1. **Endocr J. 2019 Jan 22. doi: 10.1507/endocrj.EJ18-0445. [Epub ahead of print]**
Changes in glucose metabolism based on 75-g oral glucose tolerance tests before and after surgery for adrenal Cushing's syndrome.
Tsurutani Y(1), Miyoshi K(1), Inoue K(1)(2), Takiguchi T(1), Saito J(1), Omura M(1), Nishikawa T(1).
Author information:
(1)Endocrinology and Diabetes Center, Yokohama Rosai Hospital, Yokohama 222-0036, Japan.
(2)Department of Epidemiology, UCLA Fielding School of Public Health, Los Angeles 90024, USA.

Adrenal Cushing's syndrome (CS) is caused by cortisol-producing adrenal adenoma and is frequently accompanied by glucose metabolism disorders, which are characterized by increased insulin resistance and insufficient β-cell compensation. However, considering the rarity of CS, few studies have assessed whether the glucose metabolism disorders could be ameliorated by surgical treatment. In this case series, we evaluated glucose metabolism before and after surgery in 11 patients (10 women and 1 man) who underwent unilateral adrenalectomy for overt adrenal CS between 2005 and 2016. Patients with pre-diagnosed diabetes mellitus (DM) were excluded. Pre- and post-operative 75-g oral glucose tolerance tests were performed. Cortisol secretion decreased significantly after surgery (median 24-h urinary free cortisol: 582.0 μg/day [interquartile range: 321.0-743.0 μg/day] to 31.3 μg/day [23.6-40.6 μg/day], p = 0.001). The results of the OGTT generally improved after surgery (normal glucose tolerance/impaired glucose tolerance/DM: 2/8/1 to 8/3/0), with significant decreases in the immunoreactive insulin and glucose levels. We also found a decrease in the median homeostatic model assessment of insulin resistance (2.4 [1.4-2.8] to 1.0 [0.6-1.1], p = 0.002), and increases in the median Matsuda index (3.0 [2.3-4.5] to 8.2 [6.3-11.4], p < 0.001), median insulinogenic index (0.70 [0.22-1.51] to 1.22 [0.78-1.64], p = 0.08), and median disposition index (609.1 [237.8-1,095.2] to 1,286.0 [1,034.6-1,857.6], p = 0.002). These findings indicate that adrenalectomy for adrenal CS without overt DM may help ameliorate glucose metabolism disorders, and improve both insulin resistance and insulin secretion.
DOI: 10.1507/endocrj.EJ18-0445
PMID: 30674738

2. **Ann Surg. 2019 Jan 18. doi: 10.1097/SLA.0000000000003200. [Epub ahead of print]**
The Primary Aldosteronism Surgical Outcome Score for the Prediction of Clinical Outcomes After Adrenalectomy for Unilateral Primary Aldosteronism.
Burrello J(1), Burrello A(2), Stowasser M(3), Nishikawa T(4), Quinkler M(5), Prejbisz A(6), Lenders JWM(7)(8), Satoh F(9), Mulatero P(1), Reincke M(10), Williams TA(1)(10).
Author information:
(1)Division of Internal Medicine and Hypertension, Department of Medical Sciences, University of Turin, Turin, Italy.
(2)Department of Electronics and telecommunications, Polytechnic University of Turin, Turin, Italy.
(3)Endocrine Hypertension Research Centre, University of Queensland Diamantina Institute, Greenslopes and Princess Alexandra Hospitals, Brisbane, QLD, Australia.

(4)Endocrinology and Diabetes Center, Yokohama Rosai Hospital, Yokohama, Japan.
(5)Endocrinology in Charlottenburg, Berlin, Germany.
(6)Department of Hypertension, Institute of Cardiology, Warsaw, Poland.
(7)Department of Medicine III, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany.
(8)Department of Medicine, Radboud University Medical Center, Nijmegen, The Netherlands.
(9)Division of Clinical Hypertension, Endocrinology and Metabolism, Tohoku University Graduate School of Medicine, Sendai, Japan.
(10)Department of Internal Medicine IV, Ludwig-Maximilians-University, Munich, Germany.

MINI: Clinical remission after unilateral adrenalectomy to treat unilateral primary aldosteronism is achieved in less than half of patients. A linear discriminant model with 6 presurgical predictors of clinical remission was used to build a 25-point prediction score of postsurgical clinical outcomes. The prediction score was integrated into a user-friendly online tool which can be used in a clinical setting to differentiate patients who are likely to be clinically cured after surgery from those who will need continuous surveillance after surgery due to remnant hypertension.OBJECTIVE: To develop a prediction model for clinical outcomes after unilateral adrenalectomy for unilateral primary aldosteronism.
SUMMARY BACKGROUND DATA: Unilateral primary aldosteronism is the most common surgically curable form of endocrine hypertension. Surgical resection of the dominant overactive adrenal in unilateral primary aldosteronism results in complete clinical success with resolution of hypertension without antihypertensive medication in less than half of patients with a wide between-center variability.
METHODS: A linear discriminant analysis model was built using data of 380 patients treated by adrenalectomy for unilateral primary aldosteronism to classify postsurgical clinical outcomes. The total cohort was then randomly divided into training (280 patients) and test (100 patients) datasets to create and validate a score system to predict clinical outcomes. An online tool (Primary Aldosteronism Surgical Outcome predictor) was developed to facilitate the use of the predictive score.
RESULTS: Six presurgical factors associated with complete clinical success (known duration of hypertension, sex, antihypertensive medication dosage, body mass index, target organ damage, and size of largest nodule at imaging) were selected based on classification performance in the linear discriminant analysis model. A 25-point predictive score was built with an optimal cut-off of greater than 16 points (accuracy of prediction = 79.2%; specificity = 84.4%; sensitivity = 71.3%) with an area under the curve of 0.839.
CONCLUSIONS: The predictive score and the primary aldosteronism surgical outcome predictor can be used in a clinical setting to differentiate patients who are likely to be clinically cured after surgery from those who will need continuous surveillance after surgery due to persistent hypertension.
DOI: 10.1097/SLA.0000000000003200
PMID: 30672800

3. **Neuroendocrinology. 2019 Jan 13. doi: 10.1159/000496846. [Epub ahead of print]**

Recovery of the adrenal function after pituitary surgery in patients with Cushing Disease: persistent remission or recurrence?
Serban A, Sala E, Carosi G, Del Sindaco G, Giavoli C, Locatelli M, Arosio M, Mantovani G, Ferrante E.

Background Cushing's disease (CD) represents the principal cause of endogenous hypercortisolism. The first-line therapy of CD is surgical removal of the ACTH secreting pituitary adenoma, which is generally followed by adrenal insufficiency (AI). Objective To analyse the recovery of the AI in patients with CD after pituitary surgery in relation with recurrence and persistent remission of CD. Materials and Methods Retrospective analysis on patients with CD who met the following inclusion criteria: adult age, presence of AI at 2 months after the surgical intervention, a minimum follow-up of 3 years after the surgical intervention. Results: Sixty-one patients were followed for a median of 6 years. Ten (16.3%) patients recurred during follow up. The patients who restored the adrenal function did it after a mean time of 19 months, with a significantly shorter time in the recurrence group (12.5 vs 25 months, p=0.008). All 10 patients who recurred recovered their adrenal function within 22 months. The recovery rate of AI in the persistent remission group was 37% (19/51) at 3 years and 55.8% (24/43) at 5 years. In all patients the duration of AI was negatively associated with the recurrence of disease. Conclusion The duration of postsurgical AI in patients with recurrent CD is significantly shorter than in persistently remitted CD. and this parameter may be a useful predictor for recurrence. Patients showing a normal pituitary-adrenal axis within 2 years after surgery should be strictly monitored being more at risk of disease relapse.
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DOI: 10.1159/000496846
PMID: 30636245

4. **Bull Exp Biol Med. 2019 Jan 8. doi: 10.1007/s10517-019-04362-x. [Epub ahead of print]**
Infradian Rhythms of Resistance to a Dissociative Anesthetic in Wistar Male Rats under Normal Conditions and After Surgical Removal of the Adrenal Glands and Testes.
Dzalilova DS(1), Diatroptova MA(1), Mkhitarov VA(1), Diatroptov ME(2).
Author information:
(1)Research Institute of Human Morphology, Moscow, Russia.
(2)Research Institute of Human Morphology, Moscow, Russia. diatrom@inbox.ru.

Daily dynamics of changes in the latency of a response to dissociative anesthetic tiletamine (time from injection to ataxia) was studied in mature Wistar rats. Both intramuscular and intravenous administration of the anesthetic was associated with 4-day oscillations of the latent period synchronous with the dynamics of changes in the concentration of glucocorticoid hormones. The period and phases of the infradian rhythm of resistance to the anesthetic remained unchanged after removal of both adrenal glands and testes and administration of corticosterone synthesis blocker trilostane diminishing the 4-day cycle of changes in corticosterone level. Therefore, hormones of the adrenal glands and testes do not play the key role in the mechanisms of formation of the 4-day infradian rhythm.

DOI: 10.1007/s10517-019-04362-x
PMID: 30617706

5. **BMJ Case Rep. 2018 Dec 9;11(1). pii: e226384. doi: 10.1136/bcr-2018-226384.**
Extra-adrenal pheochromocytoma presenting as inverse takotsubo-pattern cardiomyopathy treated with surgical resection.
Tafreshi S(1), Naqvi SY(2), Thomas S(2).
Author information:
(1)Department of Medicine, University of Rochester Medical Center, Rochester, New York, USA.
(2)Department of Cardiology, University of Rochester Medical Center, Rochester, New York, USA.

Pheochromocytoma is a rare catecholamine-secreting tumour that is typically located in the adrenal medulla or along the sympathetic ganglia. The typical symptoms are episodic in nature and include tachycardia, sweating and headache. These tumours can present as transient, reversible cardiomyopathy similar to takotsubo cardiomyopathy (TCM). TCM is characterised by transient hypokinesis of the left ventricular apex and is typically induced by emotional stress. We describe the case of a 26-year-old woman with a medical history significant for headaches who presented initially to her family physician with nausea, vomiting, headache and hypertension. She was started on lisinopril 10 mg daily. One week later, she presented to the emergency department with substernal severe chest pressure. Her troponin level was elevated. Coronary angiogram showed normal coronary arteries and left ventriculogram showed inverse TCM pattern. Serum catecholamines were very elevated confirming pheochromocytoma. She was successfully treated with alpha-blockers followed by surgical resection.

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PMID: 30567218
Conflict of interest statement: Competing interests: None declared.

6. **Medicine (Baltimore). 2018 Dec;97(50):e13591. doi: 10.1097/MD.0000000000013591.**
Simultaneous occurrence of primary aldosteronism due to aldosteronoma and ectopic meningioma in the adrenal gland: A case report.
Ramlagun D(1), Shadhu K(1), Sang M(2), Zhu K(1), Qin C(1), Sun M(2).
Author information:
(1)Department of Urology.
(2)Department of Endocrinology, First Affiliated Hospital of Nanjing Medical University and Jiangsu Province Hospital, Gulou District, Nanjing City, Jiangsu Province, PR China.

RATIONALE: Primary aldosteronism due to aldosteronoma is the most common form of secondary hypertension, with an estimated prevalence of 4% of hypertensive patients in primary care and around 10% of referred patients. Diagnosis is a clinical challenge with simultaneous occurrence of primary ectopic meningioma in the adrenal gland. To our knowledge this is the first reported case of simultaneous occurrence of aldosteronomas and ectopic meningioma in the adrenal

gland based on literatures.
PATIENT CONCERNS: A 30-year-old man presented with resistant hypertension for one year. The computed tomographic scans were suggestive of left adrenal gland hyperplasia.
INTERVENTION: The patient underwent partial unilateral laparoscopic adrenalectomy.
DIAGNOSIS: The histopathological examination of the resected sample confirmed primary ectopic meningioma in adrenal gland and aldosterone producing adenoma (APA). The saline load test, captopril test, and plasma aldosterone/renin ratio were indicative of primary aldosteronism (PA).
OUTCOMES: The patient had controlled blood pressure postoperatively.
LESSONS: The patient was diagnosed with PA due to APA and nonfunctional primary ectopic meningioma in the adrenal gland which is very rare and dealt with unilateral laparoscopic adrenalectomy.
DOI: 10.1097/MD.0000000000013591
PMID: 30558028 [Indexed for MEDLINE]

7. **J Endocr Soc. 2018 Sep 20;2(12):1338-1344. doi: 10.1210/js.2018-00239. eCollection 2018 Dec 1.**
Pharmacokinetics of Glucocorticoid Replacement Before and After Bariatric Surgery in Patients With Adrenal Insufficiency.
de Heide LJM(1), de Boer HHR(2), van Borren M(3), Emous M(4), Aarts E(5), de Boer H(6).
Author information:
(1)Department of Internal Medicine, Medical Center Leeuwarden, AD Leeuwarden, Netherlands.
(2)Department of Endocrinology, University Medical Center Groningen, RB Groningen, Netherlands.
(3)Department of Clinical Chemistry, Rijnstate Hospital, TA Arnhem, Netherlands.
(4)Department of Surgery, Medical Center Leeuwarden, AD Leeuwarden, Netherlands.
(5)Department of Surgery, Rijnstate Hospital, TA Arnhem, Netherlands.
(6)Department of Internal Medicine, Rijnstate Hospital, TA Arnhem, Netherlands.

Adequate glucocorticoid replacement in patients with primary or secondary adrenal insufficiency is essential to maintain general well-being. Little is known about the effects of bariatric surgery on glucocorticoid absorption. This study evaluates glucocorticoid absorption before and after bariatric surgery, with assessment of plasma cortisol profiles in five patients receiving glucocorticoid replacement therapy for primary (n = 1) or secondary (n = 4) adrenal insufficiency. One patient underwent sleeve gastrectomy (SG), one a one-anastomosis gastric bypass (mini-GB), and three a Roux-en-Y gastric bypass (RYGB). Pharmacokinetic calculations were based on plasma cortisol measurements performed during the first 6 hours after ingestion of the morning dose. Plasma cortisol profiles were very similar before and after surgery; only minor differences were observed. After SG, plasma peak cortisol concentration and cortisol area under the curve (AUC) were higher by 23% and 24%, respectively, and time to peak cortisol was 10 minutes shorter. The mini-GB had no marked effect on pharmacokinetic parameters. In the three patients who underwent RYGB, AUC changes ranged from -12% to 20%. In conclusion, in this small number of patients with adrenal insufficiency, plasma cortisol profiles were similar before and after

bariatric surgery. However, in view of individual differences in response to different types of surgery, we recommend postoperative cortisol profiling to guide appropriate glucocorticoid dose adjustment.
DOI: 10.1210/js.2018-00239
PMCID: PMC6262195
PMID: 30511036

8. **Turk J Urol. 2018 Nov 21. doi: 10.5152/tud.2018.94412. [Epub ahead of print]**
Tourniquet and adrenaline use in hypospadias surgery: a survey on the current practice in Turkey.
Ateş U(1), Ekberli G(1), Taştekin NY(1), Göllü G(1), Çakmak M(1).
Author information:
(1)Department of Pediatric Surgery, Ankara University School of Medicine, Ankara, Turkey.

OBJECTIVE: Aim of the study is to determine the hemostatic techniques among pediatric urologists in Turkey.
MATERIAL AND METHODS: Questionnaire forms were sent to 459 pediatric urologist by e-mail.
RESULTS: Ninety eight of 459 participants answered the questionnaire forms. Eighty-one (84.4%) of the participants were using tourniquet. The participants who didn't use tourniquet stated their justifications as follows: lack of need (n=10: 66.7%), development of edema, ischemia, delay of wound-graft healing and fistula risk (n=5: 33.3%). The indications of tourniquet use were stated as follows: penile (91.4%: n=74), distal (72.8%: n=59), penoscrotal (55.6%: n=45) hypospadias; fistula repair (33.3%: n=27), cripple hypospadias (33.3%: n=27), repair with flaps (30.9%: n=25), repair with grafts (27.2%: n=22), and isolated penile curvature (21%: n=17). Most commonly used tourniquet material (49.9%) was latex glove. Erection test was applied by 43.8% of participants. Scalp vein set was the most commonly (54.8%) used injector during erection test. Only 9.4% of participants were using adrenaline. Adrenaline dosages used at 1/100.000 dilution by 55.6%, lidocaine with 1/100.000 adrenaline by 44.4% of participants.
CONCLUSION: Beside a few experimental ones there is a paucity of studies that can serve as a guideline for using these techniques in the literature. There is a necessity of realizing prospective, randomized studies with long-term follow up to evidence that postoperative complications could develop secondary to hemostatic techniques and also to facilitate safe use of these techniques.
DOI: 10.5152/tud.2018.94412
PMID: 30468426

9. **Medicine (Baltimore). 2018 Nov;97(47):e13329. doi: 10.1097/MD.0000000000013329.**
Spontaneous adrenal hematoma in pregnancy: A case report.
Yang L(1), Zhu YC(2), Liu RB(1).
Author information:
(1)Department of Radiology.
(2)Department of Urology, West China Hospital of Sichuan University, Chengdu, Sichuan 610041, China.

RATIONAL: Spontaneous adrenal hematoma in pregnancy is a very rare condition.

Herein we present an additional rare case of unilateral spontaneous adrenal hematoma in a pregnant woman, aiming to share this experience and summarize the signal characteristics of simple adrenal hematoma in magnetic resonance imaging (MRI).
PATIENT CONCERNS: A 28-year old pregnant woman was referred to our hospital with a vague paroxysmal left-side back pain at 17 weeks of gestation.
DIAGNOSIS: MR scan of the abdomen revealed an 8.1 × 7.7 × 6.8 cm round mass in the left adrenal region, which showed a rim of acute hemorrhage signal. Due to the stable condition of the patient and fetus, she was admitted for observation. Repeat MR scan was performed a month later, and it showed a stable mass with marginal subacute bleeding signal.
INTERVENTIONS: Laparoscope excision of the hematoma was performed.
OUTCOMES: Simple adrenal hematoma was confirmed by pathological examinations. And the patient was discharged 3 days later with normal renal and adrenal functions.
LESSONS: The most important characteristic of adrenal hematoma is the high-signal rim on T1-weighted MR images, and the clinicians should make individualized treatment plan for every patient encountered in the future who might have different clinical conditions.
DOI: 10.1097/MD.0000000000013329
PMID: 30461650 [Indexed for MEDLINE]

10. **J Clin Endocrinol Metab. 2018 Nov 1;103(11):4089-4096. doi: 10.1210/jc.2018-01863.**
Genital Reconstructive Surgery in Females With Congenital Adrenal Hyperplasia: A Systematic Review and Meta-Analysis.
Almasri J(1)(2), Zaiem F(3), Rodriguez-Gutierrez R(4)(5), Tamhane SU(6), Iqbal AM(7), Prokop LJ(8), Speiser PW(9), Baskin LS(10), Bancos I(6), Murad MH(1)(2).
Author information:
(1)Evidence-Based Practice Research Program, Mayo Clinic, Rochester, Minnesota.
(2)Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, Minnesota.
(3)Department of Pathology, Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, Michigan.
(4)Division of Endocrinology, Department of Internal Medicine, University Hospital Dr. Jose E. Gonzalez, Autonomous University of Nuevo Leon, Monterrey, Mexico.
(5)Plataforma INVEST Medicina UANL-KER Unit Mayo Clinic, Autonomous University of Nuevo Leon, Monterrey, Mexico.
(6)Division of Endocrinology, Mayo Clinic, Rochester, Minnesota.
(7)Division of Pediatrics and Adolescent Medicine, Department of Pediatric Endocrinology, Mayo Clinic, Rochester, Minnesota.
(8)Mayo Clinic Libraries, Mayo Clinic, Rochester, Minnesota.
(9)Division of Pediatric Endocrinology, Cohen Children's Medical Center and Zucker Hofstra Northwell School of Medicine, Lake Success, New York.
(10)Department of Urology, University of California, San Francisco, California.

Background: Females with congenital adrenal hyperplasia (CAH) and atypical genitalia often undergo complex surgeries; however, their outcomes remain largely uncertain.
Methods: We searched several databases through 8 March 2016 for studies

evaluating genital reconstructive surgery in females with CAH. Reviewers working independently and in duplicate selected and appraised the studies.
Results: We included 29 observational studies (1178 patients, mean age at surgery, 2.7 ± 4.7 years; mostly classic CAH). After an average follow-up of 10.3 years, most patients who had undergone surgery had a female gender identity (88.7%) and were heterosexual (76.2%). Females who underwent surgery reported a sexual function score of 25.13 using the Female Sexual Function Index (maximum score, 36). Many patients continued to complain of substantial impairment of sensitivity in the clitoris, vaginal penetration difficulties, and low intercourse frequency. Most patients were sexually active, although only 48% reported comfortable intercourse. Most patients (79.4%) and treating health care professionals (71.8%) were satisfied with the surgical outcomes. Vaginal stenosis was common (27%), and other surgical complications, such as fistulas, urinary incontinence, and urinary tract infections, were less common. Data on quality of life were sparse and inconclusive.
Conclusion: The long-term follow-up of females with CAH who had undergone urogenital reconstructive surgery shows variable sexual function. Most patients were sexually active and satisfied with the surgical outcomes; however, some patients still complained of impairment in sexual experience and satisfaction. The certainty in the available evidence is very low.
DOI: 10.1210/jc.2018-01863
PMID: 30272250

11. **J Laparoendosc Adv Surg Tech A. 2019 Jan;29(1):19-23. doi: 10.1089/lap.2018.0286. Epub 2018 Sep 28.**

Robotic Adrenalectomy: Are We Expanding the Indications of Minimally Invasive Surgery?

Quadri P(1), Esposito S(2), Coleoglou A(1), Danielson KK(1)(2), Masrur M(1), Giulianotti PC(1).
Author information:
(1)1 Division of General, Minimally Invasive and Robotic Surgery, Department of Surgery, University of Illinois at Chicago, Chicago, Illinois.
(2)2 Division of Epidemiology and Biostatistics, University of Illinois at Chicago, Chicago, Illinois.

INTRODUCTION: Laparoscopic adrenalectomy (LA) is accepted as the gold standard treatment for most adrenal pathologies. Open surgery is still considered the standard of care for large tumors and malignancies. In the past decade, robotic adrenalectomy (RA) has become an alternative to the laparoscopic and open approaches. The aim of this study was to analyze perioperative and postoperative outcomes in a series of consecutive nonselected patients undergoing a RA, to determine whether factors that negatively affect outcomes in LA (body mass index [BMI], size, and side of the tumor) have the same impact in RA.
MATERIALS AND METHODS: This is a single-center single-surgeon retrospective study with 43 patients who underwent a RA. Patients were divided into different groups according to tumor size (cutoff values of 5 or 8 cm), tumor side (left/right), and BMI (cutoff value of kg/m2). Perioperative and postoperative outcomes included operative time, length of hospital stay, blood loss, readmissions, complications, and conversions to open.
RESULTS: There were no significant differences between the groups with tumors

<5 cm versus ≥5 cm regarding gender, age, race, BMI, American Society of Anesthesiologists (ASA) score, history of previous abdominal surgery, tumor side, and histopathological diagnosis (all P values ≥.06). There were no significant differences in any of the outcomes analyzed with respect to the tumor size (all P values ≥.14) except for a higher occurrence of complications in patients with tumors ≥8 cm versus <8 cm (P = .03). There were no significant differences in any outcomes related to side (left versus right) of the tumor nor BMI (<30 versus ≥30 kg/m2). The overall readmission and conversion rates were both 2.3% and no mortalities were registered.
CONCLUSION: Patient's BMI, tumor side, and size did not demonstrate a negative impact on perioperative and postoperative outcomes of RA. This approach could potentially expand the indications of minimally invasive surgery.
DOI: 10.1089/lap.2018.0286
PMID: 30265584

12. **Urology. 2018 Nov;121:22-28. doi: 10.1016/j.urology.2018.06.021. Epub 2018 Jun 26.**

Adrenal Cyst in Pregnancy: A Surgical Emergency.

Mandato VD(1), Mastrofilippo V(2), Kuhn E(3), Silvotti M(4), Barbieri I(5), Aguzzoli L(2), La Sala GB(6).
Author information:
(1)Unit of Obstetrics and Gynecology, Azienda Unità Sanitaria Locale, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Azienda Unità Sanitaria Locale, Reggio Emilia, Italy. Electronic address: dariomandato@gmail.com.
(2)Unit of Obstetrics and Gynecology, Azienda Unità Sanitaria Locale, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Azienda Unità Sanitaria Locale, Reggio Emilia, Italy.
(3)Unit of Pathology, Azienda Unità Sanitaria Locale, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Azienda Unità Sanitaria Locale, Reggio Emilia, Italy.
(4)Unit of Radiology, Azienda Unità Sanitaria Locale, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Azienda Unità Sanitaria Locale, Reggio Emilia, Italy.
(5)General and Emergency Surgery, University of Modena and Reggio Emilia, Reggio Emilia, Italy.
(6)Unit of Obstetrics and Gynecology, Azienda Unità Sanitaria Locale, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Azienda Unità Sanitaria Locale, Reggio Emilia, Italy; y.
DOI: 10.1016/j.urology.2018.06.021
PMID: 29958968

13. **Br J Radiol. 2018 Dec;91(1092):20180090. doi: 10.1259/bjr.20180090. Epub 2018 Jul 25.**

CT-guided percutaneous core biopsy for assessment of morphologically normal adrenal glands showing high FDG uptake in patients with lung cancer.

Chassagnon G(1), Bennani S(1), Freche G(1), Magdeleinat P(2), Mansuet-Lupo A(3), Revel MP(1).
Author information:
(1)1 Radiology Department, Groupe Hospitalier Cochin Broca Hôtel-Dieu -

Université Paris Descartes , Paris , France.
(2)2 Department of Thoracic Surgery, Groupe Hospitalier Cochin Broca Hôtel-Dieu - Université Paris Descartes , Paris , France.
(3)3 Department of Pathology, Groupe Hospitalier Cochin Broca Hôtel-Dieu - Université Paris Descartes , Paris , France.

OBJECTIVE:: Increased fludeoxyglucose (FDG) uptake in morphologically normal adrenal glands on positron emission tomography-CT (PET-CT) is a diagnostic challenge with major implications on treatment. The purpose of this retrospective study was to report our experience of CT-guided percutaneous core biopsy of morphologically normal adrenal glands showing increased FDG uptake in a context of lung cancer.
METHODS:: Biopsies for non-enlarged adrenal glands showing increased FDG uptake in lung cancer patients performed at our institution from December 2014 to December 2016 were retrospectively analyzed. Six biopsies were performed in five patients during the study period. All procedures were performed with the patients in the prone position, using a posterior approach and coaxial 17-gauge needles with 18-gauge automated cutting needles. Patient characteristics, procedural details and final pathological diagnosis were analyzed, as well as the duration of hospitalization.
RESULTS:: Five of the six biopsies (83.3%) confirmed adrenal metastasis from the primary lung cancer. No complications were reported and the patients were discharged the day after the procedure.
CONCLUSION:: The high confirmation rate of metastasis and lack of complications support performing CT-guided percutaneous biopsy of non-enlarged adrenal glands showing increased FDG uptake, for optimal management in lung cancer patients.
ADVANCES IN KNOWLEDGE:: Morphologically normal adrenal glands showing high FDG uptake in patients with lung cancer are metastasis. This manuscript shows that CT-guided percutaneous biopsy should be proposed. Increased FDG uptake in morphologically normal adrenal glands may indicate metastasis.
DOI: 10.1259/bjr.20180090
PMCID: PMC6319859 [Available on 2019-12-01]
PMID: 29906237 [Indexed for MEDLINE]

1. **World J Surg. 2019 Jan 18. doi: 10.1007/s00268-019-04910-6. [Epub ahead of print]**
18F-Fluorocholine PET/CT and Parathyroid 4D Computed Tomography for Primary Hyperparathyroidism: The Challenge of Reoperative Patients.
Amadou C(1), Bera G(2)(3), Ezziane M(4), Chami L(3)(4), Delbot T(2), Rouxel A(2), Leban M(5), Herve G(6), Menegaux F(7), Leenhardt L(1)(3), Kas A(2)(3), Trésallet C(7)(8), Ghander C(1), Lussey-Lepoutre C(9)(10).
Author information:
(1)Department of Thyroid and Endocrine Tumours, Pitié-Salpêtrière Hospital, Sorbonne University, Paris, France.
(2)Department of Nuclear Medicine, Pitié-Salpêtrière Hospital, Sorbonne University, Paris, France.
(3)Laboratoire d'imagerie biomedicale (LIB), INSERM U1146, Sorbonne University, Paris, France.
(4)Department of Radiology, Pitié-Salpêtrière Hospital, Sorbonne University, Paris, France.
(5)Laboratory of Endocrine Biochemistry, Pitié-Salpêtrière Hospital, Sorbonne University, Paris, France.
(6)Department of Histopathology, Pitié-Salpêtrière Hospital, Sorbonne University, Paris, France.
(7)Department of Endocrine Surgery, Pitié-Salpêtrière Hospital, Sorbonne University, Paris, France.
(8)Laboratoire d'imagerie fonctionnelle (LIF), INSERM U678, Sorbonne University, Paris, France.
(9)Department of Nuclear Medicine, Pitié-Salpêtrière Hospital, Sorbonne University, Paris, France. charlotte.lussey@inserm.fr.
(10)INSERM, UMR970, Paris-Cardiovascular Research Center, 75015, Paris, France. charlotte.lussey@inserm.fr.

BACKGROUND: To evaluate FCH-PET/CT and parathyroid 4D-CT so as to guide surgery in patients with primary hyperparathyroidism (pHPT) and prior neck surgery.
METHODS: Medical records of all patients referred for a FCH-PET/CT in our institution were systematically reviewed. Only patients with pHPT, a history of neck surgery (for pHPT or another reason) and an indication of reoperation were included. All patients had parathyroid ultrasound (US) and Tc-99m-sestaMIBI scintigraphy, and furthermore, some patients had 4D-CT. Gold standard was defined by pathological findings and/or US-guided fine-needle aspiration with PTH level measurement in the washing liquid.
RESULTS: Twenty-nine patients were included in this retrospective study. FCH-PET/CT identified 34 abnormal foci including 19 ectopic localizations. 4D-CT, performed in 20 patients, detected 11 abnormal glands at first reading and 6 more under FCH-PET/CT guidance. US and Tc-99m-sestaMIBI found concordant foci in 8/29 patients. Gold standard was obtained for 32 abnormal FCH-PET/CT foci in 27 patients. On a per-lesion analysis, sensitivity, specificity, positive and negative predictive values were, respectively, 96%, 13%, 77% and 50% for FCH-PET/CT, 75%, 40%, 80% and 33% for 4D-CT. On a per-patient analysis, sensitivity was 85% for FCH-PET/CT and 63% for 4D-CT. FCH-PET/CT results made it possible to successfully remove an abnormal gland in 21 patients, including 12 with a negative or discordant US/Tc-99m-sestaMIBI scintigraphy result, with a global cure rate of 73%.
CONCLUSION: FCH-PET/CT is a promising tool in the challenging population of reoperative patients with pHPT. Parathyroid 4D-CT appears as a confirmatory

imaging modality.
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PMID: 30659347

2. **J Clin Endocrinol Metab. 2019 Jan 18. doi: 10.1210/jc.2019-00121. [Epub ahead of print]**
CORRIGENDUM FOR "Lung Metastasis in Pediatric Thyroid Cancer: Radiological Pattern, Molecular Genetics, Response to Therapy, and Outcome".
[No authors listed]
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PMID: 30657924

3. **Lancet Oncol. 2018 Dec 21. pii: S1470-2045(18)30762-9. doi: 10.1016/S1470-2045(18)30762-9. [Epub ahead of print]**
Diagnosis of thyroid cancer using deep convolutional neural network models applied to sonographic images: a retrospective, multicohort, diagnostic study.
Li X(1), Zhang S(2), Zhang Q(3), Wei X(2), Pan Y(4), Zhao J(2), Xin X(2), Qin C(5), Wang X(2), Li J(6), Yang F(2), Zhao Y(7), Yang M(8), Wang Q(8), Zheng Z(9), Zheng X(9), Yang X(10), Whitlow CT(11), Gurcan MN(12), Zhang L(3), Wang X(3), Pasche BC(13), Gao M(14), Zhang W(13), Chen K(15).
Author information:
(1)Tianjin Cancer Institute, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy of Tianjin, Tianjin Medical University Cancer Institute and Hospital, Tianjin Medical University, Tianjin, China.
(2)Department of Diagnostic and Therapeutic Ultrasonography, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy of Tianjin, Tianjin Medical University Cancer Institute and Hospital, Tianjin Medical University, Tianjin, China.
(3)Department of Maxillofacial and Otorhinolaryngology Oncology, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy of Tianjin, Tianjin Medical University Cancer Institute and Hospital, Tianjin Medical University, Tianjin, China.
(4)Department of Pathology, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy of Tianjin, Tianjin Medical University Cancer Institute and Hospital, Tianjin Medical University, Tianjin, China.
(5)Department of Thyroid and Breast Surgery, Weihai Municipal Hospital, Shandong, China.
(6)Department of Ultrasonography, Weihai Municipal Hospital, Shandong, China.
(7)Department of Ultrasonography, Affiliated Hospital of Chifeng University, Inner Mongolia, China.
(8)Department of Epidemiology and Biostatistics, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy of Tianjin, Tianjin Medical University Cancer Institute and Hospital, Tianjin Medical University, Tianjin, China.
(9)Department of Ultrasonography, Integrated Traditional Chinese and Western Medicine Hospital, Jilin, China.
(10)Department of Ultrasonography, Dezhou Municiple Hospital, Shandong, China.

(11)Departments of Radiology and Biomedical Engineering, Wake Forest School of Medicine, Winston-Salem, NC, USA.
(12)Center for Biomedical Informatics Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC, USA.
(13)Wake Forest Baptist Comprehensive Cancer Center, Wake Forest Baptist Medical Center, Department of Cancer Biology, Wake Forest School of Medicine, Winston-Salem, NC, USA.
(14)Department of Thyroid and Neck Cancer, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy of Tianjin, Tianjin Medical University Cancer Institute and Hospital, Tianjin Medical University, Tianjin, China.
(15)Department of Epidemiology and Biostatistics, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy of Tianjin, Tianjin Medical University Cancer Institute and Hospital, Tianjin Medical University, Tianjin, China. Electronic address: chenkexin@tjmuch.com.

BACKGROUND: The incidence of thyroid cancer is rising steadily because of overdiagnosis and overtreatment conferred by widespread use of sensitive imaging techniques for screening. This overall incidence growth is especially driven by increased diagnosis of indolent and well-differentiated papillary subtype and early-stage thyroid cancer, whereas the incidence of advanced-stage thyroid cancer has increased marginally. Thyroid ultrasound is frequently used to diagnose thyroid cancer. The aim of this study was to use deep convolutional neural network (DCNN) models to improve the diagnostic accuracy of thyroid cancer by analysing sonographic imaging data from clinical ultrasounds.
METHODS: We did a retrospective, multicohort, diagnostic study using ultrasound images sets from three hospitals in China. We developed and trained the DCNN model on the training set, 131 731 ultrasound images from 17 627 patients with thyroid cancer and 180 668 images from 25 325 controls from the thyroid imaging database at Tianjin Cancer Hospital. Clinical diagnosis of the training set was made by 16 radiologists from Tianjin Cancer Hospital. Images from anatomical sites that were judged as not having cancer were excluded from the training set and only individuals with suspected thyroid cancer underwent pathological examination to confirm diagnosis. The model's diagnostic performance was validated in an internal validation set from Tianjin Cancer Hospital (8606 images from 1118 patients) and two external datasets in China (the Integrated Traditional Chinese and Western Medicine Hospital, Jilin, 741 images from 154 patients; and the Weihai Municipal Hospital, Shandong, 11 039 images from 1420 patients). All individuals with suspected thyroid cancer after clinical examination in the validation sets had pathological examination. We also compared the specificity and sensitivity of the DCNN model with the performance of six skilled thyroid ultrasound radiologists on the three validation sets.
FINDINGS: Between Jan 1, 2012, and March 28, 2018, ultrasound images for the four study cohorts were obtained. The model achieved high performance in identifying thyroid cancer patients in the validation sets tested, with area under the curve values of 0·947 (95% CI 0·935-0·959) for the Tianjin internal validation set, 0·912 (95% CI 0·865-0·958) for the Jilin external validation set, and 0·908 (95% CI 0·891-0·925) for the Weihai external validation set. The DCNN model also showed improved performance in identifying thyroid cancer patients versus skilled radiologists. For the Tianjin internal validation set, sensitivity was 93·4% (95% CI 89·6-96·1) versus 96·9% (93·9-98·6; p=0·003) and specificity was 86·1%

(81·1-90·2) versus 59·4% (53·0-65·6; p<0·0001). For the Jilin external validation set, sensitivity was 84·3% (95% CI 73·6-91·9) versus 92·9% (84·1-97·6; p=0·048) and specificity was 86·9% (95% CI 77·8-93·3) versus 57·1% (45·9-67·9; p<0·0001). For the Weihai external validation set, sensitivity was 84·7% (95% CI 77·0-90·7) versus 89·0% (81·9-94·0; p=0·25) and specificity was 87·8% (95% CI 81·6-92·5) versus 68·6% (60·7-75·8; p<0·0001).
INTERPRETATION: The DCNN model showed similar sensitivity and improved specificity in identifying patients with thyroid cancer compared with a group of skilled radiologists. The improved technical performance of the DCNN model warrants further investigation as part of randomised clinical trials.
FUNDING: The Program for Changjiang Scholars and Innovative Research Team in University in China, and National Natural Science Foundation of China.

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PMID: 30583848

4. **World J Surg. 2018 Dec 11. doi: 10.1007/s00268-018-04877-w. [Epub ahead of print]**
Transoral Robotic Thyroidectomy for Papillary Thyroid Carcinoma: Perioperative Outcomes of 100 Consecutive Patients.
Kim HK(1), Chai YJ(2), Dionigi G(3), Berber E(4), Tufano RP(5), Kim HY(6).
Author information:
(1)Department of Surgery, KUMC Thyroid Center, Korea University Hospital, Korea University College of Medicine, 73, Inchon-ro, Seongbuk-gu, Seoul, 02841, Republic of Korea.
(2)Department of Surgery, Seoul National University Boramae Medical Center, Seoul, Republic of Korea.
(3)Division of Endocrine Surgery, Department of Human Pathology in Adulthood and Childhood "G. Barresi", University Hospital "G. Martino", University of Messina, Messina, Italy.
(4)Center for Endocrine Surgery, Cleveland Clinic, Cleveland, OH, USA.
(5)Department of Otolaryngology-Head and Neck Surgery, The Johns Hopkins University School of Medicine, Baltimore, MD, USA.
(6)Department of Surgery, KUMC Thyroid Center, Korea University Hospital, Korea University College of Medicine, 73, Inchon-ro, Seongbuk-gu, Seoul, 02841, Republic of Korea. hoonyubkim@korea.ac.kr.

BACKGROUND: Endoscopic transoral thyroidectomy is a recently introduced technique of remote access thyroidectomy. We previously reported the feasibility of the robotic approach (TORT). Nevertheless, experience to date is limited, with scant data on outcomes in patients with papillary thyroid carcinoma (PTC).
METHODS: This was a retrospective analysis of prospectively collected data. Patients with PTC, who underwent TORT at a single center between March 2016 and February 2017, were analyzed.
RESULTS: There were a total of 100 patients (85 women, 15 men) with a mean age of 40.7 ± 9.8 years, and a mean tumor size of 0.8 ± 0.5 cm. Nine patients underwent a total thyroidectomy, and 91 underwent a lobectomy. The operative time for a total thyroidectomy and lobectomy was 270.0 ± 9.3 and 210.8 ± 32.9 min, respectively. Ipsilateral prophylactic central neck compartment dissection was performed routinely with retrieval of 5.0 ± 3.6 lymph nodes. Perioperative morbidity was present in nine patients including transient recurrent laryngeal

nerve palsy (n = 1), postoperative bleeding requiring surgical intervention (n = 1), zygomatic bruising (n = 2), chin flap perforation (n = 1), oral commissure tearing (n = 2), and chin dimpling (n = 2). There was no conversion to endoscopic or conventional open thyroid surgery.
CONCLUSION: In this study, TORT could be safely performed in a large series of patients with PTC without serious complications. In selected patients, TORT by experienced surgeons could be considered an alternative approach for remote access thyroidectomy.
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PMID: 30539261

5. **World J Surg. 2018 Dec 7. doi: 10.1007/s00268-018-04879-8. [Epub ahead of print]**
Percutaneous Microwave Ablation of Metastatic Lymph Nodes from Papillary Thyroid Carcinoma: Preliminary Results.
Zhou W(1), Chen Y(1), Zhang L(1), Ni X(1), Xu S(1), Zhan W(2).
Author information:
(1)Department of Ultrasound, Rui Jin Hospital, School of Medicine, Shanghai Jiao Tong University, 197 Ruijin 2 Rd, 200025, Shanghai, China.
(2)Department of Ultrasound, Rui Jin Hospital, School of Medicine, Shanghai Jiao Tong University, 197 Ruijin 2 Rd, 200025, Shanghai, China. shanghairuijinus@163.com.

BACKGROUND: Our purpose is to assess the effectiveness and safety of ultrasound-guided percutaneous microwave ablation (MWA) for lymph node metastases (LNMs) from papillary thyroid carcinomas (PTC).
METHODS: In total, 14 patients with recurrent PTC were enrolled in this retrospective study. The vascularity within the ablation zone was evaluated by contrast-enhanced ultrasonography (CEUS) after MWA. Patients were followed up with measurement of the size and volume of tumor, serum thyroglobulin, and clinical evaluation at 7 days, 1, 3, 6 months, and every 6 months thereafter.
RESULTS: Twenty-one LNMs were confirmed by biopsy and successfully treated by MWA in a single session. No incomplete ablation was detected by CEUS after treatment. The average largest diameter and volume of the tumors were reduced from 10.1 ± 4.7 mm (range, 3.1-20.0 mm) and 291.9 ± 255.6 mm3 (range, 11.6-766.6 mm3) to 0.9 ± 1.6 mm (range, 0-4.1 mm; $p < 0.05$) and 4.0 ± 9.0 mm3 (range, 0-31.6 mm3; $p < 0.05$) at the final follow-up. Neither progression of treated tumors nor newly suspicious LNMs could be detected after treatment. The overall complication rate was 7.1% (1/14).
CONCLUSIONS: Ultrasound-guided MWA can effectively control LNMs from PTC, but it is less safe for tumors in the central compartment. MWA may become an alternative therapy in selected PTC patients, who were ineligible or refused to undergo repeated neck explorations.
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PMID: 30536023

6. **Lancet Diabetes Endocrinol. 2019 Jan;7(1):7-8. doi: 10.1016/S2213-8587(18)30335-8. Epub 2018 Nov 27.**
Distinguishing remnant ablation from adjuvant treatment in differentiated thyroid cancer.

Tuttle RM(1).
Author information:
(1)Memorial Sloan Kettering Cancer Center, New York, NY 10021, USA. Electronic address: Tuttlem@mskcc.org.
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PMID: 30501975

7. **Lancet Diabetes Endocrinol. 2019 Jan;7(1):44-51. doi: 10.1016/S2213-8587(18)30306-1. Epub 2018 Nov 27.**

Recurrence after low-dose radioiodine ablation and recombinant human thyroid-stimulating hormone for differentiated thyroid cancer (HiLo): long-term results of an open-label, non-inferiority randomised controlled trial.

Dehbi HM(1), Mallick U(2), Wadsley J(3), Newbold K(4), Harmer C(5), Hackshaw A(6).
Author information:
(1)Cancer Research UK & UCL Cancer Trials Centre, UCL Cancer Institute, University College London, London, UK.
(2)Freeman Hospital, Newcastle upon Tyne, UK.
(3)Weston Park Hospital, Sheffield, UK.
(4)Royal Marsden Hospital, Sutton, UK.
(5)Independent Doctors Federation, London, UK.
(6)Cancer Research UK & UCL Cancer Trials Centre, UCL Cancer Institute, University College London, London, UK. Electronic address: a.hackshaw@ucl.ac.uk.

BACKGROUND: Two large randomised trials of patients with well-differentiated thyroid cancer reported in 2012 (HiLo and ESTIMABL1) found similar post-ablation success rates at 6-9 months between a low administered radioactive iodine (131I) dose (1·1 GBq) and the standard high dose (3·7 GBq). However, recurrence rates following radioactive iodine ablation have previously only been reported in observational studies, and recently in ESTIMABL1. We aimed to compare recurrence rates between radioactive iodine doses in HiLo.
METHODS: HiLo was a non-inferiority, parallel, open-label, randomised controlled factorial trial done at 29 centres in the UK. Eligible patients were aged 16-80 years with histological confirmation of differentiated thyroid cancer requiring radioactive iodine ablation (performance status 0-2, tumour stage T1-T3 with the possibility of lymph-node involvement but no distant metastasis and no microscopic residual disease, and one-stage or two-stage total thyroidectomy). Patients were randomly assigned (1:1:1:1) to 1·1 GBq or 3·7 GBq ablation, each prepared with either recombinant human thyroid-stimulating hormone (rhTSH) or thyroid hormone withdrawal. Patients were followed up at annual clinic visits. Recurrences were diagnosed at each hospital with a combination of established methods according to national standards. We used Kaplan-Meier curves and hazard ratios (HRs) for time to first recurrence, which was a pre-planned secondary outcome. This trial is registered with ClinicalTrials.gov, number NCT00415233.
RESULTS: Between Jan 16, 2007, and July 1, 2010, 438 patients were randomly assigned. At the end of the follow-up period in Dec 31, 2017, median follow-up was 6·5 years (IQR 4·5-7·6) in 434 patients (217 in the low-dose group and 217 in the high-dose group). Confirmed recurrences were seen in 21 patients: 11 who had 1·1 GBq ablation and ten who had 3·7 GBq ablation. Four of these (two in each group) were considered to be persistent disease. Cumulative recurrence rates were

similar between low-dose and high-dose radioactive iodine groups (3 years, 1·5% vs 2·1%; 5 years, 2·1% vs 2·7%; and 7 years, 5·9% vs 7·3%; HR 1·10 [95% CI 0·47-2·59]; p=0·83). No material difference in risk was seen for T3 or N1 disease. Recurrence rates were also similar among patients who were prepared for ablation with rhTSH and those prepared with thyroid hormone withdrawal (3 years, 1·5% vs 2·1%; 5 years, 2·1% vs 2·7%; and 7 years, 8·3% vs 5·0%; HR 1·62 [95% CI 0·67-3·91]; p=0·28). Data on adverse events were not collected during follow-up.
INTERPRETATION: The recurrence rate among patients who had 1·1 GBq radioactive iodine ablation was not higher than that for 3·7 GBq, consistent with data from large, recent observational studies. These findings provide further evidence in favour of using low-dose radioactive iodine for treatment of patients with low-risk differentiated thyroid cancer. Our data also indicate that recurrence risk was not affected by use of rhTSH.
FUNDING: Cancer Research UK.

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PMCID: PMC6299255
PMID: 30501974

8. **World J Surg. 2018 Nov 21. doi: 10.1007/s00268-018-4862-9. [Epub ahead of print]**
Occult Contralateral Lateral Lymph Node Metastases in Unilateral N1b Papillary Thyroid Carcinoma.
Bohec H(1), Breuskin I(1), Hadoux J(2), Schlumberger M(2), Leboulleux S(2), Hartl DM(3).
Author information:
(1)Department of Head and Neck Oncology, Gustave Roussy, Université Paris-Saclay, 114 rue Edouard Vaillant, 94805, Villejuif, France.
(2)Department of Medical Imaging, Nuclear Medicine and Endocrine Oncology, Gustave Roussy, Université Paris-Saclay, 114 rue Edouard Vaillant, 94805, Villejuif, France.
(3)Department of Head and Neck Oncology, Gustave Roussy, Université Paris-Saclay, 114 rue Edouard Vaillant, 94805, Villejuif, France. dana.hartl@gustaveroussy.fr.

OBJECTIVE: Therapeutic lateral neck dissection (ND) is recommended for N1b papillary thyroid carcinoma (PTC), while prophylactic contralateral lateral ND is not. Given the paucity of data, we investigated the frequency of and risk factors for occult lymph node metastases (LNM) in the contralateral lateral neck for N1b patients.
PATIENTS AND METHODS: This is a retrospective study conducted at a cancer center. Inclusion criteria were: unilateral PTC and ipsilateral lateral LNM confirmed by fine-needle aspiration biopsy. Patients with contralateral lateral LNM or bilateral tumor on ultrasound were excluded. All patients were treated with total thyroidectomy, bilateral central ND, ipsilateral therapeutic lateral ND and prophylactic contralateral ND of levels III-IV, followed by radioactive iodine.
RESULTS: Sixty-three patients met the inclusion criteria. Occult contralateral lateral LNM were found in 23/63 patients (36.5%) who had more LNM in ispilateral ($p = .01$) and contralateral level VI ($p < .0001$), more frequent microscopic tumor in the contralateral lobe ($p = .017$) and a trend toward being at high risk

(p = .06). Using receiver operating characteristic analysis, a cutoff of >4 LNM in ipsilateral level VI optimized sensitivity and specificity for predicting contralateral lateral LNM, with a sensitivity of 74%, specificity of 65%, positive predictive value of 55% and negative predictive value of 81%. Neck recurrence occurred in 14%, with only 1 patient recurring only in the contralateral lateral neck (1.5%).
CONCLUSION: Occult LNM in the contralateral lateral neck was found in 36.5% of patients. Five or more ipsilateral central LNM may aid in predicting contralateral lateral LNM, and high-risk patients may be more at risk. The clinical benefit of prophylactic contralateral lateral ND remains doubtful, however.
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PMID: 30465086

9. **J Clin Endocrinol Metab. 2018 Nov 19. doi: 10.1210/jc.2018-02437. [Epub ahead of print]**
Still Perfecting Radioiodine in Thyroid Cancer, After All These Years.
Wirth LJ(1).
Author information:
(1)Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts.
DOI: 10.1210/jc.2018-02437
PMID: 30462299

10. **J Clin Endocrinol Metab. 2019 Jan 1;104(1):41-48. doi: 10.1210/jc.2018-00847.**
Thyroid Cancer and Benign Nodules After Exposure In Utero to Fallout From Chernobyl.
Hatch M(1), Brenner AV(1), Cahoon EK(1), Drozdovitch V(1), Little MP(1), Bogdanova T(2), Shpak V(2), Bolshova E(2), Zamotayeva G(2), Terekhova G(2), Shelkovoy E(2), Klochkova V(2), Mabuchi K(1), Tronko M(2).
Author information:
(1)Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland.
(2)Institute of Endocrinology and Metabolism, Kiev, Ukraine.

Background: Children and adolescents exposed to radioactive iodine-131 (I-131) in fallout from the 1986 Chernobyl nuclear accident appear to be at increased risk of thyroid cancer and benign thyroid nodules. The prenatal period is also considered radiosensitive, and the fetal thyroid can absorb I-131 from the maternal circulation.
Objectives: We aimed to estimate the risk of malignant and benign thyroid nodules in individuals exposed prenatally.
Methods: We studied a cohort of 2582 subjects in Ukraine with estimates of I-131 prenatal thyroid dose (mean = 72.6 mGy), who underwent two standardized thyroid screening examinations. To evaluate the dose-response relationship, we estimated the excess OR (EOR) using logistic regression.
Results: Based on a combined total of eight cases diagnosed at screenings from 2003 to 2006 and 2012 to 2015, we found a markedly elevated, albeit not statistically significant, dose-related risk of thyroid cancer (EOR/Gy = 3.91, 95% CI: -1.49, 65.66). At cycle 2 (n = 1,786), there was a strong and significant

association between I-131 thyroid dose and screen-detected large benign nodules (≥10 mm) (EOR/Gy = 4.19, 95% CI: 0.68, 11.62; P = 0.009), but no significant increase in risk for small nodules (<10 mm) (EOR/Gy = 0.34, 95% CI: -0.67, 2.24; P = 0.604).
Conclusions: The dose effect by nodule size, with I-131 risk for large but not small nodules, is similar to that among exposed children and adolescents in Belarus. Based on a small number of cases, there is also a suggestive effect of I-131 dose on thyroid cancer risk.
DOI: 10.1210/jc.2018-00847
PMID: 30445441

11. **J Clin Endocrinol Metab. 2018 Nov 5. doi: 10.1210/jc.2018-01589. [Epub ahead of print]**
Recombinant thyrotropin vs levothyroxine withdrawal in 131I therapy of N1 thyroid cancer: a large matched cohort study (ThyrNod).
Leenhardt L(1), Leboulleux S(2), Bournaud C(3), Zerdoud S(4), Schvartz C(5), Ciappuccini R(6), Kelly A(7), Morel O(8), Dygai-Cochet I(9), Rusu D(10), Chougnet CN(11), Lion G(12), Eberlé-Pouzeratte MC(13), Catargi B(14), Kabir-Ahmadi M(15), Le Peillet Feuillet E(15), Taïeb D(16).
Author information:
(1)Pitié-Salpêtrière Hospital, Sorbonne Université, Paris, France.
(2)Gustave Roussy, Univ. Paris Saclay Villejuif, France.
(3)Hospices Civils de Lyon, Lyon, France.
(4)Institute University du cancer Toulouse, France.
(5)Jean Godinot Centre, Reims, France.
(6)François Baclesse Centre, Caen, France.
(7)Jean Perrin Centre, Clermont-Ferrand, France.
(8)Paul Papin Centre, Angers, France.
(9)Georges François Leclerc Centre, Dijon, France.
(10)René Gauducheau Centre, Nantes, France.
(11)Saint-Louis Hospital, Paris, France.
(12)CHRU de Lille, Lille, France.
(13)Montpellier Cancer Institute, Montpellier, France.
(14)St André Hospital, Bordeaux, France.
(15)Sanofi Genzyme, France.
(16)Aix-Marseille Univ, La Timone University Hospital, CERIMED, France.

Context: Recombinant human thyrotropin (rhTSH) has been shown to be an effective stimulation method for radioactive iodine (RAI) therapy in differentiated thyroid cancer including those with nodal metastases (N1 DTC).
Objectives: To demonstrate the non-inferiority of rhTSH vs thyroid hormone withdrawal (THW) in preparation to RAI regarding disease status at the first evaluation in the real-life setting in N1 DTC patients.
Design, patients: This was a French multicenter retrospective study. Groups were matched according to age (<45/≥45 years), number of N1 (≤5/>5 lymph nodes) and stage (pT1-T2/pT3).
Results: The cohort consisted of 404 pT1-T3/N1/M0 DTC, prepared with rhTSH (n=205) or THW (n=199). Pathological characteristics and initial administrated RAI activities (3.27 ±1.00 GBq) were similar between the two groups. At first evaluation (6-18 months post-RAI), disease-free status was defined by

thyroglobulin levels below threshold and a normal ultrasound. Disease-free rate was not inferior in the rhTSH group (75.1%) compared to the THW group (71.9%). The observed difference between the success rates was 3.3 % [-6.6; 13.0]; rhTSH was therefore considered non-inferior to THW as the upper limit of this interval was less than 15%. At the last evaluation (29.7± 20.7 for rhTSH and 36.7± 23.8 months for THW)), 83.5% (rhTSH) and 81.5% (THW) of patients achieved a complete response. This result was not influenced by any of the known prognostic factors. Conclusions: A preparation for initial RAI treatment with rhTSH was non-inferior to one with THW in our series of pT1-T3/N1/M0-DTC on disease-free status outcomes at the first evaluation and after three years.
DOI: 10.1210/jc.2018-01589
PMID: 30398518

12. **World J Surg. 2019 Feb;43(2):534-539. doi: 10.1007/s00268-018-4823-3.**
Risk Factors for Readmission After Parathyroidectomy for Renal Hyperparathyroidism.
Lee JD(1), Kuo EJ(1), Du L(2), Yeh MW(1), Livhits MJ(3).
Author information:
(1)Section of Endocrine Surgery, UCLA David Geffen School of Medicine, 10833 Le Conte Ave, 72-228 CHS, Los Angeles, CA, 90095, USA.
(2)Department of Biomathematics, UCLA David Geffen School of Medicine, Los Angeles, CA, 90095, USA.
(3)Section of Endocrine Surgery, UCLA David Geffen School of Medicine, 10833 Le Conte Ave, 72-228 CHS, Los Angeles, CA, 90095, USA. mlivhits@mednet.ucla.edu.

BACKGROUND: Patients with renal hyperparathyroidism (RHPT) are susceptible to major electrolyte fluctuations following parathyroidectomy, which may predispose them to early readmission. The purpose of this study is to evaluate risk factors for readmission in patients undergoing parathyroidectomy for RHPT.
METHODS: Patients with renal failure who underwent parathyroidectomy were abstracted from the California Office of Statewide Health Planning and Development (1999-2012). Multivariable logistic regression was used to identify risk factors for readmission within 30 days of discharge.
RESULTS: The cohort included 4411 patients, of whom 17% were readmitted. Procedures included subtotal parathyroidectomy (74% of cases) and total parathyroidectomy with autotransplantation (26%). Median time to readmission was 9 days (interquartile range 4-16 days). Electrolyte disturbances including hypocalcemia were present in 36% of readmissions and were the most common cause for readmission. Independent risk factors for readmission included Black race [odds ratio (OR) 1.26, 95% confidence interval (CI) 1.00-1.57], Hispanic race (OR 1.38, 95% CI 1.12-1.71), disposition with home health (OR 1.94, 95% CI 1.35-2.77), disposition to a skilled nursing facility (OR 2.30, 95% CI 1.58-3.35), and total parathyroidectomy with autotransplantation (OR 1.27, 95% CI 1.06-1.52). Advancing age (OR 0.98, 95% CI 0.98-0.99) and surgery at a high-volume hospital (OR 0.53, 95% CI 0.36-0.77) were protective against readmission.
CONCLUSIONS: Patients undergoing parathyroidectomy for RHPT have a high readmission rate, most frequently for metabolic complications. Increased postoperative vigilance, which may include outpatient laboratory monitoring, may be indicated in patients with risk factors for readmission.

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PMID: 30341470

13. **J Clin Endocrinol Metab. 2019 Jan 1;104(1):103-110. doi: 10.1210/jc.2018-01690.**
Lung Metastasis in Pediatric Thyroid Cancer: Radiological Pattern, Molecular Genetics, Response to Therapy, and Outcome.
Alzahrani AS(1)(2), Alswailem M(2), Moria Y(1), Almutairi R(1), Alotaibi M(1), Murugan AK(2), Qasem E(2), Alghamdi B(2), Al-Handi H(3).
Author information:
(1)Department of Medicine, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.
(2)Department of Molecular Oncology, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.
(3)Department of Pathology and Laboratory Medicine, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.

Context: Lung metastases are common in pediatric thyroid cancer (TC). We present an analysis of a series of lung metastases in pediatric TC.
Patients and Methods: Data from 20 patients (16 females, 4 males; median age, 14.5 years; range 10 to 18 years) were analyzed. The tumors included differentiated TC in 19 patients and poorly differentiated TC in 1 patient.
Results: Lung metastasis presented with three distinct radiological patterns: lung uptake on diagnostic radioactive iodine whole body scan (DxWBS) only in 3 patients (15%); lung uptake on DxWBS and CT scan as micrometastases (≤1 cm) in 16 patients (80%); and lung uptake on DxWBS and CT scan as macrometastases (>1 cm) in 1 patient (5%). Iodine-131 therapies were administered to all patients (median, three; range one to eight) with a median cumulative administered activity of 317.5 mCi (range, 109 to 682 mCi). None of the patients achieved a complete response but the biochemical response was substantial. During a median follow-up period of 8.2 years (range, 0.75 to 16.3 years), 1 patient (5%) died, 1 patient (5%) had a biochemically incomplete response, 2 patients (10%) had an indeterminate response, 1 patient (5%) had progressive structural disease, and 14 patients (70%) had stable structural disease. Mutational testing of 10 of 20 tumors revealed only two PIK3CA mutations in a single tumor.
Conclusions: Lung metastases are common in pediatric TC and present most frequently with bilateral radioiodine-avid micrometastases. Known single point mutations in adult TC are rare in pediatric TC. The biochemical response to iodine-131 can be substantial but resolution of structural abnormalities is rare.
DOI: 10.1210/jc.2018-01690
PMID: 30272236

14. **World J Surg. 2019 Feb;43(2):513-518. doi: 10.1007/s00268-018-4813-5.**
Usefulness of Stereotactic Radiotherapy Using the CyberKnife for Patients with Inoperable Locoregional Recurrences of Differentiated Thyroid Cancer.
Ishigaki T(1), Uruno T(2), Tanaka T(2), Ogimi Y(2), Masaki C(2), Akaishi J(2), Hames KY(2), Yabuta T(2), Suzuki A(2), Tomoda C(2), Matsuzu K(2), Ohkuwa K(2), Kitagawa W(2), Nagahama M(2), Sugino K(2), Ito K(2).
Author information:
(1)Department of Surgery, Ito Hospital, 4-3-6 Jingumae, Shibuya-ku, Tokyo,

150-8308, Japan. tippdwr@jikei.ac.jp.
(2)Department of Surgery, Ito Hospital, 4-3-6 Jingumae, Shibuya-ku, Tokyo, 150-8308, Japan.

BACKGROUND: Surgical resection is the preferred treatment for locoregional recurrence of differentiated thyroid cancer (DTC). However, some recurrences are unresectable because of their aggressive invasion or severe adhesions. On the other hand, stereotactic radiotherapy (SRT) enables high-dose irradiation to target lesions, and its usefulness for various cancers has been reported. The objective of the present study was to investigate the feasibility and efficacy of SRT as salvage treatment for locoregional recurrence of DTC.
METHODS: Between August 2011 and December 2017, 52 locoregional recurrent lesions in 31 patients with recurrent DTC were treated by SRT using the CyberKnife system. Information on the adverse events associated with SRT was retrospectively collected from the patients' medical records. Of the 52 lesions, 33 could be evaluated for therapeutic effectiveness by follow-up CT, and response was assessed using the RECIST criteria.
RESULTS: Twenty-five patients had papillary carcinoma, 5 had follicular carcinoma, and 1 had poorly differentiated cancer. SRT was delivered in one to 20 fractions, and the median dose was 30 Gy (range 15-60 Gy). Adverse events were not frequent, but 1 patient developed bilateral vocal cord palsy that required emergent tracheostomy. The median follow-up period of 33 lesions was 14 months (range 1-54 months). Complete response, partial response, stable disease, and progressive disease were seen in 10, 11, 9, and 3 patients, respectively. The 3-year local control rate was 84.6%.
CONCLUSION: SRT using the CyberKnife system was found to be a feasible and effective treatment to suppress the growth of locoregional recurrence of DTC.
DOI: 10.1007/s00268-018-4813-5
PMID: 30267291

15. **J Clin Endocrinol Metab. 2019 Feb 1;104(2):277-284. doi: 10.1210/jc.2018-00774.**
Clinical and Molecular Characteristics May Alter Treatment Strategies of Thyroid Malignancies in DICER1 Syndrome.
van der Tuin K(1), de Kock L(2), Kamping EJ(3), Hannema SE(4), Pouwels MM(5), Niedziela M(6), van Wezel T(7), Hes FJ(1), Jongmans MC(3)(8)(9), Foulkes WD(2), Morreau H(7).
Author information:
(1)Department of Clinical Genetics, Leiden University Medical Centre, Leiden, Netherlands.
(2)Department of Human Genetics, McGill University, Montreal, Quebec, Canada.
(3)Department of Clinical Genetics, Radboud University Medical Centre, Nijmegen, Netherlands.
(4)Department of Pediatrics, Leiden University Medical Centre, Leiden, Netherlands.
(5)Department of Internal Medicine, Division of Endocrinology, Medical Spectrum Twente, Enschede, Netherlands.
(6)Department of Pediatric Endocrinology and Rheumatology, Karol Jonscher's Clinical Hospital, Poznan University of Medical Sciences, Poznan, Poland.
(7)Department of Pathology, Leiden University Medical Centre, Leiden, Netherlands.

(8)Department of Medical Genetics, Utrecht University Medical Center, Utrecht, Netherlands.
(9)Princess Maxima Center for Pediatric Oncology, Utrecht, Netherlands.

Context: DICER1 syndrome is a rare autosomal-dominantly inherited disorder that predisposes to a variety of cancerous and noncancerous tumors of mostly pediatric and adolescent onset, including differentiated thyroid carcinoma (DTC). DTC has been hypothesized to arise secondarily to the increased prevalence of thyroid hyperplastic nodules in syndromic patients.
Objective: To determine somatic alterations in DICER1-associated DTC and to study patient outcomes.
Design: Retrospective series.
Setting: Tertiary referral centers.
Patients: Ten patients with germline pathogenic DICER1 variants and early-onset DTC.
Methods: Somatic DICER1 mutation analysis, extensive somatic DNA variant and gene fusion analyses were performed on all tumors.
Results: Median age at DTC diagnosis was 13.5 years and there was no recurrent or metastatic disease (median follow-up, 8 years). All thyroid specimens showed diffuse nodular hyperplasia with at least one focus suspicious of DTC but without infiltrative growth, extrathyroidal extension, vascular invasion, or lymph node metastasis. Most of the individual nodules (benign and malignant) sampled from the 10 tumors harbored distinct DICER1 RNase IIIb hotspot mutations, indicating a polyclonal composition of each tumor. Furthermore, nine of 10 DICER1-related DTCs lacked well-known oncogenic driver DNA variants and gene rearrangements.
Conclusion: On the basis of our clinical, histological, and molecular data, we consider that most DICER1-related DTCs form a low-risk subgroup. These tumors may arise within one of multiple benign monoclonal nodules; thus, hemi-thyroidectomy or, more likely, total thyroidectomy may often be required. However, radioiodine treatment may be unnecessary given the patients' ages and the tumors' low propensity for metastases.
DOI: 10.1210/jc.2018-00774
PMID: 30260442

16. **J Clin Endocrinol Metab. 2019 Mar 1;104(3):721-729. doi: 10.1210/jc.2018-01104.**
Primary Hyperparathyroidism in Pregnancy: Maternofetal Outcomes at a Quaternary Referral Obstetric Hospital, 2000 Through 2015.
Rigg J(1)(2), Gilbertson E(3)(4), Barrett HL(1)(2), Britten FL(1)(2), Lust K(1)(2).
Author information:
(1)Royal Brisbane and Women's Hospital, Herston, Queensland, Australia.
(2)The University of Queensland, Royal Brisbane Clinical Unit, Herston, Queensland, Australia.
(3)Sunshine Coast University Hospital, Birtinya, Queensland, Australia.
(4)The University of Queensland, Sunshine Coast Clinical Unit, Sunshine Coast Health Institute, Birtinya, Queensland, Australia.

Context: Primary hyperparathyroidism (PHPT) in pregnancy has historically been associated with substantial maternofetal morbidity and mortality rates. The optimal treatment and timing of surgical intervention in pregnancy remain

contested.
Objective: To compare maternofetal outcomes of medically and surgically treated patients with PHPT in pregnancy.
Design: Retrospective chart review.
Setting: Quaternary referral hospital.
Patients: Women with PHPT in pregnancy treated between 1 January 2000 and 31 December 2015.
Interventions: Medical therapy or parathyroid surgery.
Main Outcomes Measured: Timing of diagnosis; maternal corrected serum calcium concentrations; gestation, indication and mode of delivery; complications attributable to PHPT; birth weight; and admission to the neonatal intensive care unit (NICU).
Results: Twenty-two pregnancies were managed medically, and six patients underwent parathyroidectomy in pregnancy (five in trimester 2, and one at 32 weeks gestation). Most patients treated medically either had a corrected serum calcium concentration <2.85 mmol/L in early pregnancy or had PHPT diagnosed in trimester 3. Of viable medically managed pregnancies, 30% were complicated by preeclampsia, and preterm delivery occurred in 66% of this group. All preterm neonates required admission to the NICU for complications related to prematurity. All surgically treated patients delivered their babies at term, and there were no complications of parathyroid surgery.
Conclusion: Maternofetal outcomes have improved relative to that reported in early medical literature in patients treated medically and surgically, but the rates of preeclampsia and preterm delivery were higher in medically treated patients. The study was limited by its retrospective design and small sample sizes.
DOI: 10.1210/jc.2018-01104
PMID: 30247615

17. **World J Surg. 2019 Feb;43(2):540-551. doi: 10.1007/s00268-018-4802-8.**
A Propensity Score-matched Comparison Study of Surgical Outcomes in Patients with Differentiated Thyroid Cancer After Robotic Versus Open Total Thyroidectomy.
Bae DS(1), Koo DH(2).
Author information:
(1)Department of Surgery, Haeundae Paik Hospital, Inje University College of Medicine, 875 Haeundae-ro, Haeundae-gu, Busan, 612-030, Korea. md.ds.bae@gmail.com.
(2)Department of Surgery, Haeundae Paik Hospital, Inje University College of Medicine, 875 Haeundae-ro, Haeundae-gu, Busan, 612-030, Korea.

INTRODUCTION: The aim of this study, from a surgical, oncological, and functional perspective, was to identify whether bilateral axillo-breast approach robotic total thyroidectomy (RTT) for differentiated thyroid cancer (DTC) has different surgical outcomes compared to open total thyroidectomy (OTT).
METHODS: Initially, 796 patients who underwent total thyroidectomy were primarily reviewed and 178 who were ineligible for analysis were excluded. Propensity score matching analysis adjusted for clinicopathological characteristics (sex, age, body mass index, extent of central node dissection, tumor size, extrathyroidal extension, and thyroiditis) was conducted, with 246 patients in the OTT group matched with 123 patients in the RTT group.

RESULTS: There were no significant differences in surgical outcomes in terms of surgical safety and oncological safety between the OTT and RTT groups, except in mean operation times (123.51 ± 32.63 vs. 198.39 ± 37.93 min, respectively; P < 0.001). However, the median parathyroid and laryngeal function recovery times were shorter in the RTT group than in the OTT group [88 ± 33.09 (95% CI: 23.148-152.852) vs. 100 ± 16.20 (95% CI: 68.242-131.768) days; P = 0.044 and 87 ± 32.40 (95% CI: 23.489-150.511) vs. 118 ± 49.50 (95% CI: 20.985-215.015) days; P = 0.002].
CONCLUSIONS: The recovery times of laryngeal and parathyroid function were significantly shorter in RTT patients than in OTT patients for DTC. To verify a definitive conclusion about the superiority of robotic total thyroidectomy in terms of parathyroid and laryngeal function recovery, further studies may be necessary.
DOI: 10.1007/s00268-018-4802-8
PMID: 30242457

18. **World J Surg. 2019 Feb;43(2):504-512. doi: 10.1007/s00268-018-4789-1.**
Spontaneous Deceleration and Acceleration of Growth Rate in Medullary Thyroid Carcinomas Suggested by Changes in Calcitonin Doubling Times Over Long-Term Surveillance.
Miyauchi A(1), Kudo T(2), Kihara M(3), Oda H(3), Ito Y(3), Miya A(3).
Author information:
(1)Department of Surgery, Kuma Hospital, 8-2-35 Shimoyamate-dori, Chuo-ku, Kobe, 650-0011, Japan. miyauchi@kuma-h.or.jp.
(2)Department of Internal Medicine, Kuma Hospital, Kobe, Japan.
(3)Department of Surgery, Kuma Hospital, 8-2-35 Shimoyamate-dori, Chuo-ku, Kobe, 650-0011, Japan.

BACKGROUND: Based on our long-term observation of medullary thyroid carcinoma (MTC) patients, we hypothesized that some MTCs have spontaneous deceleration or regression of tumor growth over a long term and that a minority may acquire growth acceleration. We thus compared the calcitonin doubling time (Ct-DT) in the earlier and later half-periods of MTC patients' postoperative course.
METHODS: We followed 26 MTC patients (14 hereditary and 12 sporadic MTCs) with postoperative hypercalcitoninemia with periodic measurements of serum calcitonin (Ct) for >10 years without major interventions. The median period of Ct measurements was 18.3 years (range 10.6-30.2 years). We divided the individual patients' study periods into the earlier and later halves and calculated the Ct-DTs for both periods.
RESULTS: In the hereditary group, the Ct-DT in the later half-period (Later-Ct-DT) was significantly longer than that in the earlier half-period (Earlier-Ct-DT) (median 20.0 years vs. 7.1 years, p = 0.013). These values in the sporadic group were 20.0 years versus 11.1 years, respectively (p =0.774). Twelve patients (seven hereditary and five sporadic) had Later-Ct-DTs significantly longer than their Earlier-Ct-DTs (median 27.4 years vs. 4.9 years) and good prognoses. Two patients (one hereditary, one sporadic) had Later-Ct-DTs significantly shorter than their Earlier-Ct-DTs, and both developed structural recurrence and died of the disease.
CONCLUSION: Many of the hereditary and some of the sporadic MTC patients had elongated Ct-DTs over a long period, suggesting spontaneous deceleration and

regression of tumor growth. A minority of the MTC patients showed Ct-DT shortening, suggesting tumor growth acceleration.
DOI: 10.1007/s00268-018-4789-1
PMID: 30229381

19. **World J Surg. 2019 Feb;43(2):519-526. doi: 10.1007/s00268-018-4787-3.**
Appropriateness of Subadventitial Resection for Invasion of the Carotid Artery by Papillary Thyroid Carcinoma.
Moritani S(1).
Author information:
(1)Center for Head and Neck Surgery, Kusatsu General Hospital, 1660 Yabase Cho, Kusatsu, Shiga, 5258585, Japan. suemoritani@gmail.com.

BACKGROUND: Selection of surgical treatment for patients with papillary thyroid carcinoma (PTC) that includes great vessel invasion is challenging. We investigated the efficacy of tumor excision, with regard to safety of the surgical procedure and prognosis among patients with PTC invasion of the carotid or vertebral artery.
METHODS: This study is a retrospective review of patients who underwent surgical excision for PTC at our institution, between 1981 and 2010, with 49 patients treated for carotid artery invasion and nine for vertebral artery invasion.
RESULTS: Twenty patients with carotid artery invasion receiving initial treatment underwent subadventitial resection. Among 29 relapsing patients with carotid artery invasion, subadventitial resection was performed in 27 and en-block resection and reconstruction in the other two. In patients with carotid artery invasion, locoregional recurrence was identified in 14 patients, with the recurrence specific to the carotid artery in one case and distant recurrence in 15. The 10-year disease-specific survival rate was shorter among relapsing patients (21.7%) than among those receiving an initial treatment (69.3%). At 8 years after surgery, however, the survival rates were comparable between the two groups. Of the nine patients with vertebral artery invasion, two received initial treatment, with either preservation or reconstruction of the vertebral artery. The other six cases were tumor recurrences, treated by tumor and vertebral artery resection. Vertebral artery invasion was associated with carotid artery invasion in five patients and subclavian artery invasion in four.
CONCLUSIONS: Carotid artery invasion by PTC did not extend beyond the adventitia of the artery in the majority of patients. Most patients with vertebral artery invasion required tumor excision with vertebral artery resection.
DOI: 10.1007/s00268-018-4787-3
PMID: 30225564

20. **J Clin Endocrinol Metab. 2019 Feb 1;104(2):258-265. doi: 10.1210/jc.2018-01383.**
Time to Separate Persistent From Recurrent Differentiated Thyroid Cancer: Different Conditions With Different Outcomes.
Sapuppo G(1), Tavarelli M(1), Belfiore A(1), Vigneri R(1)(2), Pellegriti G(3).
Author information:
(1)Endocrinology, Department of Clinical and Experimental Medicine, Garibaldi-Nesima Medical Center, University of Catania, Catania, Italy.
(2)Institute of Biostructures and Bioimages, National Research Council, CNR,

Catania, Italy.
(3)Endocrinology, Garibaldi-Nesima Medical Center, Catania, Italy.

Context: Differentiated thyroid cancer (DTC) has an excellent prognosis, but up to 20% of patients with DTC have disease events after initial treatment, indistinctly defined as persistent/recurrent disease.
Objective: To evaluate the prevalence and outcome of "recurrent" disease (relapse after being 12 months disease-free) compared with "persistent" disease (present ab initio since diagnosis).
Design: Retrospective analysis of persistent/recurrent disease in patients with DTC (1990 to 2016) with 6.5 years of mean follow-up.
Setting: Tertiary referral center for thyroid cancer.
Patients: In total, 4292 patients all underwent surgery ± 131I treatment of DTC.
Main Outcome Measures: DTC cure of disease persistence or recurrence.
Results: A total of 639 of 4292 (14.9%) patients had disease events after initial treatment, most (498/639, 78%) with persistent disease and 141 (22%) with recurrent disease. Relative to patients with recurrent disease, patients with persistent disease were significantly older (mean age 46.9 vs 45.7 years) and with a lower female to male ratio (1.9/1 vs 4.8/1). Moreover, in this group, structured disease was more frequent (65.7% vs 41.1%), and more important, distant metastases were significantly more frequent (38.4% vs 17.0%). At multivariate analysis, male sex (OR = 1.7), age (OR = 1.02), follicular histotype (OR = 1.5), T status (T3; OR = 3), and N status (N1b; OR = 7.7) were independently associated with persistent disease. Only the N status was associated with recurrent disease (N1b; OR = 2.5).
Conclusions: In patients with DTC not cured after initial treatment, persistent disease is more common and has a worse outcome than recurrent disease. Postoperative status evaluated during first-year follow-up may have important clinical implications for planning tailored treatment strategies and long-term follow-up procedures.
DOI: 10.1210/jc.2018-01383
PMID: 30165559

21. **J Clin Endocrinol Metab. 2018 Nov 1;103(11):4216-4223. doi: 10.1210/jc.2018-00803.**
Radioactive Iodine-Related Clonal Hematopoiesis in Thyroid Cancer Is Common and Associated With Decreased Survival.
Boucai L(1), Falcone J(2), Ukena J(1), Coombs CC(3), Zehir A(4), Ptashkin R(4), Berger MF(4)(5), Levine RL(5)(6), Fagin JA(1)(5).
Author information:
(1)Division of Endocrinology, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York.
(2)Weill Cornell Medical College, New York, New York.
(3)Division of Hematology and Oncology, Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.
(4)Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, New York.
(5)Human Oncology and Pathogenesis Program, Memorial Sloan-Kettering Cancer Center, New York, New York.
(6)Department of Medicine, Leukemia Service, Memorial Sloan-Kettering Cancer

Center, New York, New York.

Context: Radioactive iodine (RAI) has been epidemiologically associated with the development of hematologic malignancies. Clonal hematopoiesis (CH) is a precursor clonal state that confers increased risk of leukemia and occurs at an elevated rate in patients with thyroid cancer relative to other solid tumors.
Objective: We explore if the high prevalence of CH may be a result of RAI exposure and whether CH may be a surrogate in the association between RAI and leukemia.
Design: CH, CH-potential driver (CH-PD), and overall survival were evaluated in 279 patients with advanced thyroid carcinoma.
Results: The prevalence of CH in patients with thyroid cancer was 37%, and that of CH-PD was 5.2%. Age was the strongest predictor of CH and CH-PD. For every year increase in age, there was a 5% and 13% increase in the odds of CH and CH-PD, respectively. RAI dose was significantly associated with CH and CH-PD, even after adjustment for age, external beam radiation therapy, and chemotherapy. For every 10 mCi increase in the dose of RAI administered, there was a 2% and 4% increase in the odds of CH and CH-PD, respectively. Patients with CH-PD previously exposed to RAI had a significantly poorer survival, even when stratified by age (heart rate = 3.75, 95% CI = 1.23 to 11.5, P = 0.02).
Conclusions: RAI was associated with a high prevalence of CH, and CH is a precursor state of hematologic malignancies. The implications of this study may favor identification of CH in patients where the risks might outweigh the benefits of receiving RAI therapy for thyroid cancer.
DOI: 10.1210/jc.2018-00803
PMCID: PMC6194804 [Available on 2019-11-01]
PMID: 30137527

22. **J Clin Endocrinol Metab. 2018 Dec 1;103(12):4609-4616. doi: 10.1210/jc.2018-01386.**

Clinical Validation of the Prognostic Stage Groups of the Eighth-Edition TNM Staging for Medullary Thyroid Carcinoma.

Park SY(1), Cho YY(2), Kim HI(3), Choe JH(4), Kim JH(4), Kim JS(4), Oh YL(5), Hahn SY(6), Shin JH(6), Kim K(7), Kim SW(1), Chung JH(1), Kim TH(1).
Author information:
(1)Division of Endocrinology and Metabolism, Department of Medicine, Thyroid Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.
(2)Division of Endocrinology and Metabolism, Department of Medicine, Gyeongsang National University Graduate School of Medicine, Jinju, Gyeongsangnam-do, Korea.
(3)Division of Endocrinology and Metabolism, Department of Medicine, Samsung Changwon Medical Center, Changwon, Gyeongsangnam-do, Korea.
(4)Division of Breast and Endocrine Surgery, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.
(5)Department of Pathology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.
(6)Department of Radiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.
(7)Statistics and Data Center, Research Institute for Future Medicine, Samsung Medical Center, Seoul, Korea.

Context: Despite advances in thyroid cancer staging systems, considerable controversy about the current staging system for medullary thyroid carcinoma (MTC) continues.
Objective: We aimed to evaluate the prognostic performance of the current eighth edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control TNM staging system (TNM-8) and the alternative proposed prognostic stage groups based on recursive partitioning analysis (TNM-RPA).
Design, Setting, and Patients: We retrospectively analyzed 182 patients with MTC treated at a single tertiary Korean hospital between 1995 and 2015.
Interventions and Main Outcome Measures: Survival analysis was conducted according to TNM-8 and TNM-RPA. The area under the receiver-operating characteristic curve (AUC), the proportion of variation explained (PVE), and the Harrell concordance index (C-index) were used to evaluate predictive performance.
Results: Under TNM-8, only two (1.1%) patients were downstaged compared with the seventh edition of the AJCC TNM staging system (TNM-7). The AUC at 10 years, PVE, and C-index were 0.679, 8.7%, and 0.744 for TNM-7 and 0.681, 8.9%, and 0.747 for TNM-8, respectively. Under TNM-RPA, 104 (57.14%) patients were downstaged compared with TNM-8. TNM-RPA had better prognostic performance with respect to cancer-specific survival (AUC at 10 years, 0.750; PVE, 20.9%; C-index, 0.881).
Conclusions: The predictive performance of the revised TNM-8 in patients with MTC has not changed despite its modification from TNM-7. The proposed changes in TNM-RPA were statistically valid and may present a more reproducible system that better estimates cancer-specific survival of individual patients.
DOI: 10.1210/jc.2018-01386
PMID: 30137493

23. **Nat Rev Endocrinol. 2018 Nov;14(11):670-683. doi: 10.1038/s41574-018-0080-7.**
Thyroid surgery for differentiated thyroid cancer - recent advances and future directions.
Wang TS(1), Sosa JA(2).
Author information:
(1)Department of Surgery, Medical College of Wisconsin, Milwaukee, WI, USA. tswang@mcw.edu.
(2)Department of Surgery, University of California at San Francisco, San Francisco, CA, USA.

Population-based studies have demonstrated that an increasing number of incidental thyroid nodules are being identified. The corresponding increase in thyroid-based diagnostic procedures, such as fine-needle aspiration biopsy, has in part led to an increase in the diagnoses of thyroid cancers and to more thyroid surgeries being performed. Small papillary thyroid cancers account for most of this increase in diagnoses. These cancers are considered to be low risk because of the excellent patient outcomes, with a 5-year disease-specific survival of >98%. As a result, controversy remains regarding the optimal management of newly diagnosed differentiated thyroid cancer, as the complications related to thyroidectomy (primarily recurrent laryngeal nerve injury and hypoparathyroidism) have considerable effects on patient quality of life. This Review highlights current debates, including undertaking active surveillance versus thyroid surgery for papillary thyroid microcarcinoma, the extent of

thyroid surgery and lymphadenectomy for low-risk differentiated thyroid cancer, and the use of molecular testing to guide decision-making about whether surgery is required and the extent of the initial operation. This Review includes a discussion of current consensus guideline recommendations regarding these topics in patients with differentiated thyroid cancer. Additionally, innovative thyroidectomy techniques (including robotic and transoral approaches) are discussed, with an emphasis on patient preferences around decision-making and outcomes following thyroidectomy.
DOI: 10.1038/s41574-018-0080-7
PMID: 30131586

24. **J Clin Endocrinol Metab. 2018 Dec 1;103(12):4384-4394. doi: 10.1210/jc.2017-02439.**
Genome-Wide Association Study Reveals Distinct Genetic Susceptibility of Thyroid Nodules From Thyroid Cancer.
Hwangbo Y(1), Lee EK(1), Son HY(2)(3), Im SW(2)(3), Kwak SJ(4), Yoon JW(5)(6), Kim MJ(5)(6), Kim J(7), Choi HS(8), Ryu CH(1), Lee YJ(1), Kim JI(2)(3)(4), Cho NH(9), Park YJ(5).
Author information:
(1)Center for Thyroid Cancer, National Cancer Center, Korea, Goyang, Republic of Korea.
(2)Department of Biochemistry and Molecular Biology, Seoul National University College of Medicine, Seoul, Republic of Korea.
(3)Genomic Medicine Institute, Medical Research Center, Seoul National University, Seoul, Republic of Korea.
(4)Department of Biomedical Sciences, Seoul National University Graduate School, Seoul, Republic of Korea.
(5)Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea.
(6)Department of Internal Medicine, Healthcare Research Institute, Seoul National University Hospital Healthcare System Gangnam Center, Seoul, Republic of Korea.
(7)Molecular Epidemiology Branch, Division of Cancer Epidemiology and Prevention, Research Institute, National Cancer Center, Goyang, Republic of Korea.
(8)Department of Internal Medicine, Kangwon National University Hospital, Kangwon National University School of Medicine, Chuncheon, Republic of Korea.
(9)Department of Preventive Medicine, Ajou University School of Medicine, Suwon, Republic of Korea.

Context: Thyroid nodules are very common, and 7% to 15% of them are diagnosed as thyroid cancer. However, the inherited genetic risk factors for thyroid nodules and their associations with thyroid cancer remain unknown.
Objective: To identify the genetic variants associated with susceptibility to thyroid nodules in comparison with thyroid cancer.
Design and Setting: We performed a three-stage genome-wide association study for thyroid nodules. The discovery stage involved a genome-wide scan of 811 subjects with thyroid nodules and 691 subjects with a normal thyroid from a population-based cohort. Replication studies were conducted in an additional 1981 cases and 3100 controls from the participants of a health checkup. We also performed expression quantitative trait loci analysis of public data.
Results: The most robust association was observed in TRPM3 (rs4745021) in the

joint analysis (OR, 1.26; P = 6.12 × 10-8) and meta-analysis (OR, 1.28; P = 2.11 × 10-8). Signals at MBIP/NKX2-1 were replicated but did not reach genome-wide significance in the joint analysis (rs2415317, P = 4.62 × 10-5; rs944289, P = 8.68 × 10-5). The expression quantitative trait loci analysis showed that TRPM3 expression was associated with the rs4745021 genotype in thyroid tissues. Conclusions: To the best of our knowledge, we have performed the first genome-wide association study of thyroid nodules and identified a susceptibility locus associated with thyroid nodules, suggesting that thyroid nodules have a genetic predisposition distinct from that of thyroid cancer.
DOI: 10.1210/jc.2017-02439
PMID: 30099483

25. **J Clin Endocrinol Metab. 2018 Nov 1;103(11):3993-4004. doi: 10.1210/jc.2018-01225.**
Primary Hyperparathyroidism.
Bilezikian JP(1).
Author information:
(1)Division of Endocrinology, Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, New York.

Background: Primary hyperparathyroidism (PHPT), the most common cause of hypercalcemia, is most often identified in postmenopausal women. The clinical presentation of PHPT has evolved over the past 40 years to include three distinct clinical phenotypes, each of which has been studied in detail and has led to evolving concepts about target organ involvement, natural history, and management.
Methods: In the present review, I provide an evidence-based summary of this disorder as it has been studied worldwide, citing key concepts and data that have helped to shape our concepts about this disease.
Results: PHPT is now recognized to include three clinical phenotypes: overt target organ involvement, mild asymptomatic hypercalcemia, and high PTH levels with persistently normal albumin-corrected and ionized serum calcium values. The factors that determine which of these clinical presentations is more likely to predominate in a given country include the extent to which biochemical screening is used, vitamin D deficiency is present, and whether parathyroid hormone levels are routinely measured in the evaluation of low bone density or frank osteoporosis. Guidelines for parathyroidectomy apply to all three clinical forms of the disease. If surgical guidelines are not met, parathyroidectomy can also be an appropriate option if no medical contraindications are present. If either the serum calcium or bone mineral density is of concern and surgery is not an option, pharmacological approaches are available and effective.
Conclusions: Advances in our knowledge of PHPT have guided new concepts in diagnosis and management.
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PMID: 30060226

26. **World J Surg. 2018 Dec;42(12):3954-3966. doi: 10.1007/s00268-018-4738-z.**
Static Prognostic Factors and Appropriate Surgical Designs for Patients with

Medullary Thyroid Carcinoma: The Second Report from a Single-Institution Study in Japan.

Ito Y(1), Miyauchi A(2), Kihara M(2), Higashiiyama T(2), Fukushima M(2), Miya A(2).
Author information:
(1)Department of Surgery, Kuma Hospital, 8-2-35, Shimoyamate-dori, Chuo-ku, Kobe, Hyogo, 650-0011, Japan. ito01@kuma-h.or.jp.
(2)Department of Surgery, Kuma Hospital, 8-2-35, Shimoyamate-dori, Chuo-ku, Kobe, Hyogo, 650-0011, Japan.
Comment in
World J Surg. 2018 Dec;42(12):3967-3968.

BACKGROUND: Medullary thyroid carcinoma (MTC) originates from calcitonin-producing cells of the thyroid. In 2009, we published our first report on the biological characteristics and prognosis of 118 MTC patients. Herein, we enrolled a larger number of patients with longer follow-up periods to further study the biological characteristics and appropriate therapies for MTC.
METHODS: In general, hemithyroidectomy and total thyroidectomy were performed for sporadic MTC confined to the thyroid lobe and for hereditary MTC with central node dissection, respectively. Moreover, prophylactic modified radical neck dissection was performed on the side of macroscopic tumors.
RESULTS: In total, 233 patients (99 hereditary and 134 sporadic) were enrolled. The median follow-up time was 128 months (range 7-445 months). Biochemical cure was obtained in 36 (62%) of the 58 patients who underwent prophylactic MND and were pathologically positive for lateral node metastasis. None of the patients had recurrence in the preserved thyroid. Distant recurrence was detected in 19 patients, and 12 died of MTC. Preoperative calcitonin and carcinoembryonic antigen levels, tumor size (T) > 4 cm, the male sex, clinical and pathological node metastases (N1), distant metastasis (M1), extrathyroid extension (Ex), and a lack of biochemical cure had prognostic impacts on distant recurrence and/or carcinoma-related mortality on univariate analysis. On multivariate analysis, Ex was independently correlated with distant recurrence, and Ex, T > 4 cm, and M1 independently affected carcinoma-related mortality.
CONCLUSION: MTC patients had excellent prognosis in our institutions, indicating that our surgical strategies were appropriate.
DOI: 10.1007/s00268-018-4738-z
PMCID: PMC6244981
PMID: 30051240

27. **Ann Surg. 2018 Dec;268(6):e62-e63. doi: 10.1097/SLA.0000000000002814.**

The Impact of Surgical Strategy on the Consequences of Secondary Hyperparathyroidism.

Uludag M(1), Kartal K.
Author information:
(1)Health Sciences University, Sisli Hamidiye Etfal Health Practice and Research Center, Istanbul, Turkey Health Sciences University, Sisli Hamidiye Etfal Health Practice and Research Center, Istanbul, Turkey.
DOI: 10.1097/SLA.0000000000002814
PMID: 29771721

28. **World J Surg. 2018 Nov;42(11):3616-3623. doi: 10.1007/s00268-018-4644-4.**
Cribriform-Morular Variant of Papillary Thyroid Carcinoma: Clinical and Pathological Features of 30 Cases.
Akaishi J(1), Kondo T(2), Sugino K(3), Ogimi Y(3), Masaki C(3), Hames KY(3), Yabuta T(3), Tomoda C(3), Suzuki A(3), Matsuzu K(3), Uruno T(3), Ohkuwa K(3), Kitagawa W(3), Nagahama M(3), Katoh R(2), Ito K(3).
Author information:
(1)Department of Surgery, Ito Hospital, 4-3-6, Jingumae, Shibuya-ku, Tokyo, 150-8308, Japan. j-akaishi@ito-hospital.jp.
(2)Department of Pathology, Yamanashi Hospital, Yamanashi, Japan.
(3)Department of Surgery, Ito Hospital, 4-3-6, Jingumae, Shibuya-ku, Tokyo, 150-8308, Japan.

BACKGROUND: Cribriform-morular variant of papillary thyroid carcinoma (CMV-PTC) is rare; it may occur in cases of familial adenomatous polyposis (FAP) or be sporadic. To clarify the clinicopathological features of CMV-PTC, the medical records of these patients were investigated retrospectively.
MATERIALS AND METHODS: Between 1979 and 2016, a total of 17,062 cases with PTC underwent initial surgery at Ito Hospital. Of these, 30 (0.2%) cases histologically diagnosed with CMV-PTC were reviewed.
RESULT: The patients were all women, with a mean age at the time of surgery of 24 years. Seven (23%) cases were thought to have FAP because they had colonic polyposis or a family history of FAP or APC gene mutation. The remaining 23 (77%) were thought to be sporadic. Multiple tumors were detected in 6 cases, with a solitary tumor in 24. One patient had lung metastasis at diagnosis. Eleven patients underwent total thyroidectomy or subtotal thyroidectomy, and 19 underwent lobectomy. Twenty-six (87%) patients underwent neck lymph node dissection. Three patients had tumor metastasis in central lymph nodes, but these were incidentally detected metastatic classical PTC (cPTC) based on histological examination. In this series, there were no cases of LN metastases of CMV-PTC. During a mean follow-up of 15 years, one patient had new cPTC in the remnant thyroid after initial surgery, and the other patients showed no signs of recurrence.
CONCLUSION: CMV-PTC occurred in young women, their long-term prognosis was excellent. Total thyroidectomy is recommended for FAP-associated CMV-PTC, but modified neck lymph node dissection is not necessary.
DOI: 10.1007/s00268-018-4644-4
PMID: 29696324 [Indexed for MEDLINE]

29. **J Clin Endocrinol Metab. 2018 Nov 1;103(11):4275-4282. doi: 10.1210/jc.2017-02529.**
p.Val804Met, the Most Frequent Pathogenic Mutation in RET, Confers a Very Low Lifetime Risk of Medullary Thyroid Cancer.
Loveday C(1), Josephs K(2), Chubb D(1), Gunning A(3), Izatt L(4), Tischkowitz M(5), Ellard S(3), Turnbull C(1)(4)(6)(7).
Author information:
(1)Division of Genetics and Epidemiology, The Institute of Cancer Research, London, United Kingdom.
(2)Department of Clinical Genetics, St George's University Hospital, London,

United Kingdom.
(3)Institute of Biomedical and Clinical Science, University of Exeter Medical School, Exeter, United Kingdom.
(4)Department of Clinical Genetics, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom.
(5)Department of Medical Genetics, University of Cambridge, Cambridge, United Kingdom.
(6)William Harvey Research Institute, Queen Mary University, London, United Kingdom.
(7)National Cancer Registration and Analysis Service, Public Health England, London, United Kingdom.

Context: To date, penetrance figures for medullary thyroid cancer (MTC) for variants in rearranged during transfection (RET) have been estimated from families ascertained because of the presence of MTC.
Objective: To gain estimates of penetrance, unbiased by ascertainment, we analyzed 61 RET mutations assigned as disease causing by the American Thyroid Association (ATA) in population whole-exome sequencing data.
Design: For the 61 RET mutations, we used analyses of the observed allele frequencies in ~51,000 individuals from the Exome Aggregation Consortium (ExAC) database that were not contributed via The Cancer Genome Atlas (TCGA; non-TCGA ExAC), assuming lifetime penetrance for MTC of 90%, 50%, and unbounded.
Setting: Population-based.
Results: Ten of 61 ATA disease-causing RET mutations were present in the non-TCGA ExAC population with observed frequency consistent with penetrance for MTC of >90%. For p.Val804Met, the lifetime penetrance for MTC, estimated from the allele frequency observed, was 4% [95% confidence interval (CI), 0.9% to 8%].
Conclusions: Based on penetrance analysis in carrier relatives of p.Val804Met-positive cases of MTC, p.Val804Met is currently understood to have high-lifetime penetrance for MTC (87% by age 70), albeit of later onset of MTC than other RET mutations. Given our unbiased estimate of penetrance for RET p.Val804Met of 4% (95% CI, 0.9% to 8%), the current recommendation by the ATA of prophylactic thyroidectomy as standard for all RET mutation carriers is likely inappropriate.
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PMCID: PMC6194854
PMID: 29590403

30. **Ann Surg. 2019 Jan;269(1):158-162. doi: 10.1097/SLA.0000000000002474.**
Surgery for Primary Hyperparathyroidism: Adherence to Consensus Guidelines in an Academic Health System.
Kuo EJ(1), Al-Alusi MA(1), Du L(2), Shieh A(3), Livhits MJ(1), Leung AM(3)(4), Yeh MW(1).
Author information:
(1)Section of Endocrine Surgery, UCLA David Geffen School of Medicine, Los Angeles, CA.
(2)Department of Biostatistics, UCLA Fielding School of Public Health, Los Angeles, CA.
(3)Division of Endocrinology, Diabetes, and Metabolism, UCLA David Geffen School of Medicine, Los Angeles, CA.

(4)Division of Endocrinology, Diabetes, and Metabolism, VA Greater Los Angeles Healthcare System, Los Angeles, CA.

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

Letizia Canu,[1,2] Janna A. W. Van Hemert,[1] Michiel N. Kerstens,[3] Robert P. Hartman,[4] Aakanksha Khanna,[5] Ivana Kraljevic,[6] Darko Kastelan,[6] Corin Badiu,[7] Urszula Ambroziak,[8] Antoine Tabarin,[9] Magalie Haissaguerre,[9] Edward Buitenwerf,[3] Anneke Visser,[10] Massimo Mannelli,[2] Wiebke Arlt,[11] Vasileios Chortis,[11] Isabelle Bourdeau,[12] Nadia Gagnon,[12] Marie Buchy,[13] Francoise Borson-Chazot,[13] Timo Deutschbein,[14] Martin Fassnacht,[14,15] Alicja Hubalewska-Dydejczyk,[16] Marcin Motyka,[16] Ewelina Rzepka,[16] Ruth T. Casey,[17] Benjamin G. Challis,[17] Marcus Quinkler,[18] Laurent Vroonen,[19] Ariadni Spyroglou,[20,21] Felix Beuschlein,[20,21] Cristina Lamas,[22] William F. Young,[5] Irina Bancos,[5] and Henri J. L. M. Timmers[1]

[1]Department of Internal Medicine, Division of Endocrinology, Radboud University Medical Center, 6500 HB Nijmegen, Netherlands; [2]Department of Experimental and Clinical Biomedical Sciences University of Florence, 59100 Florence, Italy; [3]Department of Endocrinology, University of Groningen, University Medical Center Groningen, 9713 GZ Groningen, Netherlands; [4]Department of Radiology, Mayo Clinic, Rochester, Minnesota 55905; [5]Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Mayo Clinic, Rochester, Minnesota 55905; [6]Department of Endocrinology, University Hospital Center Zagreb, Zagreb 10000, Croatia; [7]National Institute of Endocrinology C. I. Parhon, Carol Davila University of Medicine and Pharmacy, 011863 Bucharest, Romania; [8]Department of Internal Medicine and Endocrinology, Medical University of Warsaw, 02-097 Warsaw, Poland; [9]Service d'Endocrinologie Hôpital Haut-Lévêque, CHU de Bordeaux, 33600 Pessac, France; [10]Department of Applied Health Research, University of Groningen, University Medical Center Groningen, 9713 GZ Groningen, Netherlands; [11]Institute of Metabolism and Systems Research, University of Birmingham, Birmingham B15 2TT, United Kingdom; [12]Division of Endocrinology, Center Hospitalier de l'Université de Montréal, Montreal H2X 0A9, Quebec, Canada; [13]Fédération d'Endocrinologie, Groupement Hospitalier Est, Hospices Civils de Lyon, 69500 Bron F-69677, France; [14]Department of Internal Medicine I, Division of Endocrinology and Diabetes, University Hospital, University of Wuerzburg, D-97080 Wuerzburg, Germany; [15]Comprehensive Cancer Center Mainfranken, University of Wuerzburg, D-97080 Wuerzburg, Germany; [16]Department of Endocrinology, Jagiellonian University, Collegium Medicum, 31-501 Krakow, Poland; [17]Addenbrooke's Hospital, Metabolic Research Laboratories, Wellcome Trust-MRC Institute of Metabolic Science, University of Cambridge and NIHR Biomedical Research Center, Cambridge CB2 OQQ, United Kingdom; [18]Endocrinology in Charlottenburg, 10627 Berlin, Germany; [19]Department of Endocrinology, Center Hospitalier Universitaire de Liège, Liège 4000, Belgium; [20]Medizinische Klinik und Poliklinik IV Ludwig-Maximilians-Universität München, 80336 Munich, Germany; [21]Klinik für Endokrinologie, Diabetologie und Klinische Ernährung, UniversitätsSpital Zürich, 8091 Zurich, Switzerland; and [22]Endocrinology Department, Hospital General Universitario de Albacete, Albacete, Spain 02006

ORCiD numbers: 0000-0003-4995-8108 (L. Canu).

Background: Up to 7% of all adrenal incidentalomas (AIs) are pheochromocytomas (PCCs). In the evaluation of AI, it is generally recommended that PCC be excluded by measurement of plasma-free or 24-hour urinary fractionated metanephrines. However, recent studies suggest that biochemical exclusion of PCC not be performed for lesions with CT characteristics of an adrenocortical adenoma (ACA).

Aim: To determine the proportion of PCCs with ACA-like attenuation or contrast washout on CT.

Methods: For this multicenter retrospective study, two central investigators independently analyzed the CT reports of 533 patients with 548 histologically confirmed PCCs. Data on tumor size,

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Abbreviations: ACA, adrenocortical adenoma; AI, adrenal incidentalomas; APW, absolute percentage washout; ENSAT, European Network for the Study of Adrenal Tumors; ESE, European Society of Endocrinology; HU, Hounsfield unit; PCC, pheochromocytoma; RPW, relative percentage washout.

unenhanced Hounsfield units (HU), absolute percentage washout (APW), and relative percentage washout (RPW) were collected in addition to clinical parameters.

Results: Among the 376 PCCs for which unenhanced attenuation data were available, 374 had an attenuation of >10 HU (99.5%). In the two exceptions (0.5%), unenhanced attenuation was exactly 10 HU, which lies just within the range of ≤10 HU that would suggest a diagnosis of ACA. Of 76 PCCs with unenhanced HU > 10 and available washout data, 22 (28.9%) had a high APW and/or RPW, suggestive of ACA.

Conclusion: Based on the lack of PCCs with an unenhanced attenuation of <10 HU and the low proportion (0.5%) of PCCs with an attenuation of 10 HU, it seems reasonable to abstain from biochemical testing for PCC in AIs with an unenhanced attenuation of ≤10 HU. The assessment of contrast washout, however, is unreliable for ruling out PCC. (***J Clin Endocrinol Metab*** **104: 312–318, 2019)**

Adrenal pheochromocytomas (PCCs) and extra-adrenal sympathetic paragangliomas are rare tumors that arise from catecholamine-producing chromaffin cells (1). Up to 40% of chromaffin tumors are associated with hereditable tumor syndromes (2–5). The most accurate diagnostic test for the biochemical diagnosis of these tumors is the measurement of plasma free or 24-hour urinary fractionated metanephrines (6, 7). Typical symptoms and signs include headache, tremors, palpitations, sweating, and anxiety. However, up to 25% of patients do not have signs and symptoms, and up to 30% of PCCs are diagnosed following the discovery of an adrenal incidentaloma (AI) (7, 8).

The prevalence of AI on thoracic, abdominal, and pelvic CT ranges between 1.0% and 8.7% depending on age (9–14). Most AIs are adrenocortical adenoma (ACA) (12). Less prevalent causes are myelolipomas, cysts, adrenocortical carcinoma, and metastases from other malignancies. PCCs account for up to 7% of AIs (7). Unlike in situations when substantial adrenal hormone secretion or malignancy are suspected, no treatment is indicated for benign, nonfunctioning ACA. In 2016, the European Society of Endocrinology (ESE) in collaboration with the European Network for the Study of Adrenal Tumors (ENSAT) published a guideline to provide clinicians with evidence-based recommendations for clinical management of patients with AIs (7). This guideline adapts a generally accepted approach in the evaluation of AI by taking into account quantitative CT characteristics. An attenuation of ≤10 Hounsfield units (HU) on unenhanced CT or an absolute percentage washout (APW) of ≥60% or a relative percentage washout (RPW) of ≥40% on CT with delayed washout after 10 to 15 minutes are considered suggestive of ACA.

However, the guidelines and an accompanying meta-analysis (15) clearly indicated that unenhanced CT is the only reliable method to differentiate benign from malignant adrenal tumors. In addition, the guideline recommended that an endocrine work-up for AI be performed, including the measurement of plasma-free or 24-hour urinary fractionated metanephrines. However, the guideline also mentioned that it would be reasonable to avoid biochemical testing for PCC in patients who have AI with an unenhanced attenuation of ≤10 HU. Nevertheless, the authors acknowledged that only two small studies were published on this topic (16, 17). The findings in the latter studies require confirmation in more patients before substantiated statements can be made.

Of note, PCCs demonstrating an attenuation of ≤10 HU have been described, albeit rarely, in the literature (18, 19). Hence, in this international multicenter study, we retrospectively evaluated the quantitative CT characteristics of PCCs, as indicated in the radiological reports, to assess the proportion and associated characteristics of PCCs with an ACA-like attenuation on CT, taking into account both unenhanced attenuation and contrast washout measurements.

Methods

Patients

We included patients with a histologically proven PCC (single or multiple) who had undergone preoperative CT [*i.e.*, unenhanced CT (with or without contrast-enhanced CT) or contrast washout CT]. Patients with only postcontrast CT were not eligible for inclusion. Patients had been diagnosed and treated in centers affiliated with ENSAT. Participating ENSAT centers were the Mayo Clinic, Rochester, Minnesota (n = 153); Radboud University Medical Center, Nijmegen, Netherlands (n = 46); University Hospital Center Zagreb, Zagreb, Croatia (n = 43); Carol Davila University of Medicine and Pharmacy, Bucharest, Romania (n = 42); Medical University of Warsaw, Warsaw, Poland (n = 33); CHU de Bordeaux, Pessac, France (n = 29); University Medical Center Groningen, Groningen, Netherlands (n = 28); University Hospital of Florence, Florence, Italy (n = 21); University of Birmingham, Birmingham, United Kingdom (n = 20); Center Hospitalier de l'Université de Montréal, Montreal, Quebec, Canada (n = 19); Hospices Civils de Lyon, Lyon, France (n = 17); University Hospital of Wuerzburg, Wuerzburg, Germany (n = 17); University Hospital of Krakow, Krakow, Poland (n = 16); Cambridge University Hospitals, Cambridge, United Kingdom (n = 12); Endocrinology

in Charlottenburg, Berlin, Germany (n = 12); Center Hospitalier Universitaire de Liege, Liege, Belgium (n = 10); Medizinische Klinik und Poliklinik IV Ludwig-Maximilians-Universität München, Munich, Germany (n = 10); Hospital General Universitario de Albacete, Albacete, Spain (n = 5). Patients provided informed consent, under ENSAT or local institutional protocol, when required.

Two hundred fourteen patients from the two Dutch centers were also included in a previous study on this topic by Buitenwerf *et al*. (20). In the latter study, a central re-evaluation of CT images was performed to calculate unenhanced attenuation, whereas in the current study, both unenhanced attenuation and contrast washout were analyzed based on locally generated CT reports. Additional inclusion criteria were age at diagnosis ≥18 years, a diagnosis in or after 2000, availability of the CT report, and clinical annotations (age, sex, and underlying hereditary syndrome).

Biochemical testing and imaging

Biochemical testing, usually by measurement of plasma-free or 24-hour urinary fractionated metanephrines, was performed according to local protocols with corresponding reference values. If metanephrines were not available, 24-hour urine or plasma catecholamines were used, in order of preference. Biochemical phenotypes were categorized as "adrenergic," "noradrenergic," or "normal." The phenotype was classified as "adrenergic" when the increment of metanephrines, relative to the upper limits of normal, exceeded 5% of the combined metanephrine and normetanephrine increments. Patients in whom these criteria were not fulfilled and in whom normetanephrine levels exceeded the upper limits of normal were classified as "noradrenergic" (21). In addition, CT scans were obtained according to local protocols regarding contrast procedure, acquisition and reconstruction parameters, and approach to drawing the region of interest for HU measurements.

Evaluation of CT reports

Anonymized imaging reports of preoperative CT scans, generated by local radiologists as part of routine diagnostic evaluation, were submitted for central analysis. The reports were evaluated and scored independently by two observers (L.C. and J.A.W.V.H.) who were blinded to the clinical information. Type of CT examination and field of view, number and location of lesions, tumor size, unenhanced HU, APW and RPW were considered. When multiple unenhanced HU values were mentioned, the highest value was chosen for analysis. When the local report did not mention values for APW/RPW, APW and RPW were calculated according to the formulas below, provided that the required parameters were available.

$$\text{APW} = \frac{\text{HU portal venous phase-HU delayed phase}}{\text{HU portal venous phase-HU unenhanced}} \times 100\%$$

$$\text{RPW} = \frac{\text{HU portal venous phase-HU delayed phase}}{\text{HU portal venous phase}} \times 100\%$$

PCCs were classified as ACA-like according to quantitative CT characteristics in case one of the following criteria were fulfilled: (i) attenuation on unenhanced CT ≤ 10 HU or (ii) attenuation on unenhanced CT ≥ 10 HU and APW ≥ 60% and/or RPW ≥ 40%.

Data management and statistical analysis

Statistical analysis was performed with SPSS software, version 17.0 for Windows (IBM Inc., Armonk, NY). Clinical characteristics were compared between patients with PCC who had and did not have an ACA-like attenuation based on quantitative criteria. Characteristics were compared by using an unpaired t test if variables were continuous or a χ^2 test if variables were categorical. A two-sided P value of < 0.05 was considered to indicate a statistically significant difference.

Results

In total, 1011 cases of PCC and extra-adrenal sympathetic paragangliomas were screened for eligibility by the local investigators at the 18 participating centers. Four hundred seven cases were excluded, mainly because of the performance of postcontrast CT only (n = 305). After central review, 71 additional cases were excluded on the basis of a diagnosis of extra-adrenal paraganglioma rather than PCC (n = 25), lack of CT report (n = 21), incomplete CT report (n = 14), age <18 years (n = 5), lack of histological proof of PCC (n = 4), and performance of postcontrast CT only (n = 2). Of the remaining 533 patients with 548 histologically confirmed PCCs, quantitative CT characteristics were available in 368 patients with 382 PCCs (376 unenhanced HU with or without washout and 6 washout only). The clinical characteristics and information regarding HU and maximum diameter of PCCs are given in Table 1. The distribution of unenhanced attenuation (in HU) is reported in Fig. 1. Details on CT scan protocols and availability of quantitative data from radiology reports are given in Table 2.

PCCs with ACA-like attenuation or washout

Of the 376 PCCs for which unenhanced attenuation was available, 374 had an attenuation of >10 HU (99.5%) (Fig. 2). In the two exceptions (0.5%), unenhanced

Table 1. Characteristics of Patients (n = 368) and Lesions (n = 382) for Whom Quantitative CT Characteristics Were Available

Characteristic	Value
Men, n (%)	163 (44.2)
Mean age at diagnosis ± SD, y	54.01 ± 15.05
Biochemical phenotype, n (%)	
Adrenergic	200 (54.3)
Noradrenergic	111 (30.1)
Normal values	18 (4.8)
Unknown	39 (10.5)
Hereditary syndrome, n (%)	60 (16.3)[a]
Mean maximum diameter ± SD, mm	42.73 ± 21.96 (n = 306)
Mean unenhanced attenuation ± SD, HU	35.04 ± 10.95 (n = 375)

[a] *RET* (n =32), *VHL* (n = 11), *NF1* (n = 11), *SDHB* (n = 2), *SDHD* (n=2), *MAX* (n = 1), and *SDHAF2* (n = 1).

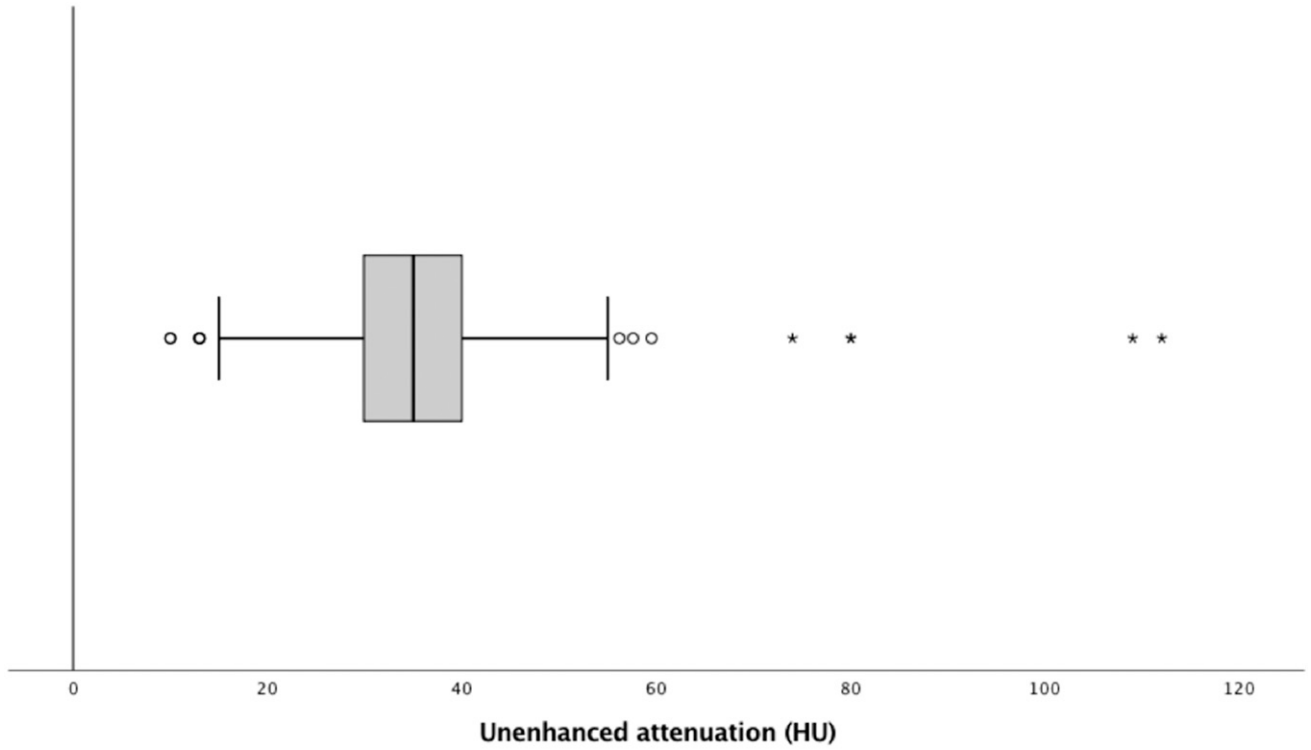

Figure 1. Distribution of unenhanced attenuation (HU, box-and-whiskers plot). Outliers (open circle); extreme values (asterisk); median (vertical line); 25% to 75% (box); 95% CI (whiskers).

attenuation was exactly 10 HU, which lies just within the range of the ≤10 HU cutoff that would suggest a diagnosis of ACA (22). Of these two PCCs, the histology reports were re-evaluated. The first lesion was a 42-mm right adrenal PCC with extensive central hemorrhage. Preoperative urine catecholamine values were reported to be in the normal range; however, metanephrines were not measured. The second lesion was a 48-mm left adrenal PCC that contained areas of prominent nodular adrenocortical hyperplasia besides PCC. No information on the biochemical phenotype could be retrieved.

Of 76 PCCs with unenhanced HU > 10 and available washout, 22 (28.9%) had an APW ≥ 60% and/or an RPW ≥ 40%, suggestive of ACA. In one additional PCC, APW/RPW was high as well, but unenhanced attenuation was unavailable. The local radiologists reported on six additional lesions with characteristics of ACA. The reasons for this, however, could not be verified because washout data were unavailable; in the two cases where unenhanced attenuation was mentioned, it was >10 HU.

The PCCs with an unenhanced attenuation of >10 HU and high APW and/or RPW (n = 22) did not differ from those with an unenhanced attenuation of >10 HU and low washout (n = 54) with respect to sex, tumor size, and hereditary syndrome (data not shown).

Of 548 PCCs, 282 (51.4%) were initially discovered as AI in 276 patients. One of 199 lesions [lesion 1 in online repository (22)] with available quantitative data was among the two lesions with 10 HU. In this subgroup,

Table 2. CT Protocols and Availability of Quantitative Data From Radiological Reports for PCCs

		CT Scan Protocol, n (%)			
Quantitative Data	**All CT Scans**	**Unenhanced**	**Unenhanced and Postcontrast**	**Contrast Washout**	**Unknown**
Total		94 (17.2)	117 (21.4)	148 (27.0)	189 (34.5)
Unenhanced HU only	298 (54.4)	55 (58.5)	40 (34.2)	24 (16.2)	179 (94.7)
Unenhanced HU and APW/RPW	78 (14.2)	NA	NA	77 (52.0)	1 (0.5)
APW/RPW only	6 (1.1)	NA	NA	6 (4.1)	NA
None	166 (30.3)	39 (41.5)	77 (65.8)	41(27.7)	9 (4.8)

Abbreviation: NA, not available.

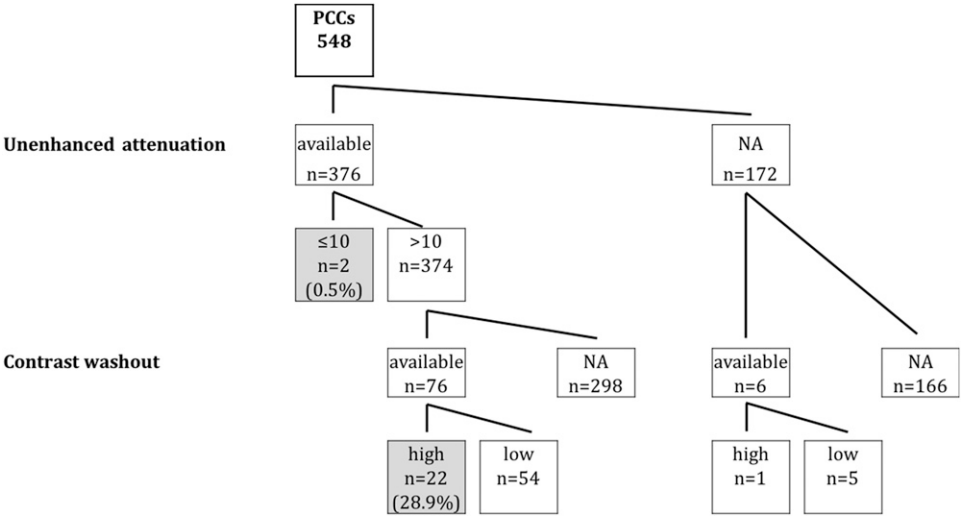

Figure 2. CT characteristics of PCCs. High washout: absolute ≥60% and/or relative ≥40%; low washout: absolute <60% and/or relative <40%. NA, not available.

of 29 PCCs with unenhanced HU > 10 and available washout, 10 (34.4%) had a high APW and/or RPW.

Discussion

We retrospectively evaluated the CT characteristics of PCC in the largest international cohort to date. Our main goal was to determine the proportion of PCCs with an ACA-like appearance based on a low unenhanced attenuation or a high contrast washout. The analysis was based on locally generated radiological reports. Unenhanced HU values were available for 376 of 548 histologically confirmed PCCs, two of which (0.5%) exhibited an attenuation of exactly 10 HU, consistent with an ACA-like attenuation according to recent ESE/ENSAT guidelines. In addition, among 76 PCCs with unenhanced HU > 10 and available washout, 22 (28.9%) showed a high APW and/or RPW, incorrectly suggesting ACA.

In 2016, ESE/ENSAT provided clinical practice guidelines for the management of patients with AIs. The guidelines recommended that, as part of the endocrine workup, PCC should be excluded by measurement of plasma free or 24-hour urinary fractionated metanephrines in all AIs. However, the guidelines stated that an exception could be made for cases in which a non–contrast-enhanced CT attenuation was ≤10 HU. A disclaimer was made that the evidence to support this exception was minimal, with two studies that showed a low likelihood of a PCC among adrenal lesions that were radiologically suggestive of ACA (16, 17). Sane *et al.* (16) examined whether PCC could be ruled out as cause of AIs on the basis of unenhanced attenuation values only. They retrospectively evaluated a cohort of 174 patients with AI. Unenhanced attenuation was available for 115 tumors. Nine patients had a PCC, and in none of these tumors was the unenhanced HU < 10. They concluded that routine measurement of metanephrines is unnecessary in an asymptomatic patient with AI, provided that the lesion is of low attenuation, small, and homogenous. Schalin-Jäntti *et al.* (17) performed a 5-year prospective follow-up study of 56 patients with 69 lipid-rich (*i.e.*, low attenuation) AIs. They found that 24-hour urinary metanephrines were normal at baseline as well as during follow-up. In addition, Jun *et al.* (19) studied 251 patients with AI and had similar results, leading to the conclusion that for small lesions (AI size ≤ 3 cm), noncontrast CT can substitute for biochemical testing for PCC. Nevertheless, all of the conclusions and recommendations made in these previous studies are based on small subsets of PCCs among cohorts of patients with AIs.

Rather than taking AI as a starting point, in the current study and in one previous report, primarily patients with PCC were selected. Buitenwerf *et al.* (20) recently conducted a retrospective study including 214 patients with 222 histologically proven PCCs. Two expert radiologists independently re-evaluated the CT scans. Only 1 PCC of 222 demonstrated an attenuation value of <10 HU. This was a rare case of ACTH-dependent Cushing disease caused by a PCC. In the current study, we found a similarly low proportion (0.5%) of PCCs with an unenhanced attenuation of ≤10 HU. In fact, none of the PCCs had an unenhanced attenuation <10 HU; in only two PCCs it was exactly 10 HU. In these two cases, histology possibly provided some explanation. Hemorrhage, necrosis, and additional adrenocortical changes (23) may result in intralesional heterogeneity, emphasizing the importance of selecting the proper region of interest for the assessment of attenuation.

In ~70% of AIs, attenuation values are ≤10 HU. This illustrates the large number of patients who might benefit from implementing radiological selection to determine in which patients biochemical screening is needed as a second-line test to rule out PCC (15). Approximately 2000 patients with adrenal incidentaloma and an attenuation value ≤10 HU would need to be biochemically screened to diagnose one case of PCC, assuming a 7% prevalence of PCC in the AI population, 70% frequency of attenuation ≤10 HU, and a false-negative rate of 0.5% of radiological classification as determined in the current study [2857 AIs in total, including 2000 AIs with ≤10 HU (70% of 2857) and 200 PCCs (7% of 2857), of which one (0.5% of 200) is misclassified by CT]. In our opinion, this observation justifies omitting biochemical screening in low-attenuation AIs to prevent false-positive test results and unnecessary costs. In the given example of 2000 low-attenuation AIs, based on $50 cost of metanephrine measurement, omitting biochemical testing would result in an immediate cost reduction of $100,000. In the context of a specificity of plasma metanephrines of ~80% to 90% (1), the true cost reduction is expected to be (much) higher when taking into account follow-up investigations prompted by false-positive biochemical testing results that could have been prevented.

Besides unenhanced HU, contrast washout rates are routinely used for the evaluation of adrenal lesions. Most ACAs with an unenhanced HU > 10 exhibit a high washout. Conversely, a high washout does not rule out PCC. We found that in almost one third of PCCs with available APW/RPW data, washout was high. This is in line with a previously meta-analysis of 10 studies by Woo *et al.* (24). They reported a rate of PCCs with a high washout pattern of 35%. Washout data for AI should therefore not be used to determine whether biochemical testing should be done.

This study had several limitations. It was a retrospective study of locally generated radiology reports from different centers using different CT machines, settings, and contrast protocols. Drawing of the region of interest for the calculation of radiodensity was done at the discretion of the local radiologist. The impact of these potential confounders, however, is probably limited, inducing minimal variations in attenuation, estimated at 1 to 2 HU (20, 25). In addition, many cases were excluded because of the availability of postcontrast CT scans only. The detail with which different quantitative parameters were reported varied considerably, leading to missing data. On the other hand, the data were extracted directly from clinical practice and thus are representative of "real life."

Conclusion

On the basis of the lack of PCCs with an unenhanced attenuation of <10 HU and the low proportion (0.5%) of PCCs with an attenuation of 10 HU, it seems reasonable to abstain from biochemical testing for PCC in AIs with an unenhanced attenuation ≤10 HU. The assessment of contrast washout, however, is unreliable for ruling out PCC.

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Correspondence and Reprint Requests: Henri J.L.M. Timmers, MD, PhD, Department of Internal Medicine, Section of Endocrinology (471), Radboud University Nijmegen Medical Center, PO Box 9101, 6500 HB Nijmegen, Netherlands. E-mail: henri.timmers@radboudumc.nl.

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