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ORIGINAL ARTICLE

Concomitant thyroid lesions in patients with primary hyperparathyroidism

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Summary *Background:* Concomitant thyroid pathologies in patients with primary hyperparathyroidism (PHPT) present a challenge in the clinical and surgical decision-making for these patients. In this study, we aimed to evaluate concomitant thyroid pathologies in patients who underwent operations for PHPT to determine the sensitivity (Sn) of neck ultrasonography (US) and Tc99m sestamibi scintigraphy in detecting parathyroid adenoma. We also aimed to determine the clinical impact of preoperative neck US in patients with PHPT.
Methods: One hundred thirty-eight patients with PHPT were included in this retrospective study. All patients underwent preoperative Tc99m sestamibi scintigraphy and/or thyroid US. Nodules of $\geq$1 cm or $<$1 cm with suspicious US features underwent fine needle aspiration biopsy (FNAB).
Results: Preoperative thyroid US revealed that 93.5% of patients with PHPT had thyroid abnormalities and 66.7% of patients had at least one thyroid nodule. Postoperative histopathology results showed that 79.2% of patients had benign thyroid disease and 20.8% of patients had malignant thyroid disease. In the detection of parathyroid adenoma, US had 89.1% Sn and Tc99m sestamibi scintigraphy had 82.6% Sn.

Conflicts of interest: The authors have no conflicts of interest to declare.

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Conclusion: We recommend the routine use of US in combination with Tc99m sestamibi scintigraphy, especially in endemic goiter regions, to detect any concomitant thyroid disease and thus determine the best surgical strategy for patients with PHPT.

1. Introduction

Primary hyperparathyroidism (PHPT) is the third most common endocrine disorder.[1,2] It is twice as common in women, and its incidence increases with age with a peak in the fifth to sixth decades of life.[1,3,4] It is caused by one or more overactive parathyroid glands, which results in elevated parathyroid hormone (PTH) and serum calcium (Ca) levels.[5]

Coexistent thyroid pathology found during neck exploration in patients with PHPT has been well described.[6] The incidence of PHPT with coexistent thyroid diseases ranges from 17% to 84% in different studies.[2,4,7–12] In addition, the incidence of synchronous thyroid cancer in patients with PHPT ranges between 2% and 24%.[2,4,7–9,11,12] It is still controversial whether the association of PHPT and nonmedullary thyroid carcinoma (NMTC) is coincidental or if pathogenetic mechanisms or risk factors such as irradiation, the goitrogenic effect of Ca or calcitonin, and genetic factors account for the coexistence of these two disorders.[13]

Surgical excision is the only curative treatment for PHPT and has been shown to be safe and effective for patients of any age.[5] Bilateral neck exploration which allows the surgeon to perform a thorough examination of the thyroid gland and examine the four parathyroid glands was traditionally performed in the surgical management of PHPT.[11,13,14] This procedure is usually helpful also for the identification and resection of tissue affected by concomitant thyroid disease.[11] Advances in imaging procedures (which provides a definitive preoperative localization of parathyroid adenomas), improved surgical techniques, and the use of intraoperative intact PTH measurement have increased the tendency toward minimally invasive approaches (MIAs) for parathyroid surgeries.[11–13] Because PHPT is caused by a solitary adenoma in 85–90% of patients[15,16], most patients can be treated with MIAs.[14] Such approaches have potential benefits, such as smaller incisions, lower morbidity, shorter length of hospitalization, and quick return to preoperative activity; however, a surgeon may miss any coexistent thyroid pathology because of the smaller surgical field.[2,5,11,13] Concomitant thyroid pathology in patients with PHPT presents a challenge in the clinical and surgical decision-making for these patients.[11] Early diagnosis and simultaneous surgical treatment, particularly for thyroid cancer, is the most important part of management.[17] A delayed diagnosis may lead to a second neck exploration, which is more difficult and associated with increased complication rates.[17] To determine the most appropriate management for PHPT, it is important to localize the pathologic parathyroid gland and diagnose concomitant thyroid disease.[18] High-resolution ultrasonography (US) and Tc99m sestamibi scintigraphy are widely accepted methods for the preoperative localization of parathyroid lesions.[5,19] Ultrasonography enables screening of the thyroid gland while simultaneously localizing the parathyroid adenoma.[17]

In this study, we aimed to evaluate concomitant thyroid pathologies in patients who underwent operations for PHPT to determine the best surgical strategy in this group of patients and to determine the clinical impact of preoperative neck US in our center.

2. Materials and methods

2.1. Patients

We retrospectively evaluated patients who underwent parathyroid surgery for PHPT between January 2010 and June 2013 in our clinic. All patients underwent preoperative parathyroid localization by Tc99m sestamibi scintigraphy and/or neck US. Patients younger than 15 years old and patients with a previous history of thyroid or parathyroid operations, percutaneous interventions, or radiotherapy of the head and neck were excluded from the study. Patients with a surgical contraindication associated with comorbid diseases (e.g., cardiovascular or respiratory system diseases) or who refused surgery were also excluded.

In our clinic, all operation indications are administered with an expert council that consists of surgeons, endocrine specialists, and nuclear medicine specialists. In this council, patients are informed about their operation indications and the operation types, and they are informed that the operation type can be changed according the situation in which the surgeon encounters. Informed consent was obtained from all patients before surgery. The study protocol followed the tenets of the 1964 Declaration of Helsinki.

2.2. Laboratory

The levels of sensitive thyroid-stimulating hormone (sTSH), free triiodothyronine (fT3), free thyroxine (fT4), thyroid autoantibodies [e.g., thyroid peroxidase antibody (anti-TPO) and thyroglobulin antibody (anti-Tg)], and thyroglobulin were measured in all patients using chemiluminescence methods (Immulite 2000; Diagnostic Products Corporation, Los Angeles, CA; and UniCel DxI 800; Beckman Coulter, Brea, CA). The normal ranges for sTSH, fT3, fT4, anti-Tg, and anti-TPO were 0.4–4 μIU/mL, 1.57–4.71 pg/mL, 0.61–1.12 ng/dL, <30 U/mL, and <10 U/mL, respectively. The serum levels of Ca, albumin,

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phosphorus, vitamin D, and PTH levels, and the 24-hour urine Ca and phosphorus excretion were evaluated (normal levels are 8.6–10 mg/dL, 3.5–5.2 g/dL, 2.5–4.5 mg/dL, 10–80 μg/L, 15–65 pg/mL, 100–300 mg/day, and 0.4–1.3 g/day, respectively). In addition, dual energy X-ray absorptiometry (DEXA) and renal US were performed to evaluate bone mineral density and nephrolithiasis, respectively.

2.3. Conventional ultrasonography and fine needle aspiration biopsy

An Esaote color Doppler US system (Model 796FDII; MAG Technology Co. Ltd., Yung-Ho City, Taipei, Taiwan) and standard US system with a superficial probe (Model LA523 13–4, 5.5–12.5 MHz) were used. The patient laid supine with his or her neck in hyperextension, and the skin was coated with acoustic material. Chronic thyroiditis was defined when the thyroid gland was diffusely heterogenous and/or hypoechoic with/without pseudonodules and fibrotic bands.[20]

The location, diameter (mm), volume, component (i.e., solid, cystic, mixed), echogenicity (i.e., hypoechoic, isoechoic, hyperechoic), border regularity, calcification, and presence of peripheral halo of nodules were evaluated. Nodules of $\geq$1 cm or $<$1 cm with questionable US features such as an irregular border, hypoechoic texture, solid component, the presence of microcalcification, and anteroposterior/transverse diameter greater than 1 underwent fine needle aspiration biopsy (FNAB).[21] This procedure was performed under US guidance using a General Logic Pro 200 system (model 2270968; GE Healthcare, Korea and Seongnam SI; Gyeonggi-do, Korea) and a 5.5-MHz to 7.5-MHz superficial probe. Written consent was obtained from all patients before the FNAB. No anesthetics were applied before the procedure. For all patients, US-guided FNAB was performed by an experienced endocrinologist using a 23-gauge needle and 20-mL syringe.

The US results were classified as normal, chronic thyroiditis, multinodular goiter/nodular goiter (MNG/NG), and chronic thyroiditis with MNG/NG.

2.4. Cytological and histopathological examination

Materials obtained by US-guided FNAB were air-dried, stained with May-Grünwald-Giemsa, and evaluated according to the Bethesda system classification.[22] The cytology results were as follows: (1) nondiagnostic, (2) benign, (3) atypia/follicular lesion of undetermined significance (AUS/FLUS), (4) follicular neoplasm/suspected follicular neoplasm, (5) suspected malignancy, and (6) malignant.[23,24] Histopathological evaluation was made in accordance with the 2004 World Health Organization criteria.[25]

2.5. Tc99m Sestamibi scintigraphy

Fifteen mCi of Tc99m methoxy-isobutyl-isonitrile (i.e., sestamibi) was intravenously injected. Anterior static images of the neck and mediastinum were taken 10 minutes and 3 hours after the injection. At the third hour, to correct the anatomic correlation and attenuation of the neck region, computed tomography and/or single-photon emission computed tomography images were taken. A distinct focus of increased or separate Tc99m sestamibi uptake relative to the thyroid gland on either the early or late images (or both) was considered positive for abnormal parathyroid tissue.

2.6. Statistical analysis

SPSS 11.5 software (Statistical Packaging of Social Science for Windows (SPSS Inc., Chicago, IL)) was used for the analysis of the variables. Descriptive statistics for continuous variables are expressed as the mean $\pm$ the standard deviation or as the median (minimum–maximum). The categorical variables are denoted as the number and percent (%). Fischer's chi-square test was used to evaluate the difference between the groups with regard to the categorical variables and Mann–Whitney *U* test was used for the nonparametric variables. We determined sensitivity of US and methoxy-isobutyl-isonitrile (MIBI). A *p* value less than 0.05 was accepted as statistically significant.

3. Results

3.1. Clinical characteristics and preoperative evaluation of the patients

One hundred fifty-one patients who underwent parathyroidectomy were evaluated. Thirteen patients were excluded from the study because of previous thyroid operations (five patients) and tertiary hyperparathyroidism (eight patients). The data of 138 patients with PHPT were finally analyzed in this study. One hundred twenty-four (89.9%) of the 138 patients were female, and 14 (10.1%) patients were male. The mean age of the patients was 51.2 $\pm$ 10.1 years (range, 22–79 years).

Preoperative laboratory evaluation showed that the mean level of serum Ca was 11.2 $\pm$ 0.77 mg/dL; albumin, 4.2 $\pm$ 0.38 g/dL, and phosphorus, 2.5 $\pm$ 0.58 mg/dL. Mean levels of serum PTH and 25-OH vitamin D were 248.5 $\pm$ 197.91 pg/mL (range, 80–1515 pg/mL; median, 190 pg/mL) and 17.5 $\pm$ 13.89 μg/L, respectively. The mean 24-hour urinary Ca excretion was 389 mg/day. According to the DEXA and urinary US results, 39.1% of patients had osteoporosis and 22.5% had nephrolithiasis.

Twelve (8.7%) patients had hypothyroidism and six (4.3%) patients had thyrotoxicosis. The remaining 120 (87%) patients had normal thyroid hormones (Table 1). The thyroid peroxidase antibody positivity rate was 28.3%, and the anti-Tg positivity rate was 32.6%.

Neck US was performed in all patients preoperatively. Neck US revealed nine (6.5%) patients had normal thyroid and 37 (26.8%) patients had chronic thyroiditis. Ninety-two (66.7%) patients had at least one thyroid nodule: of these, 73 (52.9%) patients had chronic thyroiditis and 19 (13.8%) patients did not have chronic thyroiditis (Table 1). Nodule localization was bilateral in 56 (60.9%) patients. The mean nodule diameter was 12.77 $\pm$ 10.58 mm (range 2.3–60.1 mm). Fine needle aspiration biopsy was performed in 58 patients. The FNAB cytological results

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Table 1 Preoperative thyroid function and ultrasonography findings in patients with primary hyperparathyroidism.

Variables	*n* (%)
Thyroid function	
Hypothyroidism	12 (8.7%)
Thyrotoxicosis	6 (4.3%)
Euthyroid	120 (87.0%)
Thyroid US results	
Normal	9 (6.5%)
MNG/NG	19 (13.8%)
Chronic thyroiditis + MNG/NG	73 (52.9%)
Chronic thyroiditis	37 (26.8%)
Site of parathyroid adenoma	
Right	68 (49.3%)
Left	69 (50.0%)
Bilateral	1 (0.7%)
Localization of the parathyroid adenoma	
Superior	20 (14.5%)
Inferior	118 (85.5%)

MNG, multinodular goiter; NG, nodular goiter; US, ultrasonography.

indicated possible malignancy in one patient, AUS/FLUS in four patients, was nondiagnostic in nine, and benign in 44 patients (Table 2).

Based on ultrasonography, 50% of the parathyroid adenomas were on the left side and 85.5% were located inferiorly. The mean parathyroid adenoma size was 14.04 ± 6.1 mm (range, 6–41.3 mm). Tc99m sestamibi scintigraphy was also performed in all patients and the parathyroid adenoma was localized in 114 (82.6%) patients.

3.2. Postoperative results

Based on the histopathology results, 128 (92.8%) patients had parathyroid adenomas. Six patients had atypical adenomas and three patients had hyperplasia. In one patient, parathyroid carcinoma was diagnosed histopathologically. The postoperative parathyroid histopathology results are shown in Table 3.

Thirty-two (23.2%) patients underwent parathyroidectomy, whereas 106 (76.8%) patients underwent both parathyroidectomy and thyroidectomy. Among 32 patients who underwent only parathyroidectomy, US findings were chronic thyroiditis in 17 patients, normal in seven patients, and MNG/NG in eight patients (the nodules were less than 1 cm and not ultrasonographically questionable). Lobectomy/isthmechtomy was performed in 35 patients and total thyroidectomy was performed in 71 patients. In the lobectomy group; preoperative US findings were chronic thyroiditis in 13 patients (five of these patients had Graves' disease), normal in two patients, NG in 10 patients, and chronic thyroiditis with NG in 10 patients. In this group, lobectomy was performed in 10 patients because of technical problems (8 of these patients had chronic thyroiditis and two of these patients had normal US findings preoperatively). In the total thyroidectomy group, the preoperative US findings were chronic thyroiditis in seven patients, MNG in seven patients, and chronic thyroiditis with MNG/giant nodule in 57 patients. In seven patients with chronic thyroiditis, indications for total thyroidectomy were Graves' disease in one patient, diffuse enlarged thyroid gland and cosmetic concern in two patients, compression symptoms in one patient, family history of thyroid cancer in one patient, and failure of intraoperative detection of the parathyroid adenoma in two patients (Table 4).

The postoperative thyroid histopathology results revealed that 79.2% of patients had benign thyroid disease and 22 (20.8%) patients had malignant thyroid disease. All patients with malignant disease had papillary thyroid

Table 2 Fine needle aspiration biopsy results of thyroid nodules in patients with primary hyperparathyroidism.

FNAB results	n (%)
Benign	44 (75.9%)
AUS/FLUS	4 (6.9%)
Suspicious for malignancy	1 (1.7%)
Nondiagnostic	9 (15.5%)

AUS, atypia of undetermined significance; FLUS, follicular lesion of undetermined significance; FNAB, fine-needle aspiration biopsy.
The sample comprises 58 patients.

Table 3 Operation types and postoperative parathyroid and thyroid histopathological results.

Variables	*n* (%)
Operation type	
Parathyroidectomy	32 (23.2%)
Parathyroidectomy + lobectomy/isthmectomy	35 (33%)
Parathyroidectomy + Total thyroidectomy	71 (67%)
Parathyroid histopathology	
Hyperplasia	3 (2.2%)
Adenoma	128 (92.8%)
Carcinoma	1 (0.7%)
Atypical adenoma	6 (4.3%)
Thyroid histopathology	
Benign	84 (79.2%)
Malignant	22 (20.8%)
Histopathological features of PTCs	
Tumor size	
Microcarcinoma	20 (90.91%)
Macrocarcinoma	2 (9.09%)
PTC variant	
Classical	19 (86.4%)
Follicular variant	2 (9.1%)
Tall cell variant	1(4.5%)
Vascular invasion	—
Capsular invasion	2 (9.1%)
Lymph node metastasis	1 (4.5%)
Multicentricity	7 (31.8)
Extracapsular invasion	—
Ipsilateral PTC and parathyroid lesion	14 (63.6%)

PTC, papillary thyroid carcinoma.
The sample comprises 138 patients.

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Table 4 Preoperative thyroid ultrasonography findings in patients with primary hyperparathyroidism who underwent lobectomy and total thyroidectomy.

Variables	Lobectomy (35 patients)	Total thyroidectomy (71 patients)
Thyroid US results		
Normal	2 (5.7%)	—
MNG/NG	10 (28.6%)	7 (9.9%)
Chronic thyroiditis + MNG/NG	10 (28.6%)	57 (80.2%)
Chronic thyroiditis	13 (37.1%)	7 (9.9%)

MNG, multinodular goiter; NG, nodular goiter; US, ultrasonography.
The data are presented as the number (%).

cancer (PTC) and 20 (90.91%) of these patients had microcarcinoma. In the remaining two patients, the tumor size was greater than 1 cm. One of these patients had follicular variant and the other patient had the tall cell variant of PTC. 2 of the four patients with AUS/FLUS had benign and two patients had malignant histopathology results (1 of patient had papillary microcarcinoma and one patient had follicular variant PTC). Tall cell variant PTC was diagnosed in the patient with the suspected malignancy indicated by the FNAB result. Among nine patients with nondiagnostic FNAB results, three patients had papillary microcarcinoma. Papillary carcinoma was found incidentally in four patients with preoperative chronic thyroiditis, based on the US result. In eight patients, FNAB was benign preoperatively, but histopathologically PTC was detected. In the remaining four patients with final thyroid malignancy, preoperative FNAB was not performed because nodules were smaller than 1 cm. One patient with PTC had lymph node metastasis. A total of 63.6% of PTC were on the same side with the parathyroid adenoma. The operation type and postoperative thyroid histopathology results are shown in Table 3. Ultrasonography had a Sn of 89.1% and Tc99m sestamibi had a Sn of 82.6% for the detection of parathyroid adenomas.

4. Discussion

In this study, we aimed to evaluate the prevalence of concomitant thyroid disease and thyroid malignancy in patients who underwent surgical treatment for PHPT to highlight the best surgical strategy in this group of patients. We also evaluated the Sn of neck US and Tc99m sestamibi scintigraphy for detecting parathyroid adenomas. We also attempted to determine the clinical impact of preoperative neck US in patients with PHPT.

In this study, preoperative US revealed that among all patients with PHPT, 93.5% of the patients had thyroid abnormalities and 66.7% of the patients had at least one thyroid nodule. The postoperative malignancy rate was 20.8%.

In the literature, the prevalence of thyroid disease with concomitant PHPT ranges from 18% to 84.3%; in addition, thyroid carcinoma has been reported in 1—36% of patients with PHPT.[2,4,7,11—13,26,27] Strichartz and Giuliano evaluated 308 patients who underwent operations for PHPT and revealed that 17% of patients had histologically proven thyroid disease and 4% of patients had differentiated thyroid cancer.[11] These wide variations were probably because of the variations in patient selection, surgical indications, examination methods, and the number of patients.[13,26] The true incidence of PTC in patients with PHPT is unknown because not all patients with PHPT undergo surgery, and neck exploration is impossible during a MIA, which has become more common in recent years.[28] Our higher frequency of concomitant thyroid disease and thyroid malignancy in patients with PHPT is probably because of the fact that our clinic is a highly specialized thyroid reference center in our region, preoperative thyroid examination by US is performed routinely for these patients, and thyroidectomy is performed with a higher rate. Masatsugu et al.[18] showed that of 109 patients with sporadic PHPT, 52.3% of these patients had concomitant thyroid disease and 17.4% of these patients had NMTC. They explained this high frequency by the fact that the patients who visited their center had potential thyroid disease similar to ours.[18]

The curative treatment of PHPT is surgical excision of the enlarged parathyroid gland.[17,26] The surgical approach has changed during the past 10 years owing to improved preoperative imaging techniques and the availability of intraoperative PTH assay.[17,18,29] In particular, the approach has moved from bilateral neck exploration to a unilateral MIA or limited neck exploration.[11,17,18,26,30] The potential advantages of MIA include the possible use of local anesthesia; a reduction in the operation time of up to 50%, lower incidence of hypocalcemia; and decreased hospitalization time, complication rates, and hospital charges.[17] A MIA would not be considered in a patient with a history of head and neck irradiation, a family history of thyroid cancer, or a nonlocalizable parathyroid abnormality on preoperative imaging studies.[4] In addition, the main challenge of MIA is concomitant thyroid nodules.[31,32] For a successful MIA, it is important to evaluate certain points, including whether the parathyroid adenoma is solitary, the position of the parathyroid adenoma, and the presence of possible concomitant thyroid nodular diseases.[26] If there is thyroid disease, clinical decision and management of the patients may change.[26]

In our study 106 patients underwent thyroidectomy because of the toxic MNG/Graves' disease, MNG/NG or giant nodule, or questionable or nondiagnostic FNAB results. However, 12 patients had thyroidectomy because of technical reasons.

Evaluating the thyroid gland before an operation for PHPT is essential because a delay in operation of the thyroid lesion can result with increased morbidity associated with a second neck exploration.[26] It is important that patients with unexpected thyroid malignancy be treated safely at the time of the initial operation for hyperparathyroidism.[4] Previous studies[11] have revealed that thyroid lesions of less than 1 cm are missed in 94% of patients and that lesions 1—2 cm are missed in 50% of patients with neck exploration. The preoperative absence of a palpable thyroid abnormality is insufficient to exclude thyroid disease. Many endocrine surgeons have recommended neck US before parathyroid surgery for preoperative localization to

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determine the presence of concomitant thyroid disease. In a study by Gates et al[4], preoperative thyroid US altered the operative management in nine (38%) of 24 patients who underwent surgery for PHPT; three of these nine (33%) patients had differentiated thyroid carcinoma. This finding suggests that preoperative neck US is useful for preoperative management in patients with PHPT.[4] Preoperative neck US in these patients can also eliminate the operative morbidity of the second operation.[4]

It has been determined that preoperative Tc99m sestamibi and US findings represent a reliable localization technique for parathyroid lesions when used together, and result in a nearly 90% true-positive rate.[26] Tc99m sestamibi is useful for the localization of enlarged parathyroid glands; however, its Sn and positive predictive value were unsatisfactory in patients with concomitant thyroid disease[26] and in patients with small parathyroid adenomas.[18] Concomitant thyroid disease reportedly affects the detection of parathyroid lesions with a decrease in Sn ranging from 71% to 80% for Tc99m sestamibi and 53% to 77% for US.[18] The Sn of US in parathyroid lesions ranges from 30% to 90%.[33] Ultrasonography is a useful diagnostic tool for the detection of concomitant thyroid nodules[18]; however, US cannot always detect glands deep in the neck or glands with ectopic localization, it is operator-dependent, and it has a limited scanning field.[5,18] Mazzeo et al[34] found that US and Tc99m sestamibi have similar diagnostic value with respect to detecting parathyroid lesions in patients without thyroid abnormalities (85% vs. 82%, respectively) and in patients with concomitant thyroid disease (77% vs. 80%, respectively). In patients with multigland disease, US appeared to be superior to scintigraphy (70% vs 40%).[35,36] By contrast, various studies show that Tc99m sestamibi is superior to US in patients with or without thyroid abnormalities.[34,37] In a meta-analysis, the Sn and specificity (Sp) of MIBI were determined as 90.7% and 98.8%, respectively, and these findings suggested that more than 80% of patients with PHPT would be candidates for a MIA.[17] In our study, US had a Sn of 89.1% and MIBI had a Sn of 82.6% for detecting parathyroid lesions.

The main reason for the high prevalence of concomitant thyroid disease and malignancy in PHPT remains unclear. Some authors have suggested that it can be coincidental, whereas others claim that this relationship may be because of increased endogenous Ca concentration, growth factors, epithelial growth factor, or goitrogenic factors.[26] Some other authors have suggested that previous head and neck irradiation may be a common pathogenetic factor for the development of both PHPT and NMTC.[1] In our study, no patient had undergone head or neck irradiation.

In conclusion, thyroid disease and thyroid malignancy have a high frequency in patients with PHPT. We recommend the routine use of US in combination with Tc99m sestamibi, particularly in endemic goiter regions, to detect any concomitant thyroid disease and thus determine the best surgical strategy in patients with PHPT.

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