLUSIONS: PTH spikes occurred in up to 23.5% of renal hyperparathyroidism surgical treatments and can negatively influence the intraoperative parathyroid hormone monitoring. Regarding the phenomenon of PTH spikes, it is prudent to think about the possibility of a hyperplastic supernumerary gland.

PubMed-ID: [35262789](https://pubmed.ncbi.nlm.nih.gov/35262789/)

<http://dx.doi.org/10.1007/s00268-022-06506-z>

Surgeon Volume and Outcomes in Primary Hyperparathyroidism-What Is Old Is New Again.

JAMA Surg, 157(7):589.

T. M. Ullmann, M. A. Adam and J. A. Sosa. 2022.

PubMed-ID: [35507376](https://pubmed.ncbi.nlm.nih.gov/35507376/)

<http://dx.doi.org/10.1001/jamasurg.2022.1359>

GCM2 Variants in Familial and Multiglandular Primary Hyperparathyroidism.

J Clin Endocrinol Metab, 107(5):e2021-e6.

S. Vincze, N. V. Peters, C. L. Kuo, T. C. Brown, R. Korah, T. D. Murtha, J. Bellizzi, A. Riccardi, K. Parham, T. Carling, J. Costa-Guda and A. Arnold. 2022.

CONTEXT: Multiglandular and familial parathyroid disease constitute important fractions of primary hyperparathyroidism (PHPT). Germline missense variants of GCM2, a regulator of parathyroid development, were observed in familial isolated hyperparathyroidism and sporadic PHPT. However, as these previously reported GCM2 variants occur at relatively high frequencies in the population, understanding their potential clinical utility will require both additional penetrance data and functional evidence relevant to tumorigenicity. OBJECTIVE: Determine the frequency of GCM2 variants of interest among patients with sporadic multigland or familial parathyroid disease and assess their penetrance. DESIGN AND PATIENTS: DNA-encoding PHPT-associated GCM2 germline variants were polymerase chain reaction-amplified and sequenced from 107 patients with either sporadic multigland or suspected/confirmed familial parathyroid tumors. RESULTS: GCM2 variants were observed in 9 of 107 cases (8.4%): Y282D in 4 patients (6.3%) with sporadic multigland disease; Y394S in 2 patients (11.1%) with familial PHPT and 3 (4.8%) with sporadic multigland disease. Compared with the general population, Y282D was enriched 5.9-fold in multigland disease, but its penetrance was very low (0.02%). Y394S was enriched 79-fold in sporadic multigland disease and 93-fold in familial PHPT, but its penetrance was low (1.33% and 1.04%, respectively). CONCLUSIONS: Observed in vitro-activating GCM2 variant alleles are significantly overrepresented in PHPT patients with multiglandular or familial disease compared to the general population, yet penetrance values are very low; that is, most individuals with these variants in the population have a very low risk of developing PHPT. The potential clinical utility of detecting these GCM2 variants requires further investigation, including assessing their possible role as pathogenic/low-penetrance alleles.

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<http://dx.doi.org/10.1210/clinem/dgab929>

Proactive exploration of inferior parathyroid gland using a novel meticulous thyrothymic ligament dissection technique.
Eur J Surg Oncol, 48(6):1258-63.

X. Wang, Y. Si, J. Cai, H. Lu, H. Tong, H. Zhang, J. Wen and M. Shen. 2022.

INTRODUCTION: The inferior parathyroid gland (IPTG) is widely distributed; effective techniques for its safe exploration and protection during thyroid surgery have not been documented. The thyrothymic ligament (TTL) is a connective tissue located between the thymic tongue and thyroid. This study aims to introduce a novel meticulous thyrothymic ligament dissection technique and assess its role in proactive exploration and situ preservation of IPTG. **MATERIALS AND METHODS:** 737 patients undergoing initial thyroid surgery between 2017 and 2021 in the Department of General Surgery of the First Affiliated Hospital of Nanjing Medical University were retrospectively recruited for this clinical study. In 391 of the recruited patients, the TTL was dissected, and the number and location of IPTG were recorded. Among them, 214 patients underwent total/near-total thyroidectomy (TT) plus central neck dissection (CND) were assigned to the observation group. The control group included 346 consecutive patients who underwent conventional TT plus CND. After 1:1 propensity score matching, each group contained 206 patients. The incidence of postoperative hypoparathyroidism was recorded.

RESULTS: Among the 391 patients, 596 sides were dissected, out of which 436 sides (73.2%) had TTL, and approximately 90.1% of IPTG were located and identified. A statistically significant difference in incidence of temporary (27.7 vs. 49.0%, $P < 0.001$) and permanent hypoparathyroidism (0 vs. 8.2%, $P = 0.047$) was noted between the observation group and the control group. **CONCLUSION:** The meticulous thyrothymic ligament dissection technique helps to protect IPTG in situ and reduce the incidence of postoperative hypoparathyroidism.

PubMed-ID: [35341610](https://pubmed.ncbi.nlm.nih.gov/35341610/)

<http://dx.doi.org/10.1016/j.ejso.2022.03.011>

Adrenals

Meta-Analyses

Interventions for the prevention of adrenal crisis in adults with primary adrenal insufficiency: a systematic review.

Eur J Endocrinol, 187(1):S1-S20.

L. M. Shepherd, K. A. Schmidtke, J. M. Hazlehurst, E. Melson, J. Dretzke, N. Hawks, W. Arlt, A. A. Tahrani, A. Swift and D. M. Carrick-Sen. 2022.

OBJECTIVE: The incidence of adrenal crisis (AC) remains high, particularly for people with primary adrenal insufficiency, despite the introduction of behavioural interventions. The present study aimed to identify and evaluate available evidence of interventions aiming to prevent AC in primary adrenal insufficiency. **DESIGN:** This study is a systematic review of the literature and theoretical mapping. **METHODS:** MEDLINE, MEDLINE in Process, EMBASE, ERIC, Cochrane CENTRAL, CINAHL, PsycINFO, the Health Management Information Consortium and trial registries were searched from inception to November 2021. Three reviewers independently selected studies and extracted data. Two reviewers appraised the studies for the risk of bias. **RESULTS:** Seven observational or mixed methods studies were identified where interventions were designed to prevent AC in adrenal insufficiency. Patient education was the focus of all interventions and utilised the same two behaviour change techniques, 'instruction on how to perform a behaviour' and 'pharmacological support'. Barrier and facilitator themes aiding or hindering the intervention included knowledge, behaviour, emotions, skills, social influences and environmental context and resources. Most studies did not measure effectiveness, and assessment of knowledge varied across studies. The study quality was moderate. **CONCLUSION:** This is an emerging field with limited studies available. Further research is required in relation to the development and assessment of different behaviour change interventions to prevent AC.

PubMed-ID: [35536876](https://pubmed.ncbi.nlm.nih.gov/35536876/)

<http://dx.doi.org/10.1530/EJE-21-1248>

Randomized controlled trials

- None -

Consensus Statements/Guidelines

American Association of Endocrine Surgeons Guidelines for Adrenalectomy: Executive Summary.

JAMA Surg, 157(10):870-7.

L. Yip, Q. Y. Duh, H. Wachtel, C. Jimenez, C. Sturgeon, C. Lee, D. Velazquez-Fernandez, E. Berber, G. D. Hammer, I. Bancos, J. A. Lee, J. Marko, L. F. Morris-Wiseman, M. S. Hughes, M. J. Livhits, M. A. Han, P. W. Smith, S. Wilhelm, S. L. Asa, T. J. Fahey, 3rd, T. J. McKenzie, V. E. Strong and N. D. Perrier. 2022.

IMPORTANCE: Adrenalectomy is the definitive treatment for multiple adrenal abnormalities. Advances in technology and genomics and an improved understanding of adrenal pathophysiology have altered operative techniques and indications. **OBJECTIVE:** To develop evidence-based recommendations to enhance the appropriate, safe, and effective approaches to adrenalectomy. **EVIDENCE REVIEW:** A multidisciplinary panel identified and investigated 7 categories of relevant clinical concern to practicing surgeons. Questions were structured in the framework Population, Intervention/Exposure, Comparison, and Outcome, and a guided review of medical literature from PubMed and/or Embase from 1980 to 2021 was performed. Recommendations were developed using Grading of Recommendations, Assessment, Development and Evaluation methodology and were discussed until consensus, and patient advocacy representation was included. **FINDINGS:** Patients with an adrenal incidentaloma 1 cm or larger should undergo biochemical testing and further imaging characterization. Adrenal protocol computed tomography (CT) should be used to stratify malignancy risk and concern for pheochromocytoma. Routine scheduled follow-up of a nonfunctional adrenal nodule with benign imaging characteristics and unenhanced CT with Hounsfield units less than 10 is not suggested. When unilateral disease is present, laparoscopic adrenalectomy is recommended for patients with primary aldosteronism or autonomous cortisol secretion. Patients with clinical and radiographic findings consistent with adrenocortical carcinoma should be treated at high-volume multidisciplinary centers to optimize outcomes, including, when possible, a complete R0 resection without tumor

disruption, which may require en bloc radical resection. Selective or nonselective a blockade can be used to safely prepare patients for surgical resection of paraganglioma/pheochromocytoma. Empirical perioperative glucocorticoid replacement therapy is indicated for patients with overt Cushing syndrome, but for patients with mild autonomous cortisol secretion, postoperative day 1 morning cortisol or cosyntropin stimulation testing can be used to determine the need for glucocorticoid replacement therapy. When patient and tumor variables are appropriate, we recommend minimally invasive adrenalectomy over open adrenalectomy because of improved perioperative morbidity. Minimally invasive adrenalectomy can be achieved either via a retroperitoneal or transperitoneal approach depending on surgeon expertise, as well as tumor and patient characteristics. **CONCLUSIONS AND RELEVANCE:** Twenty-six clinically relevant and evidence-based recommendations are provided to assist surgeons with perioperative adrenal care.

PubMed-ID: [35976622](https://pubmed.ncbi.nlm.nih.gov/35976622/)

<http://dx.doi.org/10.1001/jamasurg.2022.3544>

Other Articles

Cost-effectiveness of adrenal vein sampling- vs computed tomography-guided adrenalectomy for unilateral adrenaloma in primary aldosteronism.

J Endocrinol Invest, 45(10):1899-908.

S. Arjani, T. J. Bostonian, V. Prasath, P. L. Quinn and R. J. Chokshi. 2022.

PURPOSE: Adrenalectomies performed for the treatment of primary aldosteronism due to unilateral adenoma are traditionally confirmed with, and guided by, results from adrenal vein sampling (AVS). However, the usefulness of AVS at the expense of cost and complications is debated, and many institutions have independent protocols that use AVS to varying degrees. **METHODS:** Cost-effectiveness of AVS- vs computed tomography (CT)-based adrenalectomy was calculated using decision tree models. The tree was populated with values describing biochemical post-operative outcomes from the published literature; patients were placed into AVS- or CT-dependent treatment arms. Biochemical outcomes were defined based on patients' potassium levels and aldosterone-renin ratios. Patients underwent adrenalectomies and received medical management dosed based on surgical outcomes. Costs were represented by Medicare (FY2021) reimbursement rates (US\$) and quality-adjusted life-years (QALYs) were calculated using published morbidity and survival data. A willingness-to-pay of \$100,000 per QALY gained was set to determine the most cost-effective strategy. The primary outcome was the incremental cost-effectiveness ratio (ICER) associated with biochemical outcomes. **RESULTS:** The base case analyses favored the use of AVS-guided care, which cost \$307.65 more but yielded 0.78 more QALYs, resulting in an ICER of \$392.57. These results were upheld by all one-way and two-way sensitivity analyses. In 100,000 random-sampling simulations, AVS-guided care was favored 100% of the time. **CONCLUSIONS:** For patients with primary aldosteronism receiving adrenalectomies with curative intent, the more cost-effective method based on biochemical outcomes is AVS-based care. Recent literature suggests biochemical resolution should be favored over clinical resolution, due to long-term detriments of increased aldosterone independent of clinical symptoms.

PubMed-ID: [35612811](https://pubmed.ncbi.nlm.nih.gov/35612811/)

<http://dx.doi.org/10.1007/s40618-022-01821-7>

Clinical Predictors of Pseudohypoxia-Type Pheochromocytomas.

Ann Surg Oncol, 29(6):3536-46.

J. J. Baechle, P. M. Smith, C. A. Ortega, T. S. Wang, C. C. SolÓrzano and C. M. Kiernan. 2022.

INTRODUCTION: Pheochromocytomas (PCCs) are rare tumors of neural crest origin with divergent transcriptional and metabolic profiles associated with mutational cluster types. Pseudohypoxia-type (PHT) PCCs have a poor prognosis; however diagnostic genetic testing is not always available. We aimed to investigate clinical parameters predictive of PHT PCCs. **METHODS:** Patients who underwent resection and genetic testing for PCC at two academic centers from 2006-2020 were retrospectively studied. Patients with PHT mutations (SDH-AF2/B/C/D, VHL) were compared to non-pseudohypoxia-type (nonPHT) PCCs to identify widely available clinical parameters predictive of PHT PCCs. Demographic, clinical, and pathologic characteristics were compared using student's T and ANOVA tests. Operative hemodynamic instability was defined as systolic blood pressure (SBP) > 200 mmHg, SBP increase of > 30% relative to baseline, and/or heart rate (HR) > 110 bpm. Mann-Whitney U test was used to assess area under the curve (AUC), sensitivity, and specificity. Recursive partitioning was used to model predictive thresholds for PHT PCC and develop a predictive score. **RESULTS:** Of the 79 patients included in the cohort, 17 (22%) had PHT and 62 (78%) had nonPHT PCCs. PCC patients with > 2 of the examined predictive clinical parameters (preoperative weight loss [> 10% body weight], elevated preoperative hematocrit [> 50%],

normal baseline heart rate [< 100 bpm], and normal plasma metanephrines [< 0.60 nmol/L]) were more likely to have PHT PCCs (AUC = 0.831, sensitivity = 0.882, specificity = 0.694, all $p < 0.001$). CONCLUSIONS: Widely available preoperative clinical parameters including indicators of erythropoiesis (hemoglobin, hematocrit, and red blood cell count), baseline heart rate, plasma metanephrines, and weight loss may be useful predictors of PHT PCCs and may help guide management of PCCs when genetic testing is unavailable/delayed.

PubMed-ID: [35233740](https://pubmed.ncbi.nlm.nih.gov/35233740/)

<http://dx.doi.org/10.1245/s10434-022-11419-1>

Primary bilateral macronodular adrenal hyperplasia: definitely a genetic disease.

Nat Rev Endocrinol, 18(11):699-711.

I. P. Cavalcante, A. Berthon, M. C. Fragoso, M. Reincke, C. A. Stratakis, B. Ragazzon and J. Bertherat. 2022.

Primary bilateral macronodular adrenal hyperplasia (PBMAH) is an adrenal cause of Cushing syndrome. Nowadays, a PBMAH diagnosis is more frequent than previously, as a result of progress in the diagnostic methods for adrenal incidentalomas, which are widely available. Although some rare syndromic forms of PBMAH are known to be of genetic origin, non-syndromic forms of PBMAH have only been recognized as a genetic disease in the past 10 years. Genomics studies have highlighted the molecular heterogeneity of PBMAH and identified molecular subgroups, allowing improved understanding of the clinical heterogeneity of this disease. Furthermore, the generation of these subgroups permitted the identification of new genes responsible for PBMAH. Constitutive inactivating variants in *ARMC5* and *KDM1A* are responsible for the development of distinct forms of PBMAH. To date, pathogenic variants of *ARMC5* are responsible for 20-25% of PBMAH, whereas germline *KDM1A* alterations have been identified in $>90\%$ of PBMAH causing food-dependent Cushing syndrome. The identification of pathogenic variants in *ARMC5* and *KDM1A* demonstrated that PBMAH, despite mostly being diagnosed in adults aged 45-60 years, is a genetic disorder. This Review summarizes the important progress made in the past 10 years in understanding the genetics of PBMAH, which have led to a better understanding of the pathophysiology, opening new clinical perspectives.

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<http://dx.doi.org/10.1038/s41574-022-00718-y>

Adrenal Surgery in the Era of Multidisciplinary Endocrine Tumor Boards.

Horm Metab Res, 54(5):294-9.

C. Chiapponi, D. P. D. Santos, M. J. M. Hartmann, M. Schmidt, M. Faust, R. Wahba, C. J. Bruns, A. M. Schultheis and H. Alakus. 2022.

Work up of adrenal masses includes assessment of endocrine activity and malignancy risk. There is no indication for surgical removal of nonfunctional adrenal adenomas, according to the guidelines. In the present study, we aimed at evaluating the impact of a university endocrine tumor board on the quality of the indications for adrenal surgery at our institution. One hundred consecutive patients receiving primary adrenal surgery at the University Hospital of Cologne, Germany were included. Their demographics, clinic-pathologic characteristics, treatment and outcome were analyzed. In 55 (55%) cases, indication for surgery consisted in functional benign tumors, including Conn, Cushing adenomas and pheochromocytomas. Forty (40%) tumors were referred to surgery for malignancy suspicion and 5 (5%) myelolipomas were removed due to their size. Eighty-nine percent of surgeries were performed as minimally invasive procedures. Overall morbidity included two (2%) self-limiting pancreatic fistulas after left laparoscopic adrenalectomy for pheochromocytoma. All functional tumors were confirmed benign by final histology. Only 33 (82.5%) of 40 suspicious cases turned out to be malignant. Consequently, nonfunctional benign adenomas were "unnecessarily" removed in only 7 (7%) patients, with 6 (85.7%) of them having a history of extra-adrenal cancer and all of them fulfilling criteria for surgery, according to the international guidelines. In conclusion, the endocrine tumor board provided an excellent adherence to the guidelines with most surgeries being performed either for functional or malignant tumors. In nonfunctional tumors with history of extra adrenal cancer, CT guided biopsy might be considered for obviating surgery.

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<http://dx.doi.org/10.1055/a-1808-7239>

Residual Adrenal Function After Multivisceral Resection With Adrenalectomy in Adult Patients.

JAMA Surg, 157(5):415-23.

M. Fiore, M. Baia, L. Conti, F. Piccioni, L. Mariani, S. Pasquali, E. Seregini, G. Maltese, M. Galizia, S. Radaelli, A. M. Villa, F. Valenza and A. Gronchi. 2022.

IMPORTANCE: The risk of developing adrenal insufficiency (AI) following adrenalectomy has been insufficiently studied in the context of multivisceral resection (MVR). OBJECTIVE: To evaluate the incidence of AI in patients undergoing MVR with

en bloc adrenalectomy. DESIGN, SETTING, AND PARTICIPANTS: Prospective observational longitudinal study in a single referral center including 56 consecutive adult patients undergoing retroperitoneal sarcoma surgery from June 2019 to August 2020. Those who were candidates for MVR with en bloc adrenalectomy and had no preexisting adrenal impairment were considered eligible. Of these, 4 individuals were excluded because they did not receive adrenalectomy at the time of surgery and 2 because they were not considered evaluable for the main end point. Follow-up was set at 4 months after surgery, and 49 patients completed follow-up. Data were analyzed from October 2020 to September 2021. EXPOSURES: Diagnosis of AI was determined by low-dose (1 µg) adrenocorticotrophic hormone (ACTH) stimulation test with a threshold of 20 µg/dL in blood samples retrieved 30 and 60 minutes after stimulation. ACTH test was repeated on postoperative days 1 and 10 and at 4 months' follow-up. MAIN OUTCOME AND MEASURES: The primary end point was incidence and relevance of AI after MVR. Secondary end points were associations with patient- and tumor-related factors, impact on perioperative hemodynamic management, and association with postoperative morbidity and mortality. RESULTS: Fifty patients (26 female; median [IQR] age, 59 [46-67] years) were evaluable. Incidence of AI was 64% (32 of 50 patients) in the early postoperative period and 38.5% (15 of 39 patients) at follow-up. Patients with AI showed lower postoperative cortisol values. Factors associated with risk of AI at univariate analysis were high American Society of Anesthesiologists score (odds ratio [OR], 0.31; 95% CI, 0.14-0.48) and high malignancy grade (OR, 0.35; 95% CI, 0.24-0.46). Clinical outcomes not associated with AI included morbidity, mortality, reoperation rate, admission to intensive care unit, length of intensive care unit stay, total hospital stay, and long-term quality of life. CONCLUSIONS AND RELEVANCE: In this study, AI after MVR with en bloc adrenalectomy was frequent, even in patients with adequate preoperative adrenal function. Despite this, adrenalectomy can be safely performed. Patients at risk should be monitored in the long term to exclude underrated impairment of adrenal function.

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<http://dx.doi.org/10.1001/jamasurg.2021.7588>

Universal Germline Panel Testing for Individuals With Pheochromocytoma and Paraganglioma Produces High Diagnostic Yield.

J Clin Endocrinol Metab, 107(5):e1917-e23.

C. Horton, H. LaDuca, A. Deckman, K. Durda, M. Jackson, M. E. Richardson, Y. Tian, A. Yussuf, K. Jaspersen and T. Else. 2022.

BACKGROUND: Practice guidelines to identify individuals with hereditary pheochromocytomas and paragangliomas (PPGLs) advocate for sequential gene testing strategy guided by specific clinical features and predate the routine use of multigene panel testing (MGPT). OBJECTIVE: To describe results of MGPT for hereditary PPGL in a clinically and ancestrally diverse cohort. SETTING: Commercial laboratory based in the United States. METHODS: Clinical data and test results were retrospectively reviewed in 1727 individuals who had targeted MGPT from August 2013 through December 2019 because of a suspicion of hereditary PPGL. RESULTS: Overall, 27.5% of individuals had a pathogenic or likely pathogenic variant (PV), 9.0% had a variant of uncertain significance, and 63.1% had a negative result. Most PVs were identified in SDHB (40.4%), followed by SDHD (21.1%), SDHA (10.1%), VHL (7.8%), SDHC (6.7%), RET (3.7%), and MAX (3.6%). PVs in FH, MEN1, NF1, SDHAF2, and TMEM127 collectively accounted for 6.5% of PVs. Clinical predictors of a PV included extra-adrenal location, early age of onset, multiple tumors, and positive family history of PPGL. Individuals with extra-adrenal PGL and a positive family history were the most likely to have a PV (85.9%). Restricting genetic testing to SDHB/C/D misses one-third (32.8%) of individuals with PVs. CONCLUSION: Our data demonstrate a high diagnostic yield in individuals with and without established risk factors, a low inconclusive result rate, and a substantial contribution to diagnostic yield from rare genes. These findings support universal testing of all individuals with PPGL and the use of concurrent MGPT as the ideal platform.

PubMed-ID: [35026032](https://pubmed.ncbi.nlm.nih.gov/35026032/)

<http://dx.doi.org/10.1210/clinem/dgac014>

Morning serum cortisol is superior to salivary cortisone and cortisol in predicting normal adrenal function in suspected adrenal insufficiency.

Clin Endocrinol (Oxf), 96(6):916-8.

T. Kalaria, H. Buch, M. Agarwal, R. Chaudhari, C. Gherman-Ciolac, R. Chopra, V. Okeke, S. Kaur, L. Hughes, H. Sharrod-Cole, C. Ford and R. Gama. 2022.

PubMed-ID: [33290598](https://pubmed.ncbi.nlm.nih.gov/33290598/)

<http://dx.doi.org/10.1111/cen.14388>

We Asked the Experts: How Does a Surgeon Select the Optimal Approach for Minimally Invasive Adrenalectomy?

World J Surg, 46(6):1442-4.

J. Kim and S. Roman. 2022.

PubMed-ID: [35314888](https://pubmed.ncbi.nlm.nih.gov/35314888/)

<http://dx.doi.org/10.1007/s00268-022-06516-x>

Mass spectrometry-based cortisol profiling during adrenal venous sampling reveals misdiagnosis for subtyping primary aldosteronism.

Clin Endocrinol (Oxf), 96(5):680-9.

Y. Ma, H. Chen, F. Chen, J. Jiang, W. Guo, X. Li, X. Gao, Z. Lu, B. Zhou, L. Zhao and X. Li. 2022.

OBJECTIVE: Primary aldosteronism (PA) is a common form of secondary hypertension. Adrenal venous sampling (AVS) is the gold standard for subtyping PA. This study aimed to determine whether there is a difference between immunoassays and liquid chromatography-mass spectrometry (LC-MS/MS) methods for measuring cortisol levels that affect the judgement of AVS. DESIGN: This was a retrospective study. PATIENTS: Included 72 patients who were diagnosed with PA and had undergone AVS. MEASUREMENTS: Patients were grouped according to whether they received adrenocorticotrophic hormone (ACTH) stimulation during AVS, and the cortisol results were measured using immunoassay and LC-MS/MS. RESULTS: There were 48 patients in the without ACTH stimulation group and 24 in the post-ACTH stimulation group during AVS (bilateral adrenal vein cannulation success rate, 56.25% vs. 83.33%). ACTH stimulation was beneficial for increasing the success rate of AVS ($p < .001$). Immunoassays were linearly correlated with LC-MS/MS when cortisol concentrations were <1750 nmol/L ($r = .959$, $p < .001$). When cortisol concentrations were $>17,500$ nmol/L, no correlation was found between the two methods ($p = .093$). The two methods were consistent for the detection of cortisol for evaluating the success of cannulation for AVS. Five percent of patients showed discordant lateralization of aldosterone production according to the cortisol LC-MS/MS and immunoassay results in the without ACTH group, and 15% showed discordant lateralization in the post-ACTH group. CONCLUSIONS: The immunoassay method can be used to determine whether cannulation is successful. The final decision for lateralization may be more appropriate based on LC-MS/MS results.

PubMed-ID: [34970750](https://pubmed.ncbi.nlm.nih.gov/34970750/)

<http://dx.doi.org/10.1111/cen.14666>

Discriminative Capacity of CT Volumetry to Identify Autonomous Cortisol Secretion in Incidental Adrenal Adenomas.

J Clin Endocrinol Metab, 107(5):e1946-e53.

R. Olmos, N. Mertens, A. Vaidya, T. Uslar, P. Fernandez, F. J. Guarda, Z'Òiga, I. San Francisco, A. Huete and R. Baudrand. 2022.

CONTEXT: Incidentally discovered adrenal adenomas are common. Assessment for possible autonomous cortisol excess (ACS) is warranted for all adrenal adenomas, given the association with increased cardiometabolic disease. OBJECTIVE: To evaluate the discriminatory capacity of 3-dimensional volumetry on computed tomography (CT) to identify ACS. METHODS: Two radiologists, blinded to hormonal levels, prospectively analyzed CT images of 149 adult patients with unilateral, incidentally discovered, adrenal adenomas. Diameter and volumetry of the adenoma, volumetry of the contralateral adrenal gland, and the adenoma volume-to-contralateral gland volume (AV/CV) ratio were measured. ACS was defined as cortisol = 1.8 mcg/dL after 1-mg dexamethasone suppression test (DST) and a morning ACTH = 15. pg/mL. RESULTS: We observed that ACS was diagnosed in 35 (23.4%) patients. Cortisol post-DST was positively correlated with adenoma diameter and volume, and inversely correlated with contralateral adrenal gland volume. Cortisol post-DST was positively correlated with the AV/CV ratio ($r = 0.46$, $P < 0.001$) and ACTH was inversely correlated ($r = -0.28$, $P < 0.001$). The AV/CV ratio displayed the highest odds ratio (1.40; 95% CI, 1.18-1.65) and area under curve (0.91; 95% CI, 0.86-0.96) for predicting ACS. An AV/CV ratio = 1 (48% of the cohort) had a sensitivity of 97% and a specificity of 70% to identify ACS. CONCLUSION: CT volumetry of adrenal adenomas and contralateral adrenal glands has a high discriminatory capacity to identify ACS. The combination of this simple and low-cost radiological phenotyping can supplement biochemical testing to substantially improve the identification of ACS.

PubMed-ID: [35020922](https://pubmed.ncbi.nlm.nih.gov/35020922/)

<http://dx.doi.org/10.1210/clinem/dgac005>

Informing therapeutic lymphadenectomy: Location of regional metastatic lymph nodes in adrenocortical carcinoma.

Am J Surg, 223(6):1042-5.

A. Sada, A. E. Glasgow, M. L. Lyden, B. M. Dy, T. R. Foster, E. B. Habermann, I. Bancos and T. J. McKenzie. 2022.

BACKGROUND: The anatomic boundaries of lymphadenectomy for adrenocortical carcinoma (ACC) are not defined.

METHODS: Adults undergoing resection of ACC were included. Locations were categorized based on positive LN locations on final pathology. RESULTS: Of 231 resected ACC, 6% had positive LN during initial resection. Positive LN in left ACC (n = 7) were: 2 para-aortic, 2 left renal-hilar, 1 para-aortic and left renal-hilar and 1 unknown, while for right ACC (n = 7): 2 para-caval, 1 para-caval and right renal-hilar, 1 inter-aortocaval, 1 celiac, 1 para-aortic, and 1 unknown. Of 55 resections for recurrent ACC, positive LN in left ACC (n = 2) were: 1 para-aortic, and 1 para-aortic with left renal-hilar, while LN for right ACC (n = 7): 2 inter-aortocaval, 2 right renal-hilar, 2 para-caval and one retrocrural. CONCLUSION: The most common LN metastases are para-caval for right, and para-aortic and left renal-hilar for left ACC. Further studies are necessary to determine the boundaries of lymphadenectomy in ACC resection.

PubMed-ID: [34696848](https://pubmed.ncbi.nlm.nih.gov/34696848/)

<http://dx.doi.org/10.1016/j.amjsurg.2021.10.014>

The metabolic phenotype of patients with primary aldosteronism: impact of subtype and sex - a multicenter-study of 3566 Caucasian and Asian subjects.

Eur J Endocrinol, 187(3):361-72.

A. Spyroglou, L. Handgriff, L. Müller, P. Schwarzlmüller, M. Parasiliti-Caprino, C. T. Fuss, H. Remde, A. Hirsch, S. M. O'Toole, M. Thuzar, L. Petramala, C. Letizia, E. Deflorenne, L. Amar, R. Vrckovnik, T. Kocjan, C. D. Zhang, D. Li, S. Singh, T. Katabami, T. Yoneda, M. Murakami, N. Wada, N. Inagaki, M. Quinkler, E. Ghigo, M. Maccario, M. Stowasser, W. M. Drake, M. Fassnacht, I. Bancos, M. Reincke, M. Naruse and F. Beuschlein. 2022.

BACKGROUND: Accumulating evidence suggests that primary aldosteronism (PA) is associated with several features of the metabolic syndrome, in particular with obesity, type 2 diabetes mellitus, and dyslipidemia. Whether these manifestations are primarily linked to aldosterone-producing adenoma (APA) or bilateral idiopathic hyperaldosteronism (IHA) remains unclear. The aim of the present study was to investigate differences in metabolic parameters between APA and IHA patients and to assess the impact of treatment on these clinical characteristics. METHODS: We conducted a retrospective multicenter study including 3566 patients with APA or IHA of Caucasian and Asian origin. We compared the prevalence of metabolic disorders between APA and IHA patients at the time of diagnosis and 1-year post-intervention, with special references to sex differences. Furthermore, correlations between metabolic parameters and plasma aldosterone, renin, or plasma cortisol levels after 1 mg dexamethasone (DST) were performed. RESULTS: As expected, APA patients were characterized by higher plasma aldosterone and lower serum potassium levels. Only female IHA patients demonstrated significantly worse metabolic parameters than age-matched female APA patients, which were associated with lower cortisol levels upon DST. One-year post-intervention, female adrenalectomized patients showed deterioration of their lipid profile, when compared to patients treated with mineralocorticoid receptor antagonists. Plasma aldosterone levels negatively correlated with the BMI only in APA patients. CONCLUSIONS: Metabolic alterations appear more prominent in women with IHA. Although IHA patients have worse metabolic profiles, a correlation with cortisol autonomy is documented only in APAs, suggesting an uncoupling of cortisol action from metabolic traits in IHA patients.

PubMed-ID: [35895721](https://pubmed.ncbi.nlm.nih.gov/35895721/)

<http://dx.doi.org/10.1530/EJE-22-0040>

Primary aldosteronism - a multidimensional syndrome.

Nat Rev Endocrinol, 18(11):665-82.

A. F. Turcu, J. Yang and A. Vaidya. 2022.

Primary aldosteronism is a common cause of hypertension and is a risk factor for cardiovascular and renal morbidity and mortality, via mechanisms mediated by both hypertension and direct insults to target organs. Despite its high prevalence and associated complications, primary aldosteronism remains largely under-recognized, with less than 2% of people in at-risk populations ever tested. Fundamental progress made over the past decade has transformed our understanding of the pathogenesis of primary aldosteronism and of its clinical phenotypes. The dichotomous paradigm of primary aldosteronism diagnosis and subtyping is being redefined into a multidimensional spectrum of disease, which spans subclinical stages to florid primary aldosteronism, and from single-focal or multifocal to diffuse aldosterone-producing areas, which can affect one or both adrenal glands. This Review discusses how redefining the primary aldosteronism syndrome as a multidimensional spectrum will affect the approach to the diagnosis and subtyping of primary aldosteronism.

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<http://dx.doi.org/10.1038/s41574-022-00730-2>

Surgical Maneuver and Tactics of Using the Inferior Phrenic Vein as a Landmark in Retroperitoneal Laparoscopic Left Adrenalectomy.

World J Surg, 46(6):1438-41.

F. M. Wang and N. Z. Xing. 2022.

Identification and control of the central adrenal vein (CAV) are key steps in laparoscopic adrenalectomy. However, the retroperitoneal laparoscopic left adrenalectomy (RLLA) lacks identifiable anatomical landmarks and does not have advantage of quickly exposing CAV. Here, we developed surgical maneuver and tactics of using the inferior phrenic vein (IPV) as a landmark in RLLA. During operations, we searched for the IPV between superior margin of renal artery and anterior aspect of psoas major muscle, and then the left IPV was followed and applied as an anatomical landmark to identify the CAV. Moreover, our study showed that variations in the left adrenal venous anatomy occurred in cases with pheochromocytomas. The application of left IPV as a landmark to search for CAV has important clinical significance in RLLA.

PubMed-ID: [35220452](https://pubmed.ncbi.nlm.nih.gov/35220452/)
<http://dx.doi.org/10.1007/s00268-022-06494-0>

Subtyping primary aldosteronism by inconclusive adrenal vein sampling: A derivation and validation study in a tertiary centre.

Clin Endocrinol (Oxf), 97(6):849-59.

K. Zibar Tomic, T. Dusek, A. Alduk, N. Knezevic, V. Molnar, I. Kraljevic, T. Skoric Polovina, A. Balasko, M. Solak, N. Matas, H. Popovac, S. Kralik-Oguic and D. Kastelan. 2022.

OBJECTIVE: Indices based on aldosterone/cortisol (A/C) concentration in the successfully cannulated adrenal vein (AV) and in the inferior vena cava (IVC) (AV/IVC) appear to be possible markers to verify the subtype of primary aldosteronism (PA) in the case of inconclusive results of adrenal vein sampling (AVS). The variability of results in previous studies encouraged us to calculate AV/IVC and adrenal A/C cutoff values that could predict the aetiology of PA. METHODS: This retrospective study included 96 patients who underwent AVS due to PA between 2015 and 2020. The derivation cohort ultimately consisted of 60 patients with bilaterally successful AVS and a clear diagnosis of unilateral or bilateral disease. Receiver operating characteristic analysis was used to find the optimal A/C and AV/IVC cutoff values predicting the subtype of PA. The validation cohort consisted of 11 patients with either unsuccessful cannulation or a borderline lateralization index (LI), those patients underwent adrenalectomy because their indices were suggestive of unilateral disease based on the derivation cohort data. RESULTS: The cutoff values of A/C = 0.63 or AV/IVC = 0.37 identified unaffected glands with a sensitivity of 91.2% and 97.1%, respectively, and a specificity of 90.7% and 88.4%, respectively. Unilateral ipsilateral gland involvement was characterized by A/C = 3.5 or AV/IVC = 3.4 with a corresponding specificity of 100%. All patients in the validation cohort achieved biochemical remission postoperatively. CONCLUSIONS: A/C and AV/IVC cutoff values could be a useful tool to determine the subtype of PA in patients with unilateral successful AVS as well as in patients with a borderline LI.

PubMed-ID: [35781892](https://pubmed.ncbi.nlm.nih.gov/35781892/)
<http://dx.doi.org/10.1111/cen.14794>

NET

Meta-Analyses

- None -

Randomized controlled trials

Everolimus with or without bevacizumab in advanced pNET: CALGB 80701 (Alliance).

Endocr Relat Cancer, 29(6):335-44.

M. H. Kulke, F. S. Ou, D. Niedzwiecki, L. Huebner, P. Kunz, H. F. Kennecke, E. M. Wolin, J. A. Chan, E. M. O'Reilly, J. A. Meyerhardt and A. Venook. 2022.

Treatment with the MTOR inhibitor everolimus improves progression-free survival (PFS) in pancreatic neuroendocrine tumors (pNETs), but it is not known if the addition of a VEGF pathway inhibitor to an MTOR inhibitor enhances antitumor activity. We performed a randomized phase II study evaluating everolimus with or without bevacizumab in patients with advanced pNETs. One hundred and fifty patients were randomized to receive everolimus 10 mg daily with or without bevacizumab 10 mg/kg i.v. every 2 weeks. Patients also received standard dose of octreotide in both arms. The primary endpoint was PFS, based on local investigator review. Treatment with the combination of everolimus and bevacizumab resulted in improved progression-free survival compared to everolimus (16.7 months compared to 14.0 months; one-sided stratified log-rank $P = 0.1028$; hazard ratio (HR) 0.80 (95% CI 0.56-1.13)), meeting the predefined primary endpoint. Confirmed tumor responses were observed in 31% (95% CI 20%, 41%) of patients receiving combination therapy, as compared to only 12% (95% CI 5%, 19%) of patients receiving treatment with everolimus ($P = 0.0053$). Median overall survival duration was similar in the everolimus and combination arm (42.5 and 42.1 months, respectively). Treatment-related toxicities were more common in the combination arm. In summary, treatment with everolimus and bevacizumab led to superior PFS and higher response rates compared to everolimus in patients with advanced pNETs. Although the higher rate of treatment-related adverse events may limit the use of this combination, our results support the continued evaluation of VEGF pathway inhibitors in pNETs.

PubMed-ID: [35324465](https://pubmed.ncbi.nlm.nih.gov/35324465/)

<http://dx.doi.org/10.1530/ERC-21-0239>

Consensus Statements/Guidelines

- None -

Other Articles

Role of chromogranin A-derived fragments after resection of nonfunctioning pancreatic neuroendocrine tumors.

J Endocrinol Invest, 45(6):1209-17.

V. Andreasi, S. Partelli, M. F. Manzoni, F. Muffatti, L. Di Filippo, S. Crippa, A. Corti and M. Falconi. 2022.

PURPOSE: No single reliable biomarker is available for nonfunctioning pancreatic neuroendocrine tumors (NF-PanNETs). Vasostatin-1 (VS-1), the N-terminal fragment of chromogranin A (CgA), seems to be a more accurate biomarker compared to its precursor. Primary aim was to investigate the ability of VS-1, compared to total-CgA, to assess the effectiveness of surgical resection performed for NF-PanNETs. Secondary aim was to evaluate two additional CgA-derived fragments, pancreastatin (PST) and vasostatin-2 (VS-2), as possible biomarkers for NF-PanNETs. **METHODS:** Consecutive patients who underwent surgery for NF-PanNETs at San Raffaele Scientific Institute were included (n = 35). Plasma levels of CgA and CgA-derived fragments were measured by Enzyme-Linked ImmunoSorbent Assay (ELISA), preoperatively and postoperatively. **RESULTS:** Preoperative VS-1 was significantly higher compared to VS-1 measured on postoperative day 5 (POD5) (pre: 0.338 nM versus POD5: 0.147 nM, $P < 0.001$), whereas total-CgA significantly increased after surgery (pre: 1.123 nM versus POD5: 1.949 nM, $P = 0.006$). Overall, 24 patients showed = 1 feature of tumor aggressiveness (T3-T4, nodal/distant metastases, Ki67 > 5%, microvascular/perineural invasion, necrosis). The median percentage decrease in VS-1 plasma levels was 63% (IQR 28-88%) among patients with aggressive tumors, compared to 13% (IQR 0-57%) in the remaining population ($P = 0.033$). No significant differences in terms of PST ($P = 0.870$) and VS-2 ($P = 0.909$) were observed

between preoperative and postoperative time. CONCLUSION: VS-1 provides an early assessment of surgical efficacy in patients who undergo resection for NF-PanNETs, especially in those with aggressive neoplasms. Total-CgA, PST and VS-2 have no clinical utility in this setting.

PubMed-ID: [35122631](https://pubmed.ncbi.nlm.nih.gov/35122631/)

<http://dx.doi.org/10.1007/s40618-022-01750-5>

Is There a Role for Surgical Resection of Grade 3 Neuroendocrine Neoplasms?

Ann Surg Oncol, 29(11):6936-46.

L. C. Borbon, C. G. Tran, S. K. Sherman, P. H. Ear, C. Chandrasekharan, A. M. Bellizzi, J. S. Dillon, T. M. O'Dorisio and J. R. Howe. 2022.

BACKGROUND: Grade 3 (G3) gastroenteropancreatic (GEP) neuroendocrine neoplasms (NENs) are aggressive tumors with poor survival outcomes for which medical management is generally recommended. This study sought to evaluate outcomes of surgically treated G3 GEP-NEN patients. METHODS: A single-institutional prospective NEN database was reviewed. Patients with G3 GEP-NENs based on World Health Organization (WHO) 2019 definitions included well-differentiated neuroendocrine tumors (G3NET) and poorly differentiated neuroendocrine carcinomas (G3NEC). Clinicopathologic factors were compared between groups. Overall survival from G3 diagnosis was assessed by the Kaplan-Meier method. RESULTS: Surgical resection was performed for 463 patients (211 G1, 208 G2, 44 G3). Most had metastatic disease at presentation (54% G1, 69% G2, 91% G3; $p < 0.001$). The G3 cohort included 39 G3NETs and 5 G3NECs, 22 of pancreatic and 22 of midgut origin. Median overall survival (mOS; in months) was 268.1 for G1NETs, 129.9 for G2NETs, 50.5 for G3NETs, and 28.5 for G3NECs ($p < 0.001$). Over the same period, 31 G3 patients (12 G3NETs, 19 G3NECs) were treated non-surgically, with mOS of 19.0 for G3NETs and 12.4 for G3NECs. CONCLUSIONS: Surgical resection of G3 GEP-NENs remains controversial due to poor prognosis, and surgical series are rare. This large, single-institutional study found significantly lower mOS in patients with resected G3NENs than those with G1/G2 tumors, reflecting more aggressive tumor biology and a higher proportion with metastatic disease. The mOS for resected G3NETs and G3NECs exceeded historical non-surgical G3NEN series (mOS 11-19 months), suggesting surgery should be considered in carefully selected patients with G3NENs, especially those with well-differentiated tumors.

PubMed-ID: [35802214](https://pubmed.ncbi.nlm.nih.gov/35802214/)

<http://dx.doi.org/10.1245/s10434-022-12100-3>

Safety and Outcomes of Combined Pancreatic and Hepatic Resections for Metastatic Pancreatic Neuroendocrine Tumors.

Ann Surg Oncol, 29(11):6949-57.

H. Gudmundsdottir, R. Pery, R. P. Graham, C. A. Thiels, S. G. Warner, R. L. Smoot, M. J. Truty, M. L. Kendrick, T. R. Halfdanarson, E. B. Habermann, D. M. Nagorney and S. P. Cleary. 2022.

BACKGROUND: Approximately 40-50% of patients with pancreatic neuroendocrine tumors (pNETs) initially present with distant metastases. Little is known about the outcomes of patients undergoing combined pancreatic and hepatic resections for this indication. METHODS: Patients who underwent hepatectomy for metastatic pNETs at Mayo Clinic Rochester from 2000 to 2020 were retrospectively reviewed. Major pancreatectomy was defined as pancreaticoduodenectomy or total pancreatectomy, and major hepatectomy as right hepatectomy or trisegmentectomy. Characteristics and outcomes of patients who underwent pancreatectomy with simultaneous hepatectomy were compared with those of patients who underwent isolated hepatectomy (with or without prior history of pancreatectomy). RESULTS: 205 patients who underwent hepatectomy for metastatic pNETs were identified: 131 underwent pancreatectomy with simultaneous hepatectomy and 74 underwent isolated hepatectomy. Among patients undergoing simultaneous hepatectomy, 89 patients underwent minor pancreatectomy with minor hepatectomy, 11 patients underwent major pancreatectomy with minor hepatectomy, 30 patients underwent minor pancreatectomy with major hepatectomy, and 1 patient underwent major pancreatectomy with major hepatectomy. Patients undergoing simultaneous hepatectomy had more numerous liver lesions (10 or more lesions in 54% vs. 34%, $p = 0.008$), but the groups were otherwise similar. Rates of any major complications (31% versus 24%, $p = 0.43$), hepatectomy-specific complications such as bile leak, hemorrhage, and liver failure (0.8-7.6% vs. 1.4-12%, $p = 0.30-0.99$), and 90-day mortality (1.5% vs. 2.7%, $p = 0.62$) were similar between the two groups. 5-year overall survival was 64% after combined resections and 65% after isolated hepatectomy ($p = 0.93$). CONCLUSION: For patients with metastatic pNETs, combined pancreatic and hepatic resections can be performed with acceptable morbidity and mortality in selected patients at high-volume institutions.

PubMed-ID: [35731358](https://pubmed.ncbi.nlm.nih.gov/35731358/)

<http://dx.doi.org/10.1245/s10434-022-12029-7>

Sequencing of Therapies in Progressive Neuroendocrine Tumors.

Ann Surg Oncol, 29(11):6501-3.

J. R. Howe. 2022.

PubMed-ID: [35816247](https://pubmed.ncbi.nlm.nih.gov/35816247/)

<http://dx.doi.org/10.1245/s10434-022-12149-0>

International survey on opinions and use of minimally invasive surgery in small bowel neuroendocrine neoplasms.

Eur J Surg Oncol, 48(6):1251-7.

E. Kaçmaz, A. F. Engelsman, W. A. Bemelman, P. J. Tanis and E. J. M. Nieveen van Dijkum. 2022.

INTRODUCTION: Although minimally invasive surgery is becoming the standard technique in gastrointestinal surgery, implementation for small bowel neuroendocrine neoplasms (SB-NEN) is lagging behind. The aim of this international survey was to gain insights into attitudes towards minimally invasive surgery for resection of SB-NEN and current practices. METHODS: An anonymous survey was sent to surgeons between February and May 2021 via (neuro)endocrine and colorectal societies worldwide. The survey consisted of questions regarding experience of the surgeon with minimally invasive SB-NEN resection and training. RESULTS: A total of 58 responses from five societies across 20 countries were included. Forty-one (71%) respondents worked at academic centers. Thirty-seven (64%) practiced colorectal surgery, 24 (41%) endocrine surgery and 45 (78%) had experience in advanced minimally invasive surgery. An open, laparoscopic or robotic approach was preferred by 23 (42%), 24 (44%), and 8 (15%) respondents, respectively. Reasons to opt for a minimally invasive approach were mainly related to peri-operative benefits, while an open approach was preferred for optimal mesenteric lymphadenectomy and tactile feedback. Additional training in minimally invasive SB-NEN resection was welcomed by 29 (52%) respondents. Forty-three (74%) respondents were interested in collaborating in future studies, with a cumulative median (IQR) annual case load of 172 (86-258). CONCLUSIONS: Among respondents, 69% applies minimally invasive surgery for resection of SB-NEN. Arguments for specific operative approaches differ, and insufficient training in advanced laparoscopic techniques seems to be a barrier. Future collaborative studies can provide better insight in selection criteria and optimal technique.

PubMed-ID: [34823919](https://pubmed.ncbi.nlm.nih.gov/34823919/)

<http://dx.doi.org/10.1016/j.ejso.2021.11.011>

Surgical Treatment of Patients with Poorly Differentiated Pancreatic Neuroendocrine Carcinoma: An NCDDB Analysis.

Ann Surg Oncol, 29(6):3522-31.

S. R. Kaslow, G. A. Vitiello, K. Prendergast, L. Hani, S. M. Cohen, C. Wolfgang, R. S. Berman, A. Y. Lee and C. Correa-Gallego. 2022.

BACKGROUND: Consensus guidelines discourage resection of poorly differentiated pancreatic neuroendocrine carcinoma (panNEC) given its association with poor long-term survival. This study assessed treatment patterns and outcomes for this rare malignancy using the National Cancer Database (NCDDB). METHODS: Patients with non-functional pancreatic neuroendocrine tumors in the NCDDB (2004-2016) were categorized based on pathologic differentiation. Logistic and Cox proportional hazard regressions identified associations with resection and overall survival (OS). Survival was compared using Kaplan-Meier and log-rank tests. RESULTS: Most patients (83%) in the cohort of 8560 patients had well-differentiated tumors (panNET). The median OS was 47 months (panNET, 63 months vs panNEC, 17 months; $p < 0.001$). Surgery was less likely for older patients (odds ratio [OR], 0.97), patients with panNEC (OR, 0.27), and patients with metastasis at diagnosis (OR, 0.08) (all $p < 0.001$). After propensity score-matching of these factors, surgical resection was associated with longer OS (82 vs 29 months; $p < 0.001$) and a decreased hazard of mortality (hazard ratio [HR], 0.37; $p < 0.001$). Surgery remained associated with longer OS when stratified by differentiation (98 vs 41 months for patients with panNET and 36 vs 8 months for patients with panNEC). Overall survival did not differ between patients with panNEC who underwent surgery and patients with panNET who did not (both 39 months; $p = 0.294$). CONCLUSIONS: Poorly differentiated panNEC exhibits poorer survival than well-differentiated panNET. In the current cohort, surgical resection was strongly and independently associated with improved OS, suggesting that patients with panNEC who are suitable operative candidates should be considered for multimodality therapy, including surgery.

PubMed-ID: [35246811](https://pubmed.ncbi.nlm.nih.gov/35246811/)

<http://dx.doi.org/10.1245/s10434-022-11477-5>

First Differentiate and Then Operate (Or Not) : Editorial on "Surgical Treatment of Patients with Poorly Differentiated Pancreatic Neuroendocrine Carcinoma: An NCDB Analysis".

Ann Surg Oncol, 29(6):3371-2.

X. M. Keutgen. 2022.

PubMed-ID: [35230582](https://pubmed.ncbi.nlm.nih.gov/35230582/)

<http://dx.doi.org/10.1245/s10434-022-11490-8>

Continuing challenges of primary neuroendocrine tumours of the thymus: A concisereview.

Eur J Surg Oncol, 48(12):2360-8.

J. Lau, T. Ioan Cvasciuc, D. Simpson, C. d. J. M and R. Parameswaran. 2022.

Primary neuroendocrine tumours of the thymus (NETTs) are exceedingly rare tumours, usually presenting around mid-life, which have a propensity towards males and smokers. They are seen more often in those with MEN-1, but multiple different genetic mutations have been found to be involved in the tumorigenesis of NETTs. Histologically, NETTs are classified according to number of mitoses, the presence of necrosis, and the presence or absence of small cell features. NETTs display a wide spectrum of behavior, and they can be incidentally found on chest imaging, on screening in MEN-1, or present with symptoms of local compression. Advanced disease and paraneoplastic syndromes are common. CT-, PET/CT-, MRI-scans, and somatostatin receptor scintigraphy are the imaging modalities of choice both for the initial assessment as well as for monitoring after treatment. For patients with localized disease, complete surgical resection with lymphadenectomy provides the best chance of long-term, disease-free survival, and can be achieved through either an open or thoracoscopic approach. While chemotherapy-regimens based on platinum, taxane, and temozolomide are used most often, the optimum chemotherapy regimen in the adjuvant and palliative settings remains unclear, as does the role of radiotherapy. Ongoing research on the most effective use of somatostatin analogues, peptide receptor radionuclide therapy (PPRT), kinase inhibitors and immunotherapy in patients with other types of advanced neuroendocrine tumours may lead to further treatment options for NETTs in the future.

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<http://dx.doi.org/10.1016/j.ejso.2022.07.017>

Primary Tumor Resection is Associated with Improved Disease-Specific Mortality in Patients with Stage IV Small Intestinal Neuroendocrine Tumors (NETs): A Comparison of Upfront Surgical Resection Versus a Watch and Wait Strategy in Two Specialist NET Centers.

Ann Surg Oncol, 29(12):7822-32.

S. Levy, J. D. Arthur, M. Banks, N. F. M. Kok, S. W. Fenwick, R. Diaz-Nieto, M. E. van Leerdam, D. J. Cuthbertson, G. D. Valk, K. F. D. Kuhlmann and M. E. T. Tesselaar. 2022.

INTRODUCTION: Small intestinal neuroendocrine tumors (SI-NETs) often present with metastatic disease. An ongoing debate exists on whether to perform primary tumor resection (PTR) in patients with stage IV SI-NETs, without symptoms of the primary tumor and inoperable metastatic disease. OBJECTIVE: The aim of this study was to compare a treatment strategy of upfront surgical resection versus a surveillance strategy of watch and wait. METHODS: This was a retrospective cohort study of patients with stage IV SI-NETs at diagnosis, between 2000 and 2018, from two tertiary referral centers (Netherlands Cancer Institute [NKI] and Aintree University Hospital [AUH]) who had adopted contrasting treatment approaches: upfront surgical resection and watch and wait, respectively. Patients without symptoms related to the primary tumor were included. Multivariable intention-to-treat (ITT), per-protocol (PP), and instrumental variable (IV) analyses using 'institute' as an IV were performed to assess the influence of PTR on disease-specific mortality (DSM). RESULTS: A total of 557 patients were identified, with 145 patients remaining after exclusion of stage I-III disease or symptoms of the primary tumor (93 from the NKI and 52 from AUH). The cohorts differed in performance status (PS; $p = 0.006$) and tumor grade ($p < 0.001$). PTR was independently associated with reduced DSM irrespective of statistical methods employed: ITT hazard ratio [HR] 0.60, $p = 0.005$; PP HR 0.58, $p < 0.001$; and IV HR 0.07, $p = 0.019$. Other factors associated with DSM were age, PS, high chromogranin A, and somatostatin analog treatment. CONCLUSION: Taking advantage of contrasting institutional treatment strategies, this study identified PTR as an independent predictor of DSM. Future prospective studies should aim to validate these results.

PubMed-ID: [35842528](https://pubmed.ncbi.nlm.nih.gov/35842528/)

<http://dx.doi.org/10.1245/s10434-022-12030-0>

Primary Breast Neuroendocrine Tumors: An Analysis of the National Cancer Database.

Ann Surg Oncol, 29(10):6339-46.

E. O. Martinez, J. M. Jorns, A. L. Kong, J. Kijak, W. Y. Lee, C. C. Huang and C. S. Cortina. 2022.

BACKGROUND: Primary breast neuroendocrine tumors (BNETs) represent < 1% of breast cancers. Diagnosing BNETs can be challenging, and a limited amount of cohort data currently exists in literature. We aimed to describe primary BNET characteristics, treatment modalities, and survival outcomes through the National Cancer Database (NCDB). **METHODS:** A retrospective cohort analysis was performed using the NCDB from 2004 to 2017. BNET cases were compared with patients with invasive ductal carcinoma (IDC). A matched IDC cohort was created by matching patient age, race, and disease stage. Kaplan-Meier analysis was performed, and hazard ratios (HR) were calculated through the bootstrap sampling method. **RESULTS:** A total of 1389 BNET and 1,967,401 IDC cases were identified. When compared with IDC patients, BNET patients were older, had more comorbidities, and were more often male ($p < 0.01$). BNETs were larger, higher grade, and more frequently hormone receptor negative ($p < 0.01$). While BNET patients were treated with surgery and radiotherapy ($p < 0.01$) less often compared with IDC patients, they presented at later disease stage ($p < 0.001$) and received systemic treatment more frequently (53.5% vs. 40%, $p < 0.01$). Patients with BNET had increased mortality compared with the matched IDC cohort: stage 1 HR 1.8, stage 2 HR 2.0, stage 3 HR 1.8, and stage 4 HR 1.5 ($p < 0.001$ for all). **CONCLUSION:** Patients with BNET tend to present at higher clinical stages, are more frequently hormone receptor negative, and have inferior overall survival compared with patients with IDC. Further treatment strategies and studies are needed to elucidate optimal therapies to maximize patient outcomes.

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<http://dx.doi.org/10.1245/s10434-022-12123-w>

ASO Visual Abstract: Radical Resection in Enteropancreatic Neuroendocrine Tumors-Recurrence-Free Survival Rate and Definition of a Risk Score for Recurrence.

Ann Surg Oncol, 29(9):5580-1.

E. Merola, A. Pascher, A. Rinke, D. K. Bartsch, A. Zerbi, G. Nappo, C. Carnaghi, M. Ciola, M. G. McNamara, W. Zandee, E. Bertani, S. Marcucci, R. Modica, R. Gr_tzmann, N. Fazio, W. de Herder, J. W. Valle, T. M. Gress, G. Delle Fave, G. de Pretis, A. Perren, B. Wiedenmann and M. E. Pavel. 2022.

PubMed-ID: [35789310](https://pubmed.ncbi.nlm.nih.gov/35789310/)

<http://dx.doi.org/10.1245/s10434-022-12049-3>

Radical Resection in Entero-Pancreatic Neuroendocrine Tumors: Recurrence-Free Survival Rate and Definition of a Risk Score for Recurrence.

Ann Surg Oncol, 29(9):5568-77.

E. Merola, A. Pascher, A. Rinke, D. K. Bartsch, A. Zerbi, G. Nappo, C. Carnaghi, M. Ciola, M. G. McNamara, W. Zandee, E. Bertani, S. Marcucci, R. Modica, R. Gr_tzmann, N. Fazio, W. de Herder, J. W. Valle, T. M. Gress, G. D. Fave, G. de Pretis, A. Perren, B. Wiedenmann and M. E. Pavel. 2022.

BACKGROUND: Surgery with radical intent is the only potentially curative option for entero-pancreatic neuroendocrine tumors (EP-NETs) but many patients develop recurrence even after many years. The subset of patients at high risk of disease recurrence has not been clearly defined to date. **OBJECTIVE:** The aim of this retrospective study was to define, in a series of completely resected EP-NETs, the recurrence-free survival (RFS) rate and a risk score for disease recurrence. **PATIENTS AND METHODS:** This was a multicenter retrospective analysis of sporadic pancreatic NETs (PanNETs) or small intestine NETs (SiNETs) [G1/G2] that underwent R0/R1 surgery (years 2000-2016) with at least a 24-month follow-up. Survival analysis was performed using the Kaplan-Meier method and risk factor analysis was performed using the Cox regression model. **RESULTS:** Overall, 441 patients (224 PanNETs and 217 SiNETs) were included, with a median Ki67 of 2% in tumor tissue and 8.2% stage IV disease. Median RFS was 101 months (5-year rate 67.9%). The derived prognostic score defined by multivariable analysis included prognostic parameters, such as TNM stage, lymph node ratio, margin status, and grading. The score distinguished three risk categories with a significantly different RFS ($p < 0.01$). **CONCLUSIONS:** Approximately 30% of patients with EP-NETs recurred within 5 years after radical surgery. Risk factors for recurrence were disease stage, lymph node ratio, margin status, and grading. The definition of risk categories may help in selecting patients who might benefit from adjuvant treatments and more intensive follow-up programs.

PubMed-ID: [35583694](https://pubmed.ncbi.nlm.nih.gov/35583694/)

<http://dx.doi.org/10.1245/s10434-022-11837-1>

Treatment Response and Clinical Outcomes of Well-Differentiated High-Grade Neuroendocrine Tumors to Lutetium-177-DOTATATE.

Neuroendocrinology, 112(12):1177-86.

N. Raj, K. Coffman, T. Le, R. K. G. Do, J. Rafailov, Y. Choi, J. F. Chou, M. Capanu, M. Dunphy, J. J. Fox, R. K. Grewal, R. P. Reddy, C. Riedl, H. Schoder, L. Bodei and D. Reidy-Lagunes. 2022.

INTRODUCTION: Lutetium-177 (177Lu)-DOTATATE received FDA approval in 2018 to treat somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (NETs). Little data are available on response and outcomes for well-differentiated (WD) high-grade (HG) NETs treated with 177Lu-DOTATATE. MATERIALS AND METHODS: Patients with WD HG NETs treated with 177Lu-DOTATATE at MSK from 2018 to 2020 were identified. Demographics, response (RECIST 1.1), and progression-free survival (PFS) were determined. Next-generation sequencing (NGS) was performed in the archival tumor. RESULTS: Nineteen patients, all with progressive, heavily treated disease, were identified. Sites of tumor origin were: pancreas (74%), small bowel (11%), rectum (11%), and lung (5%); median Ki-67 was 32% (range 22-56). Thirteen patients (68%) completed all four 177Lu-DOTATATE cycles. Best response (N = 18 evaluable) was: 5/18 (28%) partial response, 8/18 (44%) stable disease, and 5/18 (28%) disease progression. Median PFS was 13.1 months (95% CI: 8.7-20.9). Most common treatment-related toxicities were thrombocytopenia (9 patients, 47%; G3/4, 1 patient, 5%), anemia (7 patients, 37%; G3/4, 2 patients, 11%), leukopenia (6 patients, 32%; G3/4, 0 patients), and liver function test elevation (4 patients, 21%; G3/4, 0 patients). NGS results were available from 13/19 tumors (68%). The most observed alterations were in MEN1 (6/13, 46%) and DAXX (4/13, 31%). No RB1 alterations identified. CONCLUSION: We observed a meaningful disease control rate of 72% during treatment of WD HG NETs with 177Lu-DOTATATE. In this heavily pre-treated population, more than half of patients received all four treatment cycles with toxicities largely bone marrow-related. As would be expected in WD NETs, the vast majority had alterations in chromatin remodeling genes and no RB1 alterations.

PubMed-ID: [35609558](https://pubmed.ncbi.nlm.nih.gov/35609558/)

<http://dx.doi.org/10.1159/000525216>

The management of small nonfunctional pancreatic neuroendocrine tumors: It's time to define the high-risk features.

J Surg Oncol, 126(6):1135-6.

Q. Tan, X. Chengzhi and Y. Chen. 2022.

PubMed-ID: [36004442](https://pubmed.ncbi.nlm.nih.gov/36004442/)

<http://dx.doi.org/10.1002/jso.27025>

Comprehensive Clinical Analysis of Gallbladder Neuroendocrine Neoplasms: A Large-Volume Multicenter Study During One Decade.

Ann Surg Oncol, 29(12):7619-30.

Y. Wang, B. Huang, Q. Fu, J. Wang, M. Ye, M. Hu, K. Qu, K. Liu, X. Hu, S. Wei, K. Sun, W. Xiao, B. Zhang, H. Li, J. Li, Q. Zhang and T. Liang. 2022.

BACKGROUND: This study aimed to comprehensively investigate the clinicopathologic characteristics and therapeutic situations of gallbladder neuroendocrine neoplasms (GB-NENs) in the real world via a multicenter, large-scale cohort study. METHODS: The study searched for patients in 143 hospitals in China and enrolled 154 patients with GB-NENs diagnosed in 40 hospitals between 2004 and 2021. Clinicopathologic characteristics and therapeutic approaches were analyzed retrospectively. RESULTS: The median age at the initial diagnosis of the patients with GB-NENs was 63 years (range 33-83 years), and 61.7% of the patients were women. Tumor-node-metastasis staging classified 92 patients as stage 3 or above. Based on the 2019 World Health Organization classification, 96 cases (62.3%) were confirmed pathologically as poorly differentiated neuroendocrine carcinomas, 13 cases (8.4%) as well-differentiated neuroendocrine tumors, and 45 cases as mixed neuroendocrine-non-neuroendocrine neoplasms. The liver was the most frequent metastatic site. Immunohistochemistry showed that synaptophysin was most frequently positive (80.4%), followed by chromogranin A (61.7%), and CD56 (58.4%). Computed tomography and magnetic resonance imaging showed more common clear boundaries (25/39 cases) and invasive growth features (27 cases). None of these cases had an accurate diagnosis before surgery, with a misdiagnosis rate of 100%. Surgical resection is the main treatment, and platinum-based chemotherapeutic regimens were preferred as adjuvant therapies for patients with GB-NENs. The available survival data for 74 patients showed an overall survival rate of 59% at 1 year, 33% at 3 years, and 29% at 5 years. No significant difference was found between the patients treated with and those treated without adjuvant chemotherapy.

CONCLUSIONS: Gallbladder neuroendocrine neoplasms have high malignancy and a poor prognosis. Importantly, this large-scale cohort study significantly improves our understanding of GB-NENs and will benefit the exploration of its mechanism and treatment modes. Further investigation is necessary to explore the management of this disease.

PubMed-ID: [35849293](https://pubmed.ncbi.nlm.nih.gov/35849293/)
<http://dx.doi.org/10.1245/s10434-022-12107-w>

ASO Visual Abstract: Comprehensive Clinical Analysis of Gallbladder Neuroendocrine Neoplasms-A Large-Volume Multicenter Study over One Decade.

Ann Surg Oncol, 29(12):7632-3.

Y. Wang, Q. Zhang and T. Liang. 2022.

PubMed-ID: [35896918](https://pubmed.ncbi.nlm.nih.gov/35896918/)
<http://dx.doi.org/10.1245/s10434-022-12289-3>

Risk factors for metastasis and survival of patients with T1 gastric neuroendocrine carcinoma treated with endoscopic therapy versus surgical resection.

Surg Endosc, 36(8):6162-9.

H. Ye, Y. Yuan, P. Chen and Q. Zheng. 2022.

BACKGROUND: Gastrectomy with lymphadenectomy is recommended for early gastric Neuroendocrine carcinoma (G-NEC). We attempted to determine the prevalence and risk factors of metastasis of T1 G-NEC and compare the long-term survival of patients after receiving endoscopic therapy (ET) and radical surgery. METHODS: In this study, 205 patients in total with T1 G-NEC were collected from the Surveillance Epidemiology and End Result database. Independent predictors of metastasis were identified by Logistic regression analysis, followed by the calculation of both cancer-specific survival (CSS) and overall survival (OS). RESULTS: Twenty-five patients (12.2%) were burdened with metastasis at initial diagnosis, with a prevalence of 5.2% (3/58) in mucosa lesions and 16.2% (16/99) in submucosa lesions (P = 0.045). No metastasis was detected in lesions with mucosa involvement and tumors \leq 20 mm (0%, 0/49). The most significant risk factor for metastasis was tumors $>$ 20 mm [odds ratio (OR) 18.64; 95% confidence interval (CI) 4.01-86.68; P < 0.001]. For patients with T1N0M0 G-NEC who received ET or surgery, the 10-year OS was similar between the mucosa extension and submucosa extension groups, which was 91.56% in ET group vs 87.50% in surgery group (P = 0.62) and 57.33% vs 77.83% (P = 0.11), respectively. In addition, the 10-year CSS was also similar between the mucosa extension and submucosa extension groups with 97.30% in ET vs 100% in surgery (P = 0.51) and 97.62% vs 86.49% (P = 0.65). CONCLUSIONS: In G-NEC, tumors $>$ 20 mm were considered as the most significant risk factor for metastasis. ET seemed adequate for the lesions with mucosa involvement and size \leq 2 cm.

PubMed-ID: [35507062](https://pubmed.ncbi.nlm.nih.gov/35507062/)
<http://dx.doi.org/10.1007/s00464-022-09190-1>

Minimally Invasive vs Open Pancreatectomy for Pancreatic Neuroendocrine Tumors: Multi-Institutional 10-Year Experience of 1,023 Patients.

J Am Coll Surg, 235(2):315-30.

J. Zheng, A. Pulvirenti, A. A. Javed, T. Michelakos, A. Panizza, K. K. Lee, C. R. Ferrone, A. C. Wei, J. He and A. H. Zureikat. 2022.

BACKGROUND: Resection of pancreatic neuroendocrine tumors (PNETs) may be associated with adverse perioperative outcomes compared with pancreatic adenocarcinoma given the high-risk nature of soft glands with small pancreatic ducts. The effect of minimally invasive surgery (MIS) pancreatectomy on outcomes of PNETs remains to be examined, which is the aim of this study. STUDY DESIGN: Between 2009 and 2019, 1,023 patients underwent pancreatectomy for PNETs at 4 institutions. Clinicopathologic data and perioperative outcomes of patients who underwent MIS (n = 447) and open resections (n = 576) were compared. RESULTS: Of the 1,023 patients, 51% were male, the mean age was 58, the median tumor size was 2.1 cm, and 73% were grade 1 PNETs. There were 318 (31%) pancreatoduodenectomies (PDs), 541 (53%) distal pancreatectomies (DPs), 80 (7.8%) enucleation (ENs), 72 (7%) central pancreatectomies (CPs), and 12 (1.2%) total pancreatectomies. Almost half of the patients (N = 447, 44%) had MIS operations, of which 230 (51%) were robotic and 217 (49%) were laparoscopic. Compared with open operations, MIS PDs had significantly lower operative blood loss (150 vs 400 mL, p < 0.001) and rate of clinically relevant postoperative pancreatic fistulas (CR-POPFs; 13% vs 27%, p = 0.030), and MIS DPs had a shorter length of stay (5 vs 6 days, p < 0.001). Although MIS DPs and ENs had CR-POPFs comparable with open operations, MIS CPs had a higher CR-POPF rate (45% vs 15%, p = 0.013). After adjusting for pathological differences, MIS pancreatectomy was associated with recurrence-free survival and overall survival comparable with open pancreatectomy. CONCLUSIONS: MIS pancreatectomy for PNETs is associated with improved outcomes or outcomes comparable with open resection.

PubMed-ID: [35839409](https://pubmed.ncbi.nlm.nih.gov/35839409/)
<http://dx.doi.org/10.1097/XCS.000000000000257>

General

Meta-Analyses

- None -

Randomized controlled trials

- None -

Consensus Statements/Guidelines

- None -

Other Articles

Endocrine surgeons are performing more thyroid lobectomies for low-risk differentiated thyroid cancer since the 2015 ATA guidelines.

Surgery, 172(5):1392-400.

P. C. Conroy, A. Wilhelm, L. Calthorpe, T. M. Ullmann, S. Davis, C. Y. Huang, W. T. Shen, J. Gosnell, Q. Y. Duh, S. Roman and J. A. Sosa. 2022.

BACKGROUND: The 2015 American Thyroid Association guidelines recommended either total thyroidectomy or lobectomy for surgical treatment of low-risk differentiated thyroid cancer and de-escalated recommendations for central neck dissections. The study aim was to investigate how practice patterns among endocrine surgeons have changed over time. **METHODS:** All adult patients with low-risk differentiated thyroid cancers (T1-T2, N0/Nx, M0/Mx) in the Collaborative Endocrine Surgery Quality Improvement Program (2014-2021) were identified. The outcomes between patients undergoing lobectomy versus total thyroidectomy were compared using multivariable logistic regression. The annual percent change in the proportion of lobectomies and central neck dissections performed was estimated using joinpoint regression. **RESULTS:** In total, 5,567 patients with low-risk differentiated thyroid cancers were identified. Of these, 2,261 (40.6%) were very low-risk tumors ≤ 1 cm, and 2,983 (53.6%) were low-risk tumors > 1 and ≤ 4 cm. Most patients (67.9%) underwent total thyroidectomy. Compared to total thyroidectomy, lobectomy was associated with outpatient surgery (adjusted odds ratio 5.19, $P < .001$), a decreased risk of postoperative emergency department visits (adjusted odds ratio 0.63, $P = .03$), and decreased risk of hypoparathyroidism events (adjusted odds ratio 0.03, $P < .001$). Compared to before (2014-2015), patients undergoing surgery after publication of the revised guidelines (2016-2021) had higher odds of lobectomy and lower odds of central neck dissection for tumors ≤ 1 cm (lobectomy adjusted odds ratio 2.70, $P < .001$; central neck dissections adjusted odds ratio 0.64, $P = .03$) and tumors between 1 and 4 cm (lobectomy adjusted odds ratio 2.27, $P < .001$; central neck dissection adjusted odds ratio 0.62, $P < .001$). **CONCLUSION:** After publication of the 2015 American Thyroid Association guidelines, there has been an increase in thyroid lobectomies as a proportion of all thyroid operations performed by endocrine surgeons for low-risk differentiated thyroid cancer. This has implications for reduced health care use and costs, with potential population-level benefits.

PubMed-ID: [36002375](https://pubmed.ncbi.nlm.nih.gov/36002375/)

<http://dx.doi.org/10.1016/j.surg.2022.06.031>

Effect of Medialization on Dyspnea Index in Unilateral Vocal Fold Paralysis.

Otolaryngol Head Neck Surg, 167(2):327-33.

M. R. Hoffman, B. Vandiver, N. Derise, E. R. Hapner, G. Levenson and C. B. Simpson. 2022.

OBJECTIVE: Patients with unilateral vocal fold paralysis commonly report dysphonia and dysphagia. Dyspnea also occurs, with studies on treatment-related change producing mixed results. Studies including patient-reported outcomes have focused on single-question global scales. The Dyspnea Index (DI) includes 10 questions, is specific to upper airway-related dyspnea, and may better capture these patients' symptoms. We evaluated change in DI after treatment. **STUDY DESIGN:** Retrospective review. **SETTING:** Academic medical center. **METHODS:** Forty-three patients with unilateral vocal fold paralysis underwent injection augmentation ($n = 25$) or framework surgery ($n = 18$). DI was recorded preprocedure, 2 to 4 weeks afterward, and at approximately 3 months afterward in 19 patients. Voice Handicap Index-10, Glottal Function Index, Cough Severity Index, and Eating Assessment Tool-10 were also recorded. Change in parameters and correlations were assessed. Obesity, cardiac disease, pulmonary disease, and procedure (injection vs framework surgery) were

evaluated for effect on DI. RESULTS: Twenty-four patients had an abnormal baseline DI (>10). DI decreased from 14.9 ± 13.8 to 6.5 ± 9.3 after treatment ($P < .001$; 95% CI, 4.7-12.1). Twenty-eight scores decreased, 9 remained unchanged, and 6 increased. Change in DI was influenced by the presence of cardiac disease. Decreased DI persisted at 3-month follow-up. Voice Handicap Index-10, Glottal Function Index, Cough Severity Index, and Eating Assessment Tool-10 scores decreased and were correlated with change in DI. CONCLUSION: Upper airway-related dyspnea is common in unilateral vocal fold paralysis, occurring in half of this cohort. Correcting glottic insufficiency may alleviate symptoms. Treatment decision making should consider postprocedural change in dyspnea, especially in patients for whom dyspnea is a motivating factor for seeking treatment.

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Long-Term Outcomes for Patients with Multiple Endocrine Neoplasia Type 1 and Duodenopancreatic Neuroendocrine Neoplasms.

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J. B. Liu, J. Cai, M. Dhir, A. Paniccia, A. H. Zureikat, K. M. Ramonell, K. L. McCoy, S. E. Carty and L. Yip. 2022.

BACKGROUND: Liver metastasis from duodenopancreatic neuroendocrine neoplasms (DP-NENs) is a major cause of mortality in multiple endocrine neoplasia type 1 (MEN1) patients, yet much of their natural history is unknown.

METHODS: This longitudinal, retrospective cohort study analyzed all MEN1 patients with imageable functional (F) and nonfunctional (NF) DP-NENs (1990-2021) for liver metastasis-free survival (LMFS) and overall survival (OS). RESULTS: Of 138 patients, 85 (61.6%) had imageable DP-NENs (28 F, 57 NF), and the mean largest tumor size was 1.8 ± 1.4 cm.

Multifocality was present in 32 patients (37.7%). Surgery was performed for 49 patients (57.7%). During an 11-year median follow-up period (IQR, 6-17 years), 23 (27.1%) of the patients had liver metastasis, and 19 (22.4%) patients died. Death was attributed to liver metastasis in 60% of cases. The patients with F-DP-NENs versus NF-DP-NENs more often had liver metastasis (46.4% vs. 15.8%; $p = 0.002$) but had similar 10-year LMFS (80.9 vs. 87.0%; $p = 0.44$) and OS (82.7 vs. 94.3%; $p = 0.69$). The patients with NF-DP-NENs had surgery when their tumors were larger ($p < 0.001$). Tumor size was not associated with liver metastasis ($p = 0.89$). The average growth rate was 0.04 cm/year (SE, 0.02 cm/year; $p = 0.01$) during active surveillance for NF-DP-NENs ($n = 38$). Liver metastasis developed in four patients with tumors smaller than 2 cm. The risk of liver metastasis was independent of surgery (hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.21-2.93; $p = 0.72$) and death (HR, 0.51; 95% CI, 0.08-3.06; $p = 0.46$). CONCLUSIONS: Although the observed outcomes in this study were better than historical data, small NF-DP-NENs still developed liver metastasis and liver metastasis remains a major cause of death. These results suggest that size as a sole criterion for surgery may be insufficient to predict tumor behavior.

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