1. J Clin Endocrinol Metab. 2016 Mar 10;jc20161211. [Epub ahead of print]
Association of Mutations in SLC12A1 Encoding the NKCC2 Cotransporter with Neonatal Primary Hyperparathyroidism.
Li D(1), Tian L(1), Hou C(1), Kim CE(1), Hakonarson H(1),(2), Levine MA(2),(3).
Author information:
(1)The Center for Applied Genomics, The Children's Hospital of Philadelphia, Philadelphia, PA, USA. (2)Department of Pediatrics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA. (3)Division of Endocrinology and Diabetes and the Center for Bone Health, The Children's Hospital of Philadelphia, Philadelphia, PA, USA.

CONTEXT: Primary hyperparathyroidism with hypercalciuria has not been described in the newborn period.
OBJECTIVE: Our objectives are to identify the genetic basis for neonatal primary hyperparathyroidism in a family with two affected children.
SUBJECTS: An African American boy presenting with mild neonatal primary hyperparathyroidism and hypercalciuria was evaluated at The Children's Hospital of Philadelphia. His older brother with neonatal primary hyperparathyroidism had died in infancy of multiple organ failure.
METHODS: We collected clinical and biochemical data and performed exome-sequencing (ES) analysis on DNA from the patient and his unaffected mother after negative genetic testing for known causes of primary hyperparathyroidism.
RESULTS: ES followed by Sanger sequencing disclosed two heterozygous mutations, c.1883C>A, p.(A628D) and c.2786_2787insC, p.(T931fsX10), in the SLC12A1 gene, which was previously implicated in antenatal type 1 Bartter syndrome. Sanger sequencing confirmed the two mutations in the proband and his deceased brother; both parents were heterozygous for different mutations and an unaffected sister was homozygous for wild type alleles.
CONCLUSIONS: These results demonstrate a previously unrecognized association between neonatal primary hyperparathyroidism and mutation of SLC12A1, the cause of antenatal Bartter syndrome type 1, and suggest that the loss of NKCC2 co-transporter activity influences parathyroid gland function.
PMID: 26963954  [PubMed - as supplied by publisher]

2. J Clin Endocrinol Metab. 2016 Mar 10;jc20153442. [Epub ahead of print]
Familial hypocalciuric hypercalcemia types 1 and 3 and primary hyperparathyroidism: similarities and differences.
Vargas-Poussou R(1),(2),(3), Mansour-Hendili L(1),(2),(4), Baron S(4),(5), Bertocchio JP(3),(4),(5), Travers C(1), Simian C(1), Treard C(1),(2), Baudouin V(3),(6), Beltran S(7), Broux F(8), Camard O(9), Cloarec S(10), Cormier C(11), Debussche X(12), Dubosclard E(13), Eid C(14), Haymann JP(15), Romuald Kiando S(2), Kuhn JM(16), Lefort G(17), Linglart A(18), Lucas-Pouliquen B(19), Machet MA(3),(6), Maruani G(5), Ouzounian S(20), Polak M(21), Requeda E(22), Robier D(9), Silve C(23), Souberbielle JC(24), Tack I(25), Vezzosi D(26), Jeunemaitre X(1),(2),(3),(4), Houillier P(3),(4),(5),(27),(28).
Author information:
(1)Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Service de Génétique, Paris, France. (2)INSERM, UMR970, Paris-Centre de Recherche Cardiovasculaire, Paris, France. (3)Centre de Référence des Maladies Rénales Héritaires de l'Enfant et de l'Adulte (MARHEA), Paris, France. (4)Université

CONTEXT: Familial hypocalciuric hypercalcemia (FHH) is a genetically heterogeneous condition resembling primary hyperparathyroidism (PHPT) but not curable by surgery; FHH types 1, 2 and 3 are due to loss-of-function mutations of the CASR, GNA11 or AP2S1 genes, respectively.

OBJECTIVE: To compare the phenotypes of patients with genetically proven FHH types 1 or 3 or PHPT.

DESIGN, SETTING AND PATIENTS: mutation analysis in a large cohort; cross-sectional comparison of 52 patients with FHH type 1, 22 patients with FHH type 3, 60 PHPT and 24 normal adults.

INTERVENTION: None Main outcome measures: Abnormalities of the CASR, GNA11 and AP2S1 genes, blood calcium, phosphate and parathyroid hormone (PTH) concentrations, urinary calcium excretion.

RESULTS: In 133 families, we detected 101 mutations in the CASR gene, 68 of which were previously unknown and in 19 families, the three recurrent AP2S1 mutations. No mutation was detected in the GNA11 gene. Patients with FHH type 3 had higher plasma calcium concentrations than patients with FHH type 1, despite having similar PTH concentrations and urinary calcium excretion. Renal tubular calcium reabsorption levels were higher in patients with FHH type 3 than in those with...
FHH type 1. Plasma calcium concentration was higher whereas PTH concentration and urinary calcium excretion were lower in FHH patients than in PHPT patients. In patients with FHH or PHPT, all data groups partially overlapped.

CONCLUSION: In our population, AP2S1 mutations affect calcium homeostasis more severely than CASR mutations. Due to overlap, the risk of confusion between FHH and PHPT is high.

PMID: 26963950 [PubMed - as supplied by publisher]

Pediatric differentiated thyroid carcinoma in the Netherlands: a nationwide follow-up study.
Klein Hesselink MS(1), Nies M(1), Bocca G(2), Brouwers AH(3), Burgerhof JG(4), van Dam EW(5), Havekes B(6), van den Heuvel-Eibrink MM(7), Corssmit EP(8), Kremer LC(9), Netea-Maier RT(10), van der Pal HJ(9,11), Peeters RP(12,13), Schmid KW(14), Smit JW(10), Williams GR(15), Plukker JT(16), Ronckers CM(9), van Santen HM(17), Tissing WJ(18), Links TP(1).

Author information:
(1)Department of Endocrinology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands. (2)Department of Pediatric Endocrinology, Beatrix Children's Hospital, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands. (3)Department of Nuclear Medicine and Molecular Imaging, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands. (4)Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands. (5)Department of Internal Medicine, VU University Medical Center, Amsterdam, The Netherlands. (6)Department of Internal Medicine, Division of Endocrinology, Maastricht University Medical Center, Maastricht, The Netherlands. (7)Department of Pediatric Oncology, Sophia Children's Hospital, Erasmus Medical Center, Rotterdam, The Netherlands. (8)Department of Internal Medicine, Division of Endocrinology, Leiden University Medical Center, Leiden, The Netherlands. (9)Department of Pediatric Oncology, Emma Children's Hospital, Academic Medical Center, Amsterdam, The Netherlands. (10)Department of Internal Medicine, Division of Endocrinology, Radboud University Medical Center, Nijmegen, The Netherlands. (11)Department of Medical Oncology, Academic Medical Center, Amsterdam, The Netherlands. (12)Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands. (13)Rotterdam Thyroid Center, Erasmus Medical Center, Rotterdam, The Netherlands. (14)Institute of Pathology, University Hospital Essen, University of Duisburg-Essen, Essen, Germany. (15)Department of Medicine, Imperial College London, London, United Kingdom. (16)Department of Surgical Oncology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands. (17)Department of Pediatrics, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands. (18)Department of Pediatric Oncology, Beatrix Children's Hospital, University of Groningen, University Medical Center Groningen, Groningen.

INTRODUCTION: Treatment for differentiated thyroid carcinoma (DTC) in pediatric patients is based mainly on evidence from adult series due to lack of data from pediatric cohorts. Our objective was to evaluate presentation, treatment-related complications, and long-term outcome in patients with pediatric DTC in the Netherlands.
PATIENTS AND METHODS: In this nationwide study, presentation, complications and outcome of patients with pediatric DTC (age at diagnosis ≤18 years) treated in the Netherlands between 1970 and 2013 were assessed using medical records. 

RESULTS: We identified 170 patients. Overall survival was 99.4% after median follow-up of 13.5 (range 0.3-44.7) years. Extensive follow-up data were available for 105 patients (83.8% women), treated in 39 hospitals. Median age at diagnosis was 15.6 (range 5.8-18.9) years. At initial diagnosis, 43.8% of the patients had cervical lymph node metastases; 13.3% had distant metastases. All patients underwent total thyroidectomy. Radioiodine was administered to 97.1%, with a median cumulative activity of 5.66 (range 0.74-35.15) GBq. Lifelong postoperative complications (permanent hypoparathyroidism and/or recurrent laryngeal nerve injury) were present in 32.4% of the patients. At last known follow-up, 8.6% of the patients had persistent disease and 7.6% experienced a recurrence. TSH suppression was not associated with recurrences (OR 2.00, 95% CI 0.78 to 5.17, P = 0.152).

CONCLUSIONS: Survival of pediatric DTC is excellent. Therefore, minimizing treatment-related morbidity takes major priority. Our study shows a frequent occurrence of lifelong postoperative complications. Adverse effects may be reduced by centralization of care, which is crucial for children with DTC.

PMID: 26963949 [PubMed - as supplied by publisher]


Prognostic Value of the Number of Retrieved Lymph Nodes in Pathological Nx or N0 Classical Papillary Thyroid Carcinoma.

Sung TY(1), Yoon JH(2), Song DE(3), Lee YM(1), Kim TY(4), Chung KW(1), Kim WB(4), Shong YK(4), Hong SJ(1).

Author information:
(1)Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-Gu, Seoul, 05505, Korea. (2)Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-Gu, Seoul, 05505, Korea. gsyoon@amc.seoul.kr. (3)Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea. (4)Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea.

BACKGROUND: This study evaluated the clinical implications of the number of retrieved central lymph nodes (LN) for the recurrence and recurrence-free survival (RFS) outcomes in patients with pathological Nx (pNx) or N0 classical papillary thyroid carcinoma (PTC).

METHODS: In total, 464 patients were enrolled following total thyroidectomy with central LN dissection. The risk factors related to recurrence and RFS were evaluated and compared between these groups.

RESULTS: Age, primary tumor size, and number of retrieved central LNs were independent risk factors for recurrence according to multivariate analysis (p < 0.05). The cut-off value for the number of retrieved central LNs related to recurrence was 4.5. Group 2 (pN0; ≥5 nodes) demonstrated a significantly higher proportion of patients with an ablation-stimulated thyroglobulin (sTg) level <2.0 ng/mL (84.9 vs 61.1 %; p < 0.050) and control sTg level <1.0 ng/mL (92.1 vs 79.6 %; p < 0.050) in comparison with patients in group 1 (pNx or pN0; 1-4 nodes). Perioperative complication rates were comparable between groups.
CONCLUSION: The number of retrieved central LNs is an independent risk factor for recurrence, even among patients with pNx or pN0 classical PTC. A thorough central LN dissection may therefore improve the long-term RFS rate.

PMID: 26952113  [PubMed - as supplied by publisher]
the risk of recurrent/persistent disease in this population. The
"response-to-initial-therapy" classification performed 1-2 years after initial
therapy may be more appropriate for guiding surveillance recommendations.
PMID: 26930182  [PubMed - as supplied by publisher]

6. J Clin Endocrinol Metab. 2016 Feb 22;jc20153544. [Epub ahead of print]
Effects of Dosimetrically-Guided I-131 Therapy on Hematopoiesis in Patients with
Differentiated Thyroid Cancer.
Bikas A(1),(2), Schneider M(3), Desale S(2), Atkins F(3), Mete M(2), Burman
KD(1), Wartofsky L(1), Van Nostrand D(3).
Author information:
(1)Division of Endocrinology, Department of Medicine, MedStar Washington Hospital
Center, 110 Irving St NW, WA DC 20010; (2)MedStar Health Research Institute, 110
Irving St NW, WA DC 20010; (3)Division of Nuclear Medicine, MedStar Washington
Hospital Center, 110 Irving St NW, WA DC 20010.

OBJECTIVE: To evaluate the effects of dosimetrically-guided I-131 prescribed
activities on hematopoiesis reflected by changes in complete blood counts (CBC).

DESIGN: Retrospective analysis.

SETTING: Academic center.

PATIENTS: 152 patients with differentiated thyroid cancer who had 185
dosimetrically-guided I-131 treatments.

INTERVENTIONS: None.

MAIN OUTCOME MEASURES: Repeated measure ANOVA was used for the analysis of the
differences in the averages of CBC that were documented at baseline, 1, 6, 12,
24-36 and 48-60 mo after I-131 treatment.

RESULTS: All parameters decreased to their respective nadir at 1 mo and then
gradually returned toward baseline values. White blood cells (WBC) and platelets
(PLT) were the most significantly affected cells. At 1 mo, the decrease was 29.6%
(p<0.0001) for WBC and 25% (p<0.0001) for PLT, while at 12 mo the decrease was
15.5% (p<0.0001) and 13% (p<0.0001), respectively. Lymphocytes (ALC) appeared to
be more susceptible to I-131 than neutrophils (ANC). The decreases were small in
absolute numbers for red blood cells (RBC), hematocrit (Hct) and hemoglobin (Hb)
not surpassing 10%. Multivariate analysis demonstrated that the ratio of
administered prescribed activity-to-maximum tolerated activity (MTA) was
associated with the decreases in WBC (p=0.0038), ANC (p=0.0063), RBC (p=0.029),
with borderline significance for PLT (p=0.057) and Hgb (p=0.057).

CONCLUSIONS: Dosimetrically-guided I-131 resulted in statistically significant
decreases in CBC parameters, which were more prominent in WBC and PLT. ALC were
more severely affected than ANC, while all parameters reached a nadir at 1 mo and
then gradually returned towards baseline values over the 5 years follow-up of our
study.

PMID: 26900639  [PubMed - as supplied by publisher]

print]
A comprehensive overview of the role of the RET proto-oncogene in thyroid
carcinoma.
Romei C(1), Ciampi R(1), Elisei R(1).
8. J Clin Endocrinol Metab. 2016 Feb 11;jc20153783. [Epub ahead of print]

Clinical relationship between IgG4-positive Hashimoto's thyroiditis and papillary thyroid carcinoma.

Yu Y(1), Zhang J(2), Lu G(1), Li T(3), Zhang Y(1), Yu N(1), Gao Y(1), Gao Y(1), Guo X(1).

Author information:
(1)Department of Endocrinology, Peking University First Hospital, Beijing 100034, China. (2)Department of Geriatrics, Peking University First Hospital, Beijing 100034, China. (3)Department of pathology, Peking University First Hospital, Beijing 100034, China.

CONTEXT: Hashimoto's thyroiditis (HT) can be divided into IgG4-positive and IgG4-negative HT. The potential association between IgG4-positive HT and papillary thyroid carcinoma (PTC) remains poorly understood.

OBJECTIVE: The aim was to investigate the relationship between IgG4-positive HT and PTC, and to compare the prognostic parameters of PTC patients with and without IgG4-positive HT.

DESIGN: A retrospective study.

PATIENTS AND SETTING: 66 HT patients (18 HT alone, 48 HT with PTC) with serum samples stored before operation were collected. Another 18 PTC alone patients were collected as controls.

MAIN OUTCOME MEASURES: Expression of IgG4, IgG and TGF-β1 in thyroid tissues, serum levels of IgG4, TgAb IgG, TgAb IgG4, TPOAb IgG, and TPOAb IgG4.

RESULTS: 17 (35.4%) HT with PTC patients were IgG4-positive HT, while only one patient (5.6%) was found to be IgG4-positive in HT alone group. In contrast, there were only few IgG4-positive plasma cells in PTC alone group. The
association of IgG4-positive HT and PTC was statistically significant (P < 0.05). Moreover, serum levels of TgAb IgG4 and the ratios of TgAb IgG4/TgAb IgG were significantly higher in HT with PTC and PTC alone groups than in the HT alone group (P < 0.05). Furthermore, in the HT with PTC group, the average tumor diameter of 17 IgG4-positive HT with PTC patients was 1.7 ± 0.8 cm while of 31 IgG4-negative HT with PTC patients the diameter was 1.2 ± 0.6 cm (P = 0.01). A considerably higher percentage of lymph node metastasis (41.2% vs. 12.9%; P = 0.026) was found in PTC patients with IgG4-positive HT as compared to those with IgG4-negative HT.

CONCLUSION: PTC may be facilitated by pre-existing autoimmune inflammation of IgG4-positive HT. IgG4-positive HT with PTC cases may have worse clinical outcomes. The high levels of TgAb IgG4 might present a risk factor for PTC.

PMID: 26866571  [PubMed - as supplied by publisher]

9. J Clin Endocrinol Metab. 2016 Feb 2;jc20154031. [Epub ahead of print]
Sub-clonality for BRAF mutation in papillary thyroid carcinoma is associated with earlier disease stage.
Finkel A(1), Liba L(1), Simon E(2), Bick T(2), Prinz E(1), Sabo E(1,)(2), Ben-Izhak O(2,)(3), Hershkovitz D(2,)(3).

Author information:
(1)B. Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel. (2)Institute of Pathology, Rambam Health Care Campus, Haifa, Israel. (3)TICC, Technion Integrative Cancer Center at the Ruth and Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel.

CONTEXT: The presence of driver mutations only in a subset of tumor cells within a single lesion, defined as sub-clonality, is being appreciated as a clinically significant factor. BRAF mutation is the most common driver mutation in papillary thyroid carcinoma (PTC). There are conflicting data in the literature regarding the presence of BRAF mutation sub-clonality in PTC and its clinical significance.

OBJECTIVE: The purpose of the present study was to utilize a molecular and morphometric approach to determine BRAF clonality status and its clinical-pathological correlates.

DESIGN: Fifty nine cases of PTC were studied. DNA extracted from the tumors underwent deep sequencing to determine the percentage of BRAF mutant allele copies. Additionally, we used computerized morphometry to determine the fraction of tumor cells in each sample. Using both variables we were able to determine the presence or absence of sub-clonality for BRAF mutation, which was further correlated with clinical, pathological and prognostic data.

RESULTS: BRAF mutation was found in 49 (83%) cases. The average percentage of tumor cells and of BRAF mutant alleles in the samples were 68.1±9.8 and 26±6.7, respectively. Based on the molecular and morphometric analysis, 11 (24%) cases were found to be sub-clonal for BRAF mutation. Tumors with sub-clonal BRAF mutations were significantly smaller compared to tumors with clonal mutation (0.82±0.38cm vs 1.37±0.57cm, p=0.005) and were less likely to have lymph node metastasis (0% vs 32%, p=0.03).

CONCLUSIONS: In PTC, sub-clonality for BRAF mutation is associated with earlier stage. Molecular-morphometric analysis of PTC can provide clonality information with potential clinical significance.

Thyroid cancer: Use of MDSC to assess malignancy.
Greenhill C.
PMID: 26822925 [PubMed - in process]


Preablative Stimulated Thyroglobulin Correlates to New Therapy Response System in Differentiated Thyroid Cancer.
Yang X(1), Liang J(1), Li T(1), Zhao T(1), Lin Y(1).
Author information:
(1)Department of Nuclear Medicine (X.Y., T.Z., Y.L.), Chinese Academy of Medical Sciences & Peking Union Medical College Hospital, Beijing, China; Department of Oncology (J.L.), Peking University International Hospital, Beijing, China; Department of Oncology (T.L.), the Affiliated Hospital of Qingdao University, Qingdao, Shandong Province, PRC.

CONTEXT: Studies suggested a potential value of preablative stimulated thyroglobulin (ps-Tg) on predicting the recurrent and persistent diseases of differentiated thyroid cancer, whereas its correlations with therapeutic response remain uncertain.

OBJECTIVE: To establish the correlation between ps-Tg and therapeutic response proposed in 2015 American Thyroid Association guidelines, and calculate a cutoff ps-Tg threshold for predicting a poor response.

DESIGN/SETTING: Patients who underwent total thyroidectomy and radioactive iodine therapy in a university hospital participated in this retrospective study.

PATIENTS: Totally, 452 patients with differentiated thyroid cancer were followed for a median of 38 months and were divided into three groups in terms of ps-Tg level: group 1, less than 1 ng/ml (n = 82); group 2, 1-10 ng/ml (n = 173); and group 3, at least 10 ng/ml (n = 197).

MAIN OUTCOME MEASURE: Clinical outcomes were assessed based on response to therapy restaging system, dividing responses into excellent, indeterminate, biomedical incomplete, and structural incomplete (SIR).

RESULTS: Therapeutic responses could be obviously distinguished by different ps-Tg strata. SIR was identified in none of group 1, 1.73% of group 2, and 42.74% of group 3, respectively (χ²(2) = 123.037, P < .001). A cutoff value of ps-Tg at 26.75 ng/ml was obtained by receiver operating characteristic curve for differentiating SIR from either excellent, indeterminate, or biomedical incomplete responses. The area under curve was 0.947 and negative predictive value was 96.99%. Ps-Tg was an independent predictive variable of SIR (odds ratio, 42.312; P < .001).

CONCLUSIONS: Ps-Tg has a great performance in predicting therapeutic response and providing incremental value for decision making of radioactive iodine therapy, especially for patients with high ps-Tg level.
PMID: 26789779 [PubMed - in process]

**Prognosis After Brain Metastasis from Differentiated Thyroid Carcinoma.**
Saito F(1), Uruno T(2), Shibuya H(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. f-saito@ito-hospital.jp. (2)Department of Surgery, Ito Hospital, 4-3-6 Jingumae, Shibuya-ku, Tokyo, 150-8308, Japan.

**BACKGROUND:** In patients with differentiated thyroid carcinoma (DTC), lung and bone metastasis sometimes occur. However, brain metastasis (BM) is extremely rare. Because most previous reports about BM from DTC included a relatively small number of cases, the clinical characteristics and outcomes of BM are still unclear.

**PATIENTS AND METHODS:** Between 1965 and 2013, among 961 patients who had died because of DTC, 24 patients were diagnosed with BM from DTC. One patient with BM from DTC is still alive. To identify the prognostic factors for longer survival after BM, the medical records of these 25 patients were retrospectively reviewed.

**RESULTS:** The median age at BM diagnosis was 66 years. Typical symptoms associated with BM had appeared in 20 patients (80%). The Karnofsky Performance Status (KPS) was good (≥70) in 10 patients and poor (≤60) in 15 patients. Seven patients had a single intracranial lesion of BM, 6 patients had 2 or 3 lesions, and 9 patients had 4 or more. Eleven patients did not receive any treatment for BM, and 14 patients underwent surgical resection, radiation therapy, or both. One-year and 5-year disease-specific survival rates were 28 and 10.6%, respectively. Good KPS (≥70), small number of intracranial lesions (≤3), and treatment for BM were prognostic factors for long survival on univariate analysis (p < 0.05). On multivariate analysis, only treatment for BM was significant.

**CONCLUSION:** Treatment of BM from DTC is indicated in patients who have a good KPS and fewer intracranial lesions, and some of them may achieve long survival.

PMID: 26762631  [PubMed - in process]


**Diabetes, Diabetes Treatment, and Risk of Thyroid Cancer.**
Luo J(1), Phillips L(1), Liu S(1), Wactawski-Wende J(1), Margolis KL(1).

**Author information:**
(1)Department of Epidemiology and Biostatistics (J.L.), School of Public Health, Indiana University, Bloomington, Indiana 47405; Division of Endocrinology (L.P.), Emory University, Atlanta, Georgia 30322; School of Public Health (S.L.), The Warren Alpert School of Medicine, Brown University, Providence, Rhode Island 02912; Department of Social and Preventive Medicine (J.W.-W.), University at Buffalo, Buffalo, New York 14214; and HealthPartners Institute for Education and Research (K.L.M.), Minneapolis, Minnesota 55440.

**OBJECTIVE:** The objective of this study was to assess the relationships among diabetes, diabetes treatment and thyroid cancer risk using a large prospective cohort, the Women's Health Initiative.

**METHODS:** A total of 147,934 women who were free of known cancer at baseline were
followed prospectively. Diabetes status and diabetes treatment at baseline and during follow-up were ascertained. Incident cases of thyroid cancers were confirmed by physician review of central medical records and pathology reports. Time-dependent Cox proportional hazards regressions were used to estimate hazard ratios and 95% confidence intervals for thyroid cancer risk associated with diabetes status, diabetes treatment, and duration of diabetes.

RESULTS: With a median follow-up time of 15.9 years, 391 incident thyroid cancers were identified. We found no significant associations between thyroid cancer and diabetes (hazard ratio = 1.09; 95% confidence interval, 0.79-1.52), diabetes treatment, or duration of diabetes.

CONCLUSION: Our findings do not support the hypothesis that diabetes, or treatment of diabetes is associated with risk of thyroid cancer among postmenopausal women. Studies to investigate the specific effects of hyperinsulinemia and insulin resistance on thyroid cancer risk may provide additional information.

PMID: 26760177  [PubMed - in process]


PROX1 Promotes Secretory Granule Formation in Medullary Thyroid Cancer Cells.

Ishii J(1), Yazawa T(1), Chiba T(1), Shishido-Hara Y(1), Arimasu Y(1), Sato H(1), Kamma H(1).

Author information:
(1)Department of Pathology (J.I., T.C., Y.A., H.K.), Kyorin University School of Medicine, Mitaka, Tokyo 181-8611, Japan; Department of Diagnostic Pathology (T.Y.), Chiba University Graduate School of Medicine, Chiba 260-8670, Japan; Department of Anatomic Pathology (Y.S.-H.), Tokyo Medical University, Shinjuku, Tokyo 101-0062, Japan; and Department of Anatomy (H.S.), St Marianna University School of Medicine, Kanagawa 216-8511, Japan.

Mechanisms of endocrine secretory granule (SG) formation in thyroid C cells and medullary thyroid cancer (MTC) cells have not been fully elucidated. Here we directly demonstrated that PROX1, a developmental homeobox gene, is transcriptionally involved in SG formation in MTC, which is derived from C cells. Analyses using gene expression databases on web sites revealed that, among thyroid cancer cells, MTC cells specifically and highly express PROX1 as well as several SG-forming molecule genes. Immunohistochemical analyses showed that in vivo MTC and C cells expressed PROX1, although follicular thyroid cancer and papillary thyroid cancer cells, normal follicular cells did not. Knockdown of PROX1 in an MTC cells reduced SGs detected by electron microscopy, and decreased expression of SG-related genes (chromogranin A, chromogranin B, secretogranin II, secretogranin III, synaptophysin, and carboxypeptidase E). Conversely, the introduction of a PROX1 transgene into a papillary thyroid cancer and anaplastic thyroid cancer cells induced the expression of SG-related genes. Reporter assays using the promoter sequence of chromogranin A showed that PROX1 activates the chromogranin A gene in addition to the known regulatory mechanisms, which are mediated via the cAMP response element binding protein and the repressor element 1-silencing transcription factor. Furthermore, chromatin immunoprecipitation-PCR assays demonstrated that PROX1 binds to the transcriptional regulatory element of the chromogranin A gene. In conclusion, PROX1 is an important regulator of
endocrine SG formation in MTC cells.

PMID: 26760117 [PubMed - in process]

Long-Term Outcome of Follicular Thyroid Carcinoma in Patients Undergoing Surgical Intervention for Skeletal Metastases.
Mishra A(1), Kumar C(2), Chand G(2), Agarwal G(2), Agarwal A(2), Verma AK(2), Mishra SK(2).

Author information:
(1)Department of Endocrine Surgery, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Raebareli Road, Lucknow, 226 014, India. anjali@sgpgi.ac.in.
(2)Department of Endocrine Surgery, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Raebareli Road, Lucknow, 226 014, India.

BACKGROUND: A large proportion of follicular thyroid carcinoma (FTC) patients in developing countries present with overt skeletal metastases (SM). These patients often require surgical interventions for prevention of morbidity, palliation of symptoms, and facilitation of radioiodine therapy (RAIT). Scarce literature is available about the long-term outcome of such patients. The aim of this study was to evaluate the long-term outcome of FTC patients undergoing surgical intervention for SM.

METHODS: We retrospectively reviewed the data of FTC patients with SM (January 1990-December 2011). Out of 91 patients with SM, 32 had surgical interventions for SM. All had total thyroidectomy performed.

RESULTS: The mean age of the patients was 48.5 years (M:F = 1:2). Majority (93.7 %) had synchronous metastases and 22 % had multiple SM. The surgical interventions for SM included: laminectomy (50 %), resection of skull metastases (18.8 %), resection of manubrium sterni (18.8 %), partial clavicle excision (9.4 %), and hemimandibulectomy (3.1 %). The main intents were palliation (50 %) and facilitation of RAIT (37.5 %). 84 % patients received RAIT. Median follow-up was 52 months (mean = 50 ± 37). Five- (56 vs 63 %) and 10-year (28 vs 23 %) overall survival (OS) did not differ significantly (p = 0.968) from those not having interventions for SM. On univariate analysis tumor invasion (p = 0.006) and synchronous presentation of SM (p = 0.043) were significant risk factors for OS, whereas on multivariate analysis tumor invasion (p = 0.006) was significant.

CONCLUSIONS: Surgical interventions directed at SM in FTC patients with overt multiple SM might not result in improve OS. However, considering reasonable long-term survival, interventions should be considered for desired palliation and preservation of body function.

PMID: 26757717 [PubMed - in process]

Thiazide-Associated Hypercalcemia: Incidence and Association With Primary Hyperparathyroidism Over Two Decades.
Griebeler ML(1), Kearns AE(1), Ryu E(1), Thapa P(1), Hathcock MA(1), Melton LJ 3rd(1), Wermers RA(1).

Author information:
(1)Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Department of
CONTEXT: Thiazide diuretics, the antihypertensive agent prescribed most frequently worldwide, are commonly associated with hypercalcemia. However, the epidemiology and clinical features are poorly understood.

OBJECTIVE: To update the incidence of thiazide-associated hypercalcemia and clarify its clinical features.

PATIENTS AND METHODS: In a population-based descriptive study, Olmsted County, Minnesota, residents with thiazide-associated hypercalcemia were identified through the Rochester Epidemiology Project and the Mayo Clinic Laboratory Information System from 2002-2010 and were added to the historical cohort beginning in 1992.

MAIN OUTCOME: Incidence rates were adjusted to the 2010 United States white population.

RESULTS: Overall, 221 Olmsted County residents were identified with thiazide-associated hypercalcemia an average of 5.2 years after initiation of treatment. Subjects were older (mean age, 67 years) and primarily women (86.4%). The incidence of thiazide-associated hypercalcemia increased after 1997 and peaked in 2006 with an annual incidence of 20 per 100 000, compared to an overall rate of 12 per 100 000 in 1992-2010. Severe hypercalcemia was not observed in the cohort despite continuation of thiazide treatment in 62.4%. Of patients discontinuing thiazides, 71% continued to have hypercalcemia. Primary hyperparathyroidism was diagnosed in 53 patients (24%), including five patients who underwent parathyroidectomy without thiazide discontinuation.

CONCLUSIONS: Many patients with thiazide-associated hypercalcemia have underlying primary hyperparathyroidism. Additionally, a sharp rise in thiazide-associated hypercalcemia incidence began in 1998, paralleling the increase observed in primary hyperparathyroidism in this community. Case ascertainment bias from targeted osteoporosis screening is the most likely explanation.

PMID: 26751196  [PubMed - in process]

Robust Thyroid Gene Expression and Radioiodine Uptake Induced by Simultaneous Suppression of BRAF V600E and Histone Deacetylase in Thyroid Cancer Cells.
Author information:
(1)Laboratory for Cellular and Molecular Thyroid Research (W.C., R.L., G.Z., M.X.), Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21287; and Department of Nuclear Medicine (H.W.), Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 200092, China.

CONTEXT: Use of BRAF V600E inhibitors to restore thyroid iodide-handling gene expression and radioactive iodine (RAI) avidity is an attractive therapeutic strategy for RAI-refractory thyroid cancer, but recent initial clinical responses
were modest. Given histone deacetylation at the sodium/iodide symporter promoter by histone deacetylase (HDAC) as a mechanism, simultaneously targeting BRAF V600E and HDAC could be a more effective strategy.

OBJECTIVES: The objective of the study was to test whether suppressing both BRAF V600E and HDAC could more effectively induce thyroid gene expression and RAI uptake in thyroid cancer cells.

RESEARCH DESIGN: We tested the BRAF V600E inhibitor PLX4032 (vemurafenib) and the HDAC inhibitor SAHA (vorinostat), two major anticancer drugs currently approved for clinical use, in inducing thyroid gene expression and RAI uptake in thyroid cancer cells.

RESULTS: PLX4032 alone induced a modest expression of thyroid genes and RAI uptake preferentially in thyroid cancer cells harboring BRAF V600E. SAHA showed an effect in a genetic-independent manner in all the cells. A robust synergistic effect on thyroid gene expression and RAI uptake was observed in BRAF V600E-positive thyroid cancer cells when the two inhibitors were simultaneously used. This was dramatically enhanced further by TSH; triple combination of PLX4032, SAHA, and TSH showed the most robust effect on thyroid gene expression and RAI uptake in cells harboring BRAF V600E. Abundant sodium/iodide symporter protein expression in thyroid cancer cells under these conditions was confirmed by immunofluorescent microscopy.

CONCLUSIONS: Simultaneously suppressing BRAF V600E and HDAC, particularly when cotreated with TSH, induced a far more robust expression of thyroid genes and RAI uptake in thyroid cancer cells than suppressing BRAF V600E alone. Triple combination of PLX4032, SAHA, and TSH is a specific robust regimen to restore RAI avidity in RAI-refractory BRAF V600E-positive thyroid cancer, which warrants clinical trials to confirm.

PMID: 26751190  [PubMed - in process]


Effect of Low Vitamin D on Volumetric Bone Mineral Density, Bone Microarchitecture, and Stiffness in Primary Hyperparathyroidism.

Walker MD(1), Nishiyama KK(1), Zhou B(1), Cong E(1), Wang J(1), Lee JA(1), Kepley A(1), Zhang C(1), Guo XE(1), Silverberg SJ(1).

Author information:

CONTEXT: Patients with 25-hydroxyvitamin D deficiency (25OHD <20 ng/ml) and primary hyperparathyroidism (PHPT) have more severe disease reflected by higher serum PTH levels compared to those with vitamin D levels in the insufficient (20-29 ng/ml) or replete range (≥30 ng/ml).

OBJECTIVE: To study the effect of low vitamin D in PHPT on volumetric bone mineral density (vBMD), bone microarchitecture, and bone strength.

DESIGN, SETTING, AND PARTICIPANTS: This is a cross-sectional analysis of 99 PHPT patients with and without 25OHD insufficiency and deficiency from a university hospital.
OUTCOME MEASURES: Bone microarchitecture and strength were assessed with high-resolution peripheral quantitative computed tomography (HRpQCT), microfinite element analysis, and individual trabecula segmentation.

RESULTS: In this cohort, 25OHD levels were deficient in 18.1%, insufficient in 35.4% and replete in 46.5%. Those with lower 25OHD levels had higher PTH (P < .0001), were younger (P = .001) and tended to weigh more (P = .053). There were no age-, weight- and sex-adjusted between-group differences (<20 vs 20-29 vs ≥30 ng/ml) in any HRpQCT, microfinite element analysis, or individual trabecula segmentation indices. Because few participants had 25OHD below 20 ng/ml, we also compared those with 25OHD below 30 vs at least 30 ng/ml and found only a trend toward lower adjusted cortical vBMD (3.1%, P = .08) and higher cortical porosity (least squares mean ± SEM 7.5 ± 0.3 vs 6.6 ± 0.3%, P = .07) at the tibia but not the radius. Stiffness did not differ at either site. In multiple regression analysis, 25OHD accounted for only three of the 49.2% known variance in cortical vBMD; 25OHD was not significant in the model for cortical porosity at the tibia.

CONCLUSION: Low 25OHD levels are associated with higher PTH levels in PHPT, but contrary to our hypothesis, these differences did not significantly affect vBMD or microarchitecture, nor did they result in lower stiffness. Low vitamin D in PHPT using current 25OHD thresholds for insufficiency and deficiency did not significantly affect skeletal integrity as assessed by HRpQCT.

PMID: 26745256  [PubMed - in process]


Author information:
(1)Department of Surgery, Mayo Clinic, 200 First St. SW, Rochester, MN, 55905, USA. glee727@gmail.com. (2)Department of Surgery, Mayo Clinic, 200 First St. SW, Rochester, MN, 55905, USA. (3)Department of Nuclear Medicine, Mayo Clinic, Rochester, MN, USA. (4)Department of Surgery, Mayo Clinic, 200 First St. SW, Rochester, MN, 55905, USA. richards.melanie@mayo.edu.

INTRODUCTION: Focused parathyroidectomy in primary hyperparathyroidism (1°HPT) is possible with accurate preoperative localization and intraoperative PTH monitoring (IOPTH). The added benefit of multimodal imaging techniques for operative success is unknown.

METHOD: Patients with 1°HPT, who underwent parathyroidectomy in 2012-2014 at a single institution, were retrospectively reviewed. Only the patients who underwent the standardized multimodal imaging workup consisting of (123)I/(99)Tc-sestamibi subtraction scintigraphy, SPECT, and SPECT/CT were assessed.

RESULTS: Of 360 patients who were identified, a curative operation was performed in 96 %, using pre-operative imaging and IOPTH. Imaging analysis showed that (123)I/(99)Tc-sestamibi had a sensitivity of 86 % (95 % CI 82-90 %), positive predictive value (PPV) 93 %, and accuracy 81 %, based on correct lateralization. SPECT had a sensitivity of 77 % (95 % CI 72-82 %), PPV 92 % and accuracy 72 %. SPECT/CT had a sensitivity of 75 % (95 % CI 70-80 %), PPV of 94 %, and accuracy 71 %. There were 3 of 45 (7 %) patients with negative sestamibi imaging that had
an accurate SPECT and SPECT/CT. Of 312 patients (87%) with positive uptake on sestamibi (93% true positive, 7% false positive), concordant findings were present in 86% SPECT and 84% SPECT/CT. In cases where imaging modalities were discordant, but at least one method was true-positive, (123)I/(99)Tc-sestamibi was significantly better than both SPECT and SPECT/CT (p < 0.001). The inclusion of SPECT and SPECT/CT in 1°HPT imaging protocol increases patient cost up to 2.4-fold.

CONCLUSION: (123)I/(99)Tc-sestamibi subtraction imaging is highly sensitive for preoperative localization in 1°HPT. SPECT and SPECT/CT are commonly concordant with (123)I/(99)Tc-sestamibi and rarely increase the sensitivity. Routine inclusion of multimodality imaging technique adds minimal clinical benefit but increases cost to patient in high-volume setting.

PMID: 26732668 [PubMed - in process]

Clinical Analysis of Familial Nonmedullary Thyroid Carcinoma.
Zhang Q(1), Yang S(2), Meng XY(3), Chen G(2), Pang RZ(2).
Author information:
(1)Department of Thyroid Surgery, The First Hospital of Jilin University, 71 Xinmin Street, Changchun, 130021, People's Republic of China. jluzhangqiang@163.com. (2)Department of Thyroid Surgery, The First Hospital of Jilin University, 71 Xinmin Street, Changchun, 130021, People's Republic of China. (3)Department of Thyroid Surgery, The First Hospital of Jilin University, 71 Xinmin Street, Changchun, 130021, People's Republic of China. 7919728@qq.com.

OBJECTIVE: To analyze the clinical characteristics of familial nonmedullary thyroid carcinoma (FNMTC), in order to provide evidence for early diagnosis and treatment.

METHODS: We retrospectively investigated the inpatients between September 2006 and September 2013 in the First Bethune Hospital of Jilin University, in which 78 patients with FNMTC from 31 families were analyzed by a comparison with 3445 control cases from the patients with sporadic nonmedullary thyroid carcinoma (SNMTC).

RESULTS: There was no significant difference in gender, age, and tumor size between FNMTC and SNMTC patients. However, the characteristics of disease in multifoci, neck lymph node metastasis, invasion to the surrounding tissues, and coexistence with Hashimoto disease in two types of cancer patients show significant difference. They are: multifoci: 71.8% (56/78) in FNMTC versus 46.3% (1595/3445) in SNMTC; neck lymph node metastasis: 52.6% (41/78) in FNMTC versus 33.3% (1148/3445) in SNMTC; surrounding tissue invasion: 64.1% (50/78) in FNMTC versus 48.5% (1670/3445) in SNMTC; coexistence with Hashimoto disease: 30.8% (24/78) in FNMTC versus 20.0% (689/3445) in SNMTC.

CONCLUSION: Lymph node metastasis, multifoci, invasion to the surrounding tissues, and combination with chronic lymphocytic thyroiditis are the main features of FNMTC, which suggests the extent of the operation for FNMTC patients should be amplified properly.

PMID: 26711636 [PubMed - in process]

Dec 15.

Thyroid cancer in 2015: Molecular landscape of thyroid cancer continues to be deciphered.
Nikiforov YE(1).
Author information:
(1)Department of Pathology, University of Pittsburgh, 3477 Euler Way, Room 8031, Pittsburgh, Pennsylvania 15213, USA.
PMID: 26668120  [PubMed - in process]

Results of a Fifteen-Year Follow-up Program in Patients Operated with Unilateral Neck Exploration for Primary Hyperparathyroidism.
Thier M(1,)(2), Nordenström E(3), Almquist M(3), Bergenfelz A(3).
Author information:
(1)Department of Clinical Sciences, Lund University, Lund, Sweden.
mark.thier@skane.se. (2)Department of Surgery, Skane University Hospital, Lund University, 221 85, Lund, Sweden. mark.thier@skane.se. (3)Department of Clinical Sciences, Lund University, Lund, Sweden.

BACKGROUND: Since the introduction of unilateral parathyroidectomy for primary hyperparathyroidism (pHPT) it has been debated wherever this approach is associated with greater long-term risk for recurrence compared to bilateral neck exploration.

METHODS: This is a prospective study based on a structured 15-year follow-up program in patients with non-hereditary, sporadic pHPT, undergoing first time surgery with unilateral or focused neck exploration (unilateral procedures), with the use of intraoperative PTH (iOPTH) between 1989 and 2010.

RESULTS: 292 patients were analyzed. The median age of the patients was 66 years [interquartile range (IQR) 57-75], and 234 (80.4 %) were female. The median preoperative level of total calcium was 2.74 mmol/L (IQR 2.63-2.85 mmol/L) and the median PTH level was 10 pmol/L (IQR 7.4-14 pmol/L). The median follow-up time was 5 years (IQR 1-10 years). Some 275 patients were followed for 1 year (94.2 %/275 person-years/5 patients deceased), 164 for 5 years (56.2 %/820 person-years/31 patients deceased), 70 for 10 years (24.0 %/700 patient-years/57 patients deceased) and 51 (17.5 %/765 patient-years/69 patients deceased) for 15 years after surgery. Three patients (1.1 %) had signs of persistent disease. One patient recurred in pHPT at 5 years postoperatively during 15 years of follow-up. Histopathology indicated solitary parathyroid adenoma at primary surgery.

CONCLUSION: Patients with pHPT operated with unilateral procedures and iOPTH, had a low risk for long-term recurrence during a 15 years follow-up program.
PMID: 26661636  [PubMed - in process]

Presentation and Outcomes After Surgery for Primary Hyperparathyroidism During an 18-Year Period.
Thier M(1), Nordenström E(2), Bergenfelz A(2), Almquist M(2).
Author information:
(1)Department of Surgery, Lund University Hospital, 221 85, Lund, Sweden.
PURPOSE: The objective of this study is to analyze whether the trend towards operating on patients with less severe primary hyperparathyroidism (pHPT) than earlier is reflected in a change of preoperative presentation and surgical outcome.

METHODS: In this longitudinal cohort study, patients with pHPT subjected to first time surgery were compared in three time periods: 1989-1994, 1995-2000, and 2001-2006 in this longitudinal cohort study.

RESULTS: There were 404 patients. Median levels of preoperative ionized calcium were lower in 2001-2006 compared to 1989-1994; 1.45 versus 1.50 versus 1.45 mmol/L; p < 0.001. Preoperative parathyroid hormone levels in patients with parathyroid adenoma were lower in 2001-2006 than in 1989-1994; 10.0 versus 11.6 pmol/L; p 0.04. Median preoperative bone mineral density, BMD, in the whole cohort did not differ between time periods. Median pre- and postoperative glomeruli filtration rate, GFR, and 25-hydroxy-vitamin D3 remained unchanged between period 1 and period 3. Adenoma weight was lower in 2001-2006 than 1989-1994; 0.70 versus 0.50 g; p 0.04. Cure rate did not change during observation time. There was no evidence for differences in change of BMD (femoral neck) after surgery between period 2 and 3 1995-2000 and 2001-2006, 0.798 versus 0.795 g/cm²; p 0.67. GFR did not change significantly between 1989-1994 and 2001-2006, 74 versus 77 mL/min; p 0.43.

CONCLUSIONS: A significant change towards operating patients with smaller adenomas and lower preoperative calcium levels was evident throughout the observation period, but this did not correlate with differences in preoperative renal or skeletal function. We found no evidence for a change of postoperative renal function or skeletal function during observation time.

PMID: 26578321  [PubMed - in process]


Author information:
(1)Department of Transplantation and Endocrine Surgery, Nagoya 2nd Red Cross Hospital, 2-9 Myoken-cho, Showa-ku, Nagoya, 466-8650, Japan. ubanamadako@yahoo.co.jp. (2)Department of Transplantation and Endocrine Surgery, Nagoya 2nd Red Cross Hospital, 2-9 Myoken-cho, Showa-ku, Nagoya, 466-8650, Japan.

BACKGROUND: Reoperative parathyroidectomy (RPTX) because parathyroid glands have been missed is frequently required in patients with secondary hyperparathyroidism (SHPT). The usual locations of these missed glands in patients with SHPT are yet to be fully elucidated.

METHODS: We retrospectively investigated the locations of missed glands in 165 patients who underwent RPTX for persistent or recurrent SHPT at our institution from August 1982 to July 2014. At our institution, total parathyroidectomy with forearm autograft is the routine operative procedure for SHPT. We also routinely resect the thymic tongue.
RESULTS: Of 165 patients, 82 underwent initial parathyroidectomy at our institution (Group A), and the remaining 83 underwent initial parathyroidectomy at other institutions (Group B). A total of 239 parathyroid glands were resected (Group A, 93; Group B, 146). Missed glands were most commonly located in the mediastinum (Group A, 22/93) and the thymic tongue (Group B, 31/146).

CONCLUSIONS: In patients with persistent or recurrent SHPT, ectopic parathyroid glands are frequently located in the mediastinum and thymic tongue. Therefore, resecting the thymic tongue during the initial operation may reduce the need for RPTX.

PMID: 26563219  [PubMed - in process]

Trends in Prevalence of Thyroid Cancer Over Three Decades: A Retrospective Cohort Study of 17,526 Surgical Patients.
Konturek A(1), Barczyński M(2), Stopa M(2), Nowak W(2).
Author information:
(1)Department of Endocrine Surgery, 3rd Chair of General Surgery, Jagiellonian University Medical College, 37 Prądnicka Street, 31-202, Krakow, Poland.
okont@mp.pl. (2)Department of Endocrine Surgery, 3rd Chair of General Surgery, Jagiellonian University Medical College, 37 Prądnicka Street, 31-202, Krakow, Poland.

INTRODUCTION: Thyroid cancer (TC) incidence has been increasing in recent years. The aim of this study was to investigate our institution-based estimates of operative volumes for TC over the last three decades.
MATERIALS AND METHODS: This was a retrospective cohort study of patients undergoing thyroid surgery at our institution. Patient characteristics were reviewed in three subgroups: Group I (treated in 1981-1986), Group II (treated in 1987-2002), and Group III (treated in 2003-2012).
RESULTS: TC was diagnosed in 1578/17,526 (9.0 %) thyroid operations. Incidence of TC increased from 3.7 % in Group I to 10.4 % in Group III (p < 0.001). Incidence of papillary TC increased from 40.6 % in Group I to 81.3 % in Group III (p < 0.001). In the latter group, 23.5 % of all papillary TCs were diagnosed in patients with Hashimoto's disease. Meanwhile, incidence of anaplastic TC decreased from 16.2 % in Group I to 2.1 % in Group III patients (p < 0.001). pT1 tumors were diagnosed in 8.1 % Group I and 54.8 % Group III (p < 0.001), whereas pT4 tumors were identified in 40.5 % Group I, 2.4 % Group II, and 0.84 % Group III subjects (p < 0.001). pT3 tumors were found in 51.6 % Group I, whereas multifocal papillary TCs were found in 15.7 % Group III patients, the latter with a higher prevalence of pN1 stage (p < 0.001).
CONCLUSIONS: The following trends in surgical volume for TC were identified throughout the study period: a fivefold increase of thyroid operations for TC, a threefold increase in incidence of papillary TC, and an eightfold decrease in incidence of anaplastic TC. It is of interest that a significant increase in incidence of multifocal papillary TC in young female patients with Hashimoto's disease was found over time.
PMCID: PMC4746222
PMID: 26560150  [PubMed - in process]
Parapharyngeal Metastasis of Papillary Thyroid Carcinoma.
Moritani S(1).
Author information:
(1)Department of Head and Neck Surgery, Kusatsu General Hospital, 1660, Yabase-cho, Kusatsu, Shiga, Japan. suemoritani@gmail.com.

BACKGROUND: Nodal involvement of papillary thyroid carcinoma (PTC) commonly occurs in the paratracheal region and the internal jugular chain. Lymph node metastasis in the parapharyngeal space (PPS) is rare. In this report, we describe our experience and surgical outcomes of patients with PPS metastasis of PTC.

METHODS: Clinical data of patients with PTC who underwent surgery at our institution between January 2006 and December 2013 were retrospectively reviewed, and 22 patients with PPS metastasis were enrolled.

RESULTS: There were 2 primary and 20 secondary cases of PPS metastasis. Involvement of the jugular nodes was noted before or at the time of PPS metastasis detection in all cases. A transcervical surgical approach with partial resection of the mandibular angle was performed in 21 patients, while 1 patient underwent extirpation of the PPS metastasis via a transoral approach. Although curative resection was performed in 21 patients, the PPS metastasis was not removable in 1 patient owing to an invaded internal carotid artery at the skull base. Twelve and 6 patients had locoregional and distant recurrence, respectively. Of the 12 patients with locoregional recurrence, isolated locoregional recurrence in the PPS occurred in 1. Eight patients died of distant or locoregional recurrence, with a median survival time of 91.7 months.

CONCLUSIONS: For patients who experience recurrence after thyroid surgery, the possibility of PPS metastasis should be considered. In this series, all patients with PPS metastasis also had previous unilateral or bilateral cervical metastasis. Despite curative attempt, most patients experienced local or distant recurrence.

PMID: 26552910  [PubMed - in process]

Quality of Life in Thyroid Cancer is Similar to That of Other Cancers with Worse Survival.
Applewhite MK(1), James BC(2), Kaplan SP(2), Angelos P(2), Kaplan EL(2), Grogan RH(2), Aschebrook-Kilfoyl B(3).
Author information:
(1)Endocrine Surgery Research Group, Department of Surgery, The University of Chicago, 5841 S. Maryland Ave. MC 4052, Chicago, IL, 60637, USA. megan.applewhite@uchospitals.edu. (2)Endocrine Surgery Research Group, Department of Surgery, The University of Chicago, 5841 S. Maryland Ave. MC 4052, Chicago, IL, 60637, USA. (3)Division of Epidemiology, Department of Health Studies, The University of Chicago, 5841 S. Maryland Ave. MC 2007, N112, Chicago, IL, 60637, USA. brisa@uchicago.edu.

BACKGROUND: The incidence of thyroid cancer is increasing. As such, the number of survivors is rising, and it has been shown that their quality of life (QOL) is worse than expected. Using results from the North American Thyroid Cancer Survivorship Study (NATCSS), a large-scale survivorship study, we aim to compare
the QOL of thyroid cancer survivors to the QOL of survivors of other types of cancer.

METHODS: The NATCSS assessed QOL overall and in four subcategories: physical, psychological, social, and spiritual well-being using the QOL-Cancer Survivor (QOL-CS) instrument. Studies that used the QOL-CS to evaluate survivors of other types of cancers were compared to the NATCSS findings using two-tailed t tests.

RESULTS: We compared results from NATCSS to QOL survivorship studies in colon, glioma, breast, and gynecologic cancer. The mean overall QOL in NATCSS was 5.56 (on a scale of 0-10, where 10 is the best). Overall QOL of patients with thyroid cancer was similar to that of patients with colon cancer (mean 5.20, p = 0.13), glioma (mean 5.96, p = 0.23), and gynecologic cancer (mean 5.59, p = 0.43). It was worse than patients surveyed with breast cancer (mean 6.51, p < 0.01).

CONCLUSIONS: We found the self-reported QOL of thyroid cancer survivors in our study population is overall similar to or worse than that of survivors of other types of cancer surveyed with the same instrument. This should heighten awareness of the significance of a thyroid cancer diagnosis and highlights the need for further research in how to improve care for this enlarging group of patients.

PMID: 26546191  [PubMed - in process]

Characteristics of Persistent Hyperparathyroidism After Renal Transplantation.
Yamamoto T(1), Tominaga Y(2), Okada M(2), Hiramitsu T(2), Tsujita M(2), Goto N(2), Narumi S(2), Watarai Y(2).

Author information:
(1)Department of Transplant and Endocrine Surgery, Nagoya Daini Red Cross Hospital, 2-9 Myouken Chou Showa Ku, Nagoya, Aichi, Japan.
tyamamoto@med.nagoya-u.ac.jp. (2)Department of Transplant and Endocrine Surgery, Nagoya Daini Red Cross Hospital, 2-9 Myouken Chou Showa Ku, Nagoya, Aichi, Japan.

BACKGROUND: Persistent hyperparathyroidism (HPT) after renal transplantation (RTx), termed tertiary HPT (THPT), is not uncommon. However, risk factors and appropriate operative procedures for THPT are poorly understood.

METHODS: A retrospective study of patients who underwent RTx without pre-transplant parathyroidectomy (PTx) was performed at our hospital between January 2001 and March 2011. Risk factors for the development of THPT were investigated by comparing THPT and non-THPT groups. We retrospectively analyzed patients with THPT who underwent total PTx with forearm autograft. Pre- and postoperative (1 year after PTx) laboratory results were analyzed for PTx efficacy.

RESULTS: Data for 520 patients were analyzed. On multivariate analysis, long dialysis duration (p = 0.009, hazard ratio (HR) 1.01), large maximum parathyroid gland size before RTx (p = 0.003, HR 1.23), pre-RTx high intact parathyroid hormone (iPTH) (p = 0.041, HR 1.01), post-RTx (<2 weeks) high calcium (Ca) (p < 0.001, HR 25.04), and post-RTx high alkaline phosphatase (ALP) (p = 0.027, HR 0.99) were identified as risk factors for THPT. Patients who underwent PTx showed significant improvement compared with baseline for serum Ca, phosphorus, iPTH, and ALP. Serum creatinine showed no significant difference.

CONCLUSIONS: Several risk factors for THPT development were identified. PTx for patients with THPT significantly improved serum Ca, iPTH, ALP, and phosphorous levels. There was no significant difference in renal function after PTx.
Therefore, total PTx with forearm autograft may be an appropriate surgical approach for patients with THPT.

PMID: 26546189  [PubMed - in process]

Long-Term Surveillance of Treated Hyperparathyroidism for Multiple Endocrine Neoplasia Type 1: Recurrence or Hypoparathyroidism?
Fyrsten E(1), Norlén O(1), Hessman O(1), Stålberg P(1), Hellman P(2).
Author information:
(1)Department of Surgical Sciences, University Hospital, Uppsala University, 75185, Uppsala, Sweden. (2)Department of Surgical Sciences, University Hospital, Uppsala University, 75185, Uppsala, Sweden. per.hellman@surgsci.uu.se.

BACKGROUND: Primary hyperparathyroidism (HPT) in multiple endocrine neoplasia type 1 (MEN1) is surgically treated with either a subtotal parathyroidectomy removing 3 or 3.5 glands (SPX), less than 3 glands (LSPX), or a total parathyroidectomy with autotransplantation (TPX). Previous studies with shorter follow-up have shown that LSPX and SPX are associated with recurrent HPT, and TPX with hypocalcemia and substitution therapy. We examined the situation after long-term follow-up (median 20.6 years).

METHODS: Sixty-nine patients with MEN1 HPT underwent 110 operations, the first operation being 31 LSPX, 30 SPX, and 8 TPX. Thirty patients underwent reoperative surgery in median 120 months later, as completion to TPX (n = 12), completion of LSPX to SPX (n = 9), extirpation of single glands (n = 3) still resulting in LSPX, and resection of forearm grafts (n = 3). Nine patients underwent a second, and 2 a third reoperation. In 24 patients genetic testing confirmed MEN1, and in the remaining heredity and phenotype led to the diagnosis.

RESULTS: TPX had higher risk for hypoparathyroidism necessitating substitution therapy, at latest follow-up 50 %, compared to SPX (16 % after 3-6 months; none at latest follow-up). Recurrent HPT was common after LSPX, leading to 24 reoperations in 17 patients. No need for substitution therapy after SPX indicated forthcoming recurrent disease. Not having hypocalcemia in the postoperative period and less radical surgery than TPX were significantly associated to risk for recurrence. Further, mutation in exon 3 in the MEN1 gene may eventually be linked to risk of recurrence.

CONCLUSION: LSPX is highly associated with recurrence and TPX with continuous hypoparathyroidism, also after long-term follow-up. SPX should be the chosen method in the majority of patients with MEN1 HPT.

PMID: 26541865  [PubMed - in process]

Outcomes for patients with papillary thyroid cancer who do not undergo prophylactic central neck dissection.
Nixon IJ(1), Wang LY(1), Ganly I(1), Patel SG(1), Morris LG(1), Migliacci JC(1), Tuttle RM(2), Shah JP(1), Shaha AR(1).
Author information:
(1)Head and Neck Surgery, Memorial Sloan Kettering Cancer Center, New York, USA. (2)Department of Endocrinology, Memorial Sloan Kettering Cancer Center, New York, USA.
BACKGROUND: The role of prophylactic central neck dissection (CND) in the management of papillary thyroid cancer (PTC) is controversial. This report describes outcomes of an observational approach in patients without clinical evidence of nodal disease in PTC.

METHODS: All patients who had surgery between 1986 and 2010 without CND for PTC were identified. All patients had careful clinical assessment of the central neck during preoperative and perioperative evaluation, with any suspicious nodal tissue excised for analysis. The cohort included patients in whom lymph nodes had been removed, but no patient had undergone a formal neck dissection. Recurrence-free survival (RFS), central neck RFS and disease-specific survival (DSS) were calculated using the Kaplan-Meier method.

RESULTS: Of 1798 patients, 397 (22·1 per cent) were men, 1088 (60·5 per cent) were aged 45 years or more, and 539 (30·0 per cent) had pT3 or pT4 disease. Some 742 patients (41·3 per cent) received adjuvant treatment with radioactive iodine. At a median follow-up of 46 months the 5-year DSS rate was 100 per cent. Five-year RFS and central neck RFS rates were 96·6 and 99·1 per cent respectively.

CONCLUSION: Observation of the central neck is safe and should be recommended for all patients with PTC considered before and during surgery to be free of central neck metastasis.

© 2015 BJS Society Ltd Published by John Wiley & Sons Ltd. PMID: 26511531 [PubMed - in process]


Wang TS(1), Goffredo P(2), Sosa JA(3),(4), Roman SA(3).

Author information:
(1)Department of Surgery, Medical College of Wisconsin, Milwaukee, WI, USA. tswang@mcw.edu. (2)Department of Surgery, University of Iowa, Iowa City, IA, USA. (3)Department of Surgery, Duke University, Durham, NC, USA. (4)Duke Clinical Research Institute, Durham, NC, USA.

PMID: 26475786 [PubMed - in process]


Lim ST(1), Jeon YW(1), Suh YJ(2).

Author information:
(1)Division of Breast & Thyroid Surgical Oncology, Department of Surgery, College of Medicine, St. Vincent's Hospital, The Catholic University of Korea, Jungbu-daero 93, Paldal-gu, Suwon-Si, Gyeonggi-do, 442-723, Republic of Korea. yjsuh@catholic.ac.kr.

BACKGROUND: The association between surgical extent and prognosis in papillary thyroid carcinoma originating in the isthmus is unclear.
METHODS: We included 233 patients with early-stage, node-negative papillary thyroid cancer originating in the isthmus; 126 were treated by lobectomy plus isthmusectomy with ipsilateral central neck dissection and 97 were treated by total thyroidectomy with bilateral central neck dissection. Subgroup analysis was performed according to tumor size (≤1 vs. >1 cm) to evaluate whether tumor size had a significant impact on determining the optimal extent of surgery in our cohort.

RESULTS: Total thyroidectomy patients had longer recurrence-free survival (RFS) than those treated by lobectomy plus isthmusectomy. Subgroup analysis showed that this was true only for tumors >1 cm. In multivariate analysis, total thyroidectomy was an independent risk factor for RFS only for tumors >1 cm.

CONCLUSIONS: Lobectomy plus isthmusectomy may be optimal for early-stage, node-negative papillary thyroid carcinoma originating in the isthmus for tumors ≤1 cm; total thyroidectomy might be better for tumors >1 cm.

PMID: 26446448 [PubMed - in process]

