Seasonal Variability in Vitamin D Levels No Longer Detectable in Primary Hyperparathyroidism.
Cong E(1), Walker MD(1), Kepley A(1), Zhang C(1), McMahon DJ(1), Silverberg SJ(1).
Author information:
(1)Department of Medicine, Columbia University, College of Physicians and Surgeons, NY, NY 10032.

CONTEXT: Seasonal variability in 25-hydroxyvitamin D (25OHD) and parathyroid hormone (PTH) levels in the general population has been associated with differences in bone turnover markers, bone density and fracture risk. Seasonal variability in 25OHD and PTH levels has also been reported in primary hyperparathyroidism (PHPT).

OBJECTIVE: Given the widespread use of vitamin D supplements, we sought to determine whether patients with PHPT still demonstrated seasonal variation in 25OHD levels.

DESIGN AND SETTING: This cross-sectional study was conducted at a university medical center at a Northeastern US latitude (New York City, NY).

PATIENTS: 100 PHPT patients participated in the study.

OUTCOME: measures: We assessed vitamin D supplement use and seasonal variation in serum 25OHD.

RESULTS: Patients had PHPT (mean ± SD) calcium: 10.8 ± 1.0 mg/dl; PTH: 85 ± 48 pg/ml) with a mean 25OHD level of 29 ± 10 ng/ml. While only one-fifth of participants had vitamin D deficiency (19% < 20 ng/ml), more than half were either deficient or insufficient (54% < 30 ng/ml). Sun exposure varied by season, but there were no seasonal differences in levels of 25OHD, PTH, bone markers or BMD, or in the prevalence of 25OHD <20 or <30 ng/ml. Most (65%) of the participants took supplemental vitamin D (dose among users: mean 1643 ± 1496 IU; median1000 IU daily), and supplement users had markedly better vitamin D status than non-users (25OHD<20 ng/ml: 8% vs. 40%, p<0.0001; <30 ng/ml: 40% vs. 80%, p=0.0001; ≥30 ng/ml: 60% vs. 20%, p=0.0001).

CONCLUSIONS: We found no evidence of seasonal variation in 25OHD levels or PHPT disease severity in the Northeastern US. This change is likely due to widespread high vitamin D supplement intake, which has resulted in better vitamin D status among supplement users and can mask the effect of season on serum 25OHD levels.

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Recent changes in the clinical outcome of papillary thyroid carcinoma with cervical lymph node metastasis.
Jeon MJ(1), Kim WG(1), Mi Choi Y(1), Kwon H(1), Song DE(2), Lee YM(3), Sung TY(3), Yoon JH(3), Hong SJ(3), Hwan Baek J(4), Hyun Lee J(4), Ryu JS(5), Kim TY(1), Shong YK(1), Chung KW(3), Kim WB(1).

Author information:
(1)Departments of Internal Medicine. (2)Pathology. (3)Surgery. (4)Radiology and. (5)Nuclear Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul 138-736, Korea.

CONTEXT: The prognosis of papillary thyroid cancer (PTC) with cervical lymph node
Metastasis has changed with increased detection of subclinical metastatic LNs. The number and size of metastatic LNs were proposed as new prognostic factors in PTC with cervical LN metastasis (N1).

OBJECTIVE: To evaluate changes in N1 PTC characteristics and clinical outcome over time and to confirm the prognostic value of the number and size of metastatic LNs.

DESIGN AND PATIENTS: This study included 1,815 N1 PTC patients diagnosed between 1997 and 2011. Patients were classified into three risk groups according to the number and size of metastatic LNs: very low risk, ≤ 5 and < 0.2 cm; low risk, ≤ 5 and ≥ 0.2 cm; and high risk, > 5.

MAIN OUTCOME MEASURES: Response to initial therapy and disease-free survival (DFS). Results: Metastatic LNs became smaller and the ratio of metastatic LNs, which represents the extent of LN involvement and the completeness of surgery, decreased significantly over time. The proportion of patients with excellent response significantly increased from 33% to 67% over time (P < .001). These improvements were more evident in the low- and high-risk groups than in the very low-risk group. The DFS 5 years after initial surgery was also significantly increased from 73% to 91% over time (P < .001). The new LN classification was strongly associated with outcome. Patients in the very low-risk group had longer DFS than those in the low- and high-risk groups during the study period.

CONCLUSIONS: The clinical outcome of N1 PTC has significantly changed over time with the earlier detection of thyroid cancers with less extensive LN involvement. More complete surgical neck dissection also might be responsible for these changes. The number and size of metastatic LNs are important prognostic factors of recurrence in N1 PTC.

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Serum Leptin Levels and Well-Differentiated Thyroid Cancer: A True Association: Reply.
Abdel-Aziz TE(1), Rehem RA, Elwafa WA.
Author information:
(1)Endocrine Unit, Department of General Surgery, Faculty of Medicine, Alexandria University, Alexandria, Egypt, t.abdel-aziz@ucl.ac.uk.
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4. J Clin Endocrinol Metab. 2015 Jun 16;jc20152132. [Epub ahead of print]
Parathyroidectomy halts the deterioration of renal function in primary hyperparathyroidism.
Tassone F(1), Guarnieri A(2), Castellano E(1), Baffoni C(1), Attanasio R(3), Borretta G(1).
Author information:
(1)Division of Endocrinology and Metabolism, Santa Croce and Carle Hospital, Cuneo, Italy. (2)Division of Nephrology, Santa Croce and Carle Hospital, Cuneo, Italy. (3)Endocrinology Service, Galeazzi Institute IRCCS, Milan, Italy.

OBJECTIVE: Decreased renal function has been consistently included among factors prompting recommendation for surgery in primary hyperparathyroidism (PHPT). However, most retrospective studies addressing this issue did not show an
improvement in renal function after parathyroidectomy (PTX). The aim of this study was to investigate changes in renal function after PTX in PHPT patients splitted according to renal function at diagnosis.

DESIGN: Retrospective cross-sectional study.

PATIENTS AND METHODS: We studied 109 consecutive PHPT patients before and after PTX. Biochemical evaluation included fasting total and ionized serum calcium, phosphate, creatinine, immunoreactive intact PTH, and 25-hydroxyvitaminD3 [25(OH)D3] levels. Glomerular Filtration Rate (GFR) was assessed with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

RESULTS: Mean (± SD) CKD-EPI estimated (e)GFR at diagnosis was 82.4±19.3 mL/min/1.73 m(2) (median 84.8 mL/min/1.73 m(2), interquartile range 25.7 mL/min/1.73 m(2)). Patients with eGFR equal or higher than 60 mL/min/1.73 m(2) (group 1, n = 95) were significantly younger than patients with eGFR lower than 60 mL/min/1.73 m(2) (group 2, n = 14, p <0.0003). After PTX eGFR did not change in patients of group 2 (p = 0.509), whereas it was significantly reduced in patients of group 1 (p <0.0002). The difference in eGFR between baseline and post-PTX values was negatively correlated with baseline serum creatinine (R=-0.27, p = 0.0052) and positively with baseline CKD-EPI eGFR (R = 0.32, p = 0.0062). At multiple regression analysis only systolic blood pressure and baseline CKD-EPI eGFR were independent predictors of GFR variation.

CONCLUSION: Surgical cure of PHPT halts renal function deterioration in patients with coexisting renal disease. Our study thus supports the indication for surgery in patients with eGFR less than 60 mL/min/1.73 m(2), as recommended by current guidelines. Moreover, our data show that presurgical renal function is a relevant predictor of renal function after PTX.

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Vitamin D in Primary Hyperparathyroidism: Effects on Clinical, Biochemical and Densitometric Presentation.

Walker MD(1), Cong E(1), Lee JA(2), Kepley A(1), Zhang C(1), McMahon DJ(1), Silverberg SJ(1).

Author information:
(1)Department of Medicine, Columbia University, College of Physicians and Surgeons, NY, NY 10032. (2)Department of Surgery, Columbia University, College of Physicians and Surgeons, NY, NY 10032.

CONTEXT: Vitamin D (25OHD) deficiency (<20ng/ml) and insufficiency (20-29ng/ml) are common in primary hyperparathyroidism (PHPT) but data regarding their skeletal effects in PHPT are limited.

OBJECTIVE: To evaluate the association between 25OHD levels and PHPT severity.

DESIGN, SETTINGS, AND PARTICIPANTS: This is a cross-sectional analysis of 100 PHPT patients with and without 25OHD insufficiency and deficiency from a university hospital setting.

OUTCOME: Measures: We measured calcitropic hormones, bone turnover markers (BTMs) and bone mineral density (BMD) by dual x-ray absorptiometry (DXA).

RESULTS: Lower 25OHD was associated with some (PTH: r=-0.42, p<0.0001; 1,25-dihydroxyvitamin-D: r=-0.27, p=0.008; serum PO4: r=0.31, p=0.002) but not all (serum/urine calcium) indicators of PHPT severity. Lower 25OHD was also associated with younger age, higher BMI, male gender, better renal function and
lower vitamin D intake. Comparison of those with deficient 25OHD (<20ng/ml; 19%) vs. insufficient (20-29ng/ml; 35%) vs. replete (≥30ng/ml; 46%) demonstrated more severe PHPT as reflected by higher PTH (mean±SEM: 126±10 vs. 81±7 vs. 72±7pg/ml, p<0.0001) but no difference in nephrolithiasis, osteoporosis, fractures, serum or urinary calcium, BTMs or BMD after adjustment for age and weight. In women, T-scores at the 1/3 radius were lower in those with 25OHD 20-29ng/ml, compared to those who were vitamin D replete (p=0.048). In multiple regression modeling, 25OHD but not PTH was an independent predictor of 1/3 radius BMD.

CONCLUSION: Vitamin D deficiency is associated with more severe PHPT as reflected by PTH levels, but effects on BMD are limited to the cortical 1/3 radius and are quite modest. These data support International Guidelines that consider PHPT patients with 25OHD < 20 ng/ml to be deficient. However, in this cohort with few profoundly vitamin D deficient patients, vitamin D status did not appear to significantly impact clinical presentation or bone density.

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Letter to the Editor: Could Low Phosphate Level Be the Reason for High Risk of Hypertension in Normocalcemic Primary Hyperparathyroidism?
Kizilgul M(1), Beketaev I(1), Dolapoglu A(1).
Author information:
(1)Department of Endocrinology and Metabolism (M.L.), Diskapi Teaching and Research Hospital, 06490 Ankara, Turkey; and Center for Stem Cell Engineering (I.B.) and Cardiovascular Surgery Department (A.D.), Texas Heart Institute, Houston, TX 77030 E-mail: ahmetdolapoglu@yahoo.com.
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Hypertension, Antihypertensive Medications, and Risk of Incident Primary Hyperparathyroidism.
Vaidya A(1), Curhan GC(1), Paik JM(1), Kronenberg H(1), Taylor EN(1).
Author information:
(1)Division of Endocrinology, Diabetes, and Hypertension (A.V.), Division of Renal Medicine (G.C.C., J.M.P.), Channing Division of Network Medicine (G.C.C., J.M.P., E.N.T.), Brigham and Women's Hospital (A.V., G.C.C., J.M.P., E.N.T.), and Endocrine Unit (H.K.), Massachusetts General Hospital, Harvard Medical School (A.V., G.C.C., J.M.P., H.K.), Boston, Massachusetts 02115; and Division of Nephrology and Transplantation (E.N.T.), Maine Medical Center, Portland, Maine 04102.

CONTEXT: Hypertension is associated with higher PTH levels, and specific antihypertensive medications may modulate PTH. Whether hypertension or the use of specific antihypertensive medications influences the risk of developing incident primary hyperparathyroidism (P-HPHT) is not known.
OBJECTIVE: The purpose of this study was to investigate whether a history of hypertension and the use of specific antihypertensive medications determine the risk for developing P-HPHT in a large prospective study.
DESIGN/PARTICIPANTS: A longitudinal prospective cohort of female nurses in the
Nurses’ Health Study I (n = 75 600), who did not have P-HPTH at baseline and completed a questionnaire assessment of lifetime history of P-HPTH were followed from 1986 to 2008. Most participants were white and postmenopausal.

SETTING: The study was a nationwide cohort study.

MAIN OUTCOME MEASURE: Incident P-HPTH was assessed initially via questionnaire and then was confirmed by medical record review. Cox proportional hazards models were used to adjust for potential confounders.

RESULTS: We documented 347 incident cases of P-HPTH during 1 719 416 person-years of follow-up. The age-adjusted relative risk (RR) for incident P-HPTH associated with hypertension was 1.80 (95% confidence interval [CI], 1.43-2.26), and the multivariate-adjusted RR was 1.45 (95% CI, 1.10-1.91). Among participants with a history of hypertension, the use of furosemide, when compared with the use of other antihypertensive medications, was associated with increased risk for developing P-HPTH; age-adjusted RR for incident P-HPTH was 1.79 (95% CI, 1.15-2.79) and multivariate-adjusted RR was 1.71 (95% CI, 1.08-2.71).

CONCLUSIONS: In a large longitudinal prospective cohort study of mostly older white women, a history of hypertension and use of furosemide were associated with a significantly higher risk of developing P-HPTH.

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High Diagnostic Accuracy Based on CLDN10, HMGA2, and LAMB3 Transcripts in Papillary Thyroid Carcinoma.
Barros-Filho MC(1), Marchi FA(1), Pinto CA(1), Rogatto SR(1), Kowalski LP(1).
Author information:
(1)International Research Center/AC Camargo Cancer Center (M.C.B.F., F.A.M., C.A.P., S.R.R., S.R.R.), Sao Paulo 01509-010, SP, Brazil; and Faculty of Medicine (S.R.R.), Sao Paulo State University, Botucatu 18618-970, SP, Brazil.

CONTEXT: Thyroid nodules are common in adult population and papillary thyroid carcinoma (PTC) is the most frequent malignant finding. The natural history of PTC remains poorly understood and current diagnostic methods limitations are responsible for a significant number of potentially avoidable surgeries.

OBJECTIVE: This study aimed to identify molecular markers to improve the diagnosis of thyroid lesions.

DESIGN: Gene expression profiling was performed using microarray in 61 PTC and 13 surrounding normal tissues (NT). A reliable gene list was established using cross-study validation (138 matched PTC/NT from external databases). Results were collectively interpreted by in silico analysis. A panel of 28 transcripts was evaluated by RT-qPCR, including benign thyroid lesions (BTL) and other follicular cell-derived thyroid carcinomas (OFDTC). A diagnostic algorithm was developed (training set: 23 NT, 8 BTL, and 86 PTC), validated (independent set: 10 NT, 140 BTL, 120 PTC, and 12 OFDTC) and associated with clinical features.

RESULTS: GABRB2 was ranked as the most frequently up-regulated gene in PTC (cross-study validation). Altered genes in PTC suggested a loss of T4 responsiveness and dysregulation of retinoic acid metabolism, highlighting the putative activation of EZH2 and histone deacetylases (predicted in silico). An algorithm combining CLDN10, HMGA2, and LAMB3 transcripts was able to discriminate
tumors from BTL samples (94% sensitivity and 96% specificity in validation set). High algorithm scores were associated with regional lymph node metastases. CONCLUSIONS: A promising tool with high performance for PTC diagnosis based on three transcripts was designed with the potential to predict lymph node metastasis risk.
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Therapy: Lenvatinib and radioiodine-refractory thyroid cancers.
Dunn L(1), Fagin JA(1).
Author information:
(1)Department of Medicine, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA.
PMID: 25824678 [PubMed - in process]

Predictive factors for occult contralateral carcinoma in patients with unilateral papillary thyroid microcarcinoma by preoperative ultrasonographic and pathological features.
Lee YC(1), Eun YG, Sohn YM, Rhee SY, Hong IK, Chon S, Oh SJ, Kim DY.
Author information:
(1)Department of Otolaryngology-Head and Neck Surgery, School of Medicine, Kyung Hee University, #1 Hoegi-dong, Dongdaemun-gu, Seoul, 130-702, Korea.
BACKGROUND: The surgical extent and indication for treatment in patients with papillary thyroid microcarcinoma (PTMC) remain a controversial issue. The aim of this study was to investigate the predictive factor for contralateral occult carcinoma in patients with unilateral PTMC by preoperative ultrasonographic and pathological features.
METHODS: Of the total patients who underwent thyroidectomy, 455 patients with PTMC confined to one unilateral lobe as diagnosed using preoperative ultrasonography (US) were enrolled in the study. Occult contralateral carcinoma was defined as tumor foci in the contralateral lobe that was not detected preoperatively, but was detected pathologically. All patients underwent preoperative US review to investigate the US features of PTMC such as laterality, location, size, internal component, echogenicity, margin, calcification shape, multifocality, bilaterality, extrathyroidal extension, and location with respect to the trachea. Clinicopathological data were also analyzed.
RESULTS: Of the total of 455 patients who underwent total thyroidectomy for preoperatively detected unilateral PTMC, 71 patients (15.6 %) had contralateral occult carcinoma. Clinicopathological characteristics did not significantly differ between patients with and without contralateral occult carcinoma. Multivariate analysis showed that the absence of a well-defined margin and the presence of a probably benign nodule in the contralateral lobe were independent predictive factors for contralateral occult carcinoma in patients with unilateral PTMC in preoperative US images.
CONCLUSION: We demonstrated that an absence of a well-defined margin and the presence of a probably benign nodule in the contralateral lobe were independent
predictive factors for contralateral occult carcinoma in patients with unilateral PTMC in preoperative US. The prediction of contralateral occult carcinoma in unilateral PTMC using preoperative US features could be useful for determining the optical extent of surgery.

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Author information:
(1)Department of Surgery, Ito Hospital, 4-3-6, Jingumae, Shibuya-ku, Tokyo, 150-8308, Japan, j-akaishi@ito-hospital.jp.

BACKGROUND: Diffuse sclerosing variant (DSV) of papillary thyroid carcinoma (PTC) is a rare variant more common among younger patients.

MATERIALS AND METHODS: Excluding patients with microcarcinoma, 5848 patients with PTC underwent initial surgery between 1995 and 2011. Twenty-two patients (0.4 %) were histologically diagnosed with DSV, of whom 20 (91 %) were <45 years old. We compared clinicopathologic characteristics and outcomes between patients with DSV and those with classical PTC <45 years old. Univariate analysis by the Kaplan-Meier method in relation to cause-specific survival (CSS) and disease-free survival (DFS) rates was performed with regard to the following variables: sex; anti-thyroglobulin antibody (TgAb) positivity; presence of distant metastasis; pathological lymph node metastasis; extra-thyroidal invasion; and pathological variant (classical vs. DSV).

RESULTS: The 20 patients with DSV <45 years old comprised 18 females and 2 males. Frequencies of TgAb, pN1b, and local recurrence were higher in the DSV group than in the classical PTC group. Ten-year CSS and DFS rates for PTC patients <45 years old were 99.7 and 88.6 % in the classical PTC group and 100 and 60.5 % in the DSV group. CSS rate did not differ between groups, but DFS rate was significantly lower in the DSV group than in the classical PTC group (p < 0.0001, log-rank test). Multivariate analysis identified DSV group and pN1b as prognostic factors for recurrence in young PTC patients.

CONCLUSIONS: Most DSV patients were young and had a background of chronic thyroiditis. Outcomes for DSV were very good, but recurrence was more common than in classical PTC.

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Lee HS(1), Kim SW, Hong JC, Lee KD.
Author information:
(1)Department of Otolaryngology-Head and Neck Surgery, Kosin University Gospel Hospital, Kosin University College of Medicine, Am-Nam Dong 34, Seo-Gu, Busan, 602-702, South Korea.

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**VEGF-D and A Preoperative Serum Levels Predict Nodal and Distant Metastases in Differentiated Thyroid Cancer Patients.**  
Lai CW(1), Duh QY, Chen CW, Chuang FJ, Chang YJ, Lin MT, Wu MH.  
Author information:  
(1)Department of Surgery, Buddhist Tzu Chi General Hospital, Taipei branch, Taipei, Taiwan.  

BACKGROUND: Preoperative tumor aggressiveness biomarkers may help surgeons decide the extent of an operation. However, whether serum angiogenetic factors can be used to predict the prognosis of patients with differentiated thyroid cancer is still unclear.  
METHODS: Seventy-six DTC patients were prospectively recruited. Preoperative serum samples were collected and measured for Tie-2, Ang-1, Ang-2, VEGF-A, and VEGF-D levels. The potential correlations between their serum levels and clinicopathologic features as well as their prognoses were analyzed.  
RESULTS: Older age (>45 years old) and higher VEGF-A serum levels were independent predictors of extrathyroidal extension. The VEGF-D serum level was an independent factor for lymph node metastases and VEGF-A was an independent factor for distant metastases. None of these serum angiogenetic factors were significantly different between patients who were disease free and those with recurrences. The presence of lymph node metastases was the only independent factor for recurrence over the 2-year follow-up.  
CONCLUSION: Preoperative serum VEGF-A and VEGF-D levels were significantly elevated in DTC patients with distant and lymph node metastases. These findings, when combined with other clinicopathological factors, may help in surgical decisions.  
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**Is Normocalcemic Primary Hyperparathyroidism Harmful or Harmless?**  
Chen G(1), Xue Y(1), Zhang Q(1), Xue T(1), Yao J(1), Huang H(1), Liang J(1), Li L(1), Lin W(1), Lin L(1), Shi L(1), Cai L(1), Wen J(1).  
Author information:  
(1)Department of Endocrinology (G.C., Y.X., T.X., J.Y., H.H., J.L., L.Li., W.L., L.Lin., L.S., L.C., J.W.), Fujian Provincial Hospital Key Laboratory of Endocrinology, Fujian Medical University, Fuzhou, 350001, China; and Department of Information (Q.Z.), Fujian Provincial Hospital, Fujian Medical University, Fuzhou, 350001, China.  

CONTEXT: Primary hyperparathyroidism (PHPT) is reported to be associated with an increased frequency of hypertension, however, information in this regard is sparse in relation to normocalcemic primary hyperparathyroidism (NPHPT).  
OBJECTIVE: The aim of this study was to determine the association between NPHPT and blood pressure.  
DESIGN, SETTING, AND PATIENTS: We retrospectively enrolled 940 patients who visited the Fujian Provincial Hospital between September 2010 and December 2013.
with a measured serum parathyroid hormone (PTH) and calcium level. Among them, 11 patients were diagnosed with NPHPT, while 296 cases with normal PTH and albumin-adjusted serum calcium.

MAIN OUTCOMES MEASURES: Systolic blood pressure (SBP), diastolic blood pressure (DBP), intact serum PTH, and serum calcium were recorded.

RESULTS: There were no significant differences between subjects identified with NPHPT and those with normal PTH in terms of age, sex, body mass index, serum calcium, 25-Hydroxyvitamin D, serum creatinine, fasting plasma glucose, triglycerides, total cholesterol, high density lipoprotein, and low density lipoprotein. The subjects with a diagnosis of NPHPT had higher levels of SBP (141.9 ± 20.2 vs 131.2 ± 16.5, P = .041) and DBP (85.2 ± 12.4 vs 76.8 ± 10.3, P = .026) than the subjects in the cohort with normal PTH. After adjustment for all potential confounders, risks (odds ratios and 95% confidence interval) of SBP and DBP in NPHPT patients were 1.035 (1.000, 1.071) and 1.063 (1.004, 1.125), respectively (P < .05).

CONCLUSIONS: The NPHPT had higher risk of high blood pressure than subjects with normal PTH. It is worth considering the necessity of more aggressive therapeutic intervention aimed to normalize PTH even if patients with NPHPT continue to be normocalcemic.

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Intraoperative surgical decision using intraoperative frozen section in papillary thyroid cancer: reply.
Park YM(1), Lee BJ.
Author information:
(1)Department of Otorhinolaryngology, Pundang Jesaeng Hospital, Deajin Medical Center, Seongnam, Gyeonggi, Korea.
PMID: 25651966  [PubMed - in process]

Papillary Thyroid Carcinoma with Exclusive Involvement of a Functioning Recurrent Laryngeal Nerve may be Treated with Shaving Technique.
Bansal N(1), Mishra SK, Sabaretnam M.
Author information:
(1)Endocrine Surgery Department, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India.
PMID: 25651965  [PubMed - in process]

Intraoperative frozen section for the evaluation of extrathyroidal extension in papillary thyroid cancer.
Prajapati OP(1), Verma AK, Sabaretnam M.
Author information:
(1)Endocrine Surgery Department, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India.
PMID: 25566976  [PubMed - in process]