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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 biomédicale (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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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 Municipality 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; $p=0\cdot003$) 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.

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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, Incheon-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, Incheon-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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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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6. Lancet Diabetes Endocrinol. 2019 Jan;7(1):7-8. doi:

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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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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.

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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 ipsilateral ($p = .01$) 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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Still Perfecting Radioiodine in Thyroid Cancer, After All These Years.

Wirth LJ(1).

Author information:

(1)Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts.

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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.

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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), Schwartz 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 ($< 45 / \geq 45$ years), number of N1 ($\leq 5 / > 5$ 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.

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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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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.

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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.

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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.

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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.

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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.

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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.

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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.

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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.

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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 (hazard ratio = 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.

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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.

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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.

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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.

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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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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), Higashiyama 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.

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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.

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28. World J Surg. 2018 Nov;42(11):3616-3623. doi: 10.1007/s00268-018-4644-4.

Cribiform-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: Cribiform-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.

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29. J Clin Endocrinol Metab. 2018 Nov 1;103(11):4275-4282. doi:

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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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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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