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Predicting coexisting thyroid cancer with primary hyperparathyroidism in an endemic region of multinodular goiter: evaluating the effectiveness of preoperative inflammatory markers

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Purpose: The aim is to examine the efficacy of inflammatory indicators to predict thyroid cancer in patients with primary hyperparathyroidism (PHPT) in an endemic region of nodular goiter.
Methods: The prospective database was reviewed to identify patients operated on with the diagnosis of PHPT and thyroid disease between April 2015 and June 2021. Permanent pathologic reports were used as the gold standard for diagnosis. Detailed imaging data with peripheral blood inflammation indices were analyzed to assess their predictive values for concomitant PHPT with thyroid cancer. Postoperative complications and the duration of hospitalization were also reviewed.
Results: Thyroid malignancy accompanying PHPT was found in 13 patients (26.0%) out of 50 who had concurrent surgery. The analysis regarding inflammatory indexes revealed nothing significant between thyroid cancer and preoperative blood biochemistry ($P > 0.05$). In the concurrent surgery group, recurrent laryngeal nerve injury was observed in 1 patient (2.0%) and the mean hospital stay was longer.
Conclusion: In endemic regions of nodular thyroid disease, thyroid cancer might accompany PHPT. The value of inflammatory indexes to predict thyroid malignancy in PHPT is controversial and should not be employed in the surgical decision-making process.
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Key Words: Primary hyperparathyroidism, Thyroid neoplasms, Neck ultrasound, Sestamibi scan, Inflammatory indices

INTRODUCTION

Primary hyperparathyroidism (PHPT) is an underdiagnosed endocrine disease caused by excessive secretion of parathyroid hormone (PTH) due to parathyroid adenoma, hyperplasia, or rare malignancy [1]. Particularly in endemic regions of nodular goiter, detailed evaluation of patients regarding possible accompanying thyroid pathologies is of paramount importance in the preoperative period. The first imaging modality to detect concurrent thyroid and parathyroid diseases is ultrasound, and specific imaging techniques can be employed in cases of unequivocal findings to localize the parathyroid lesion, including ^{99m}technetium-sestamibi scanning, single-photon emission CT, and 4-dimensional CT [2]. Thyroid pathologies are detected by high-resolution neck ultrasound, and diagnosis is achieved by fine-needle aspiration (FNA) cytology [3]. While

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success in thyroid ultrasound requires experience, FNA cytology of thyroid nodules may be limited because of the presence of multiple nodules in endemic regions [4]. Moreover, the prediction of malignancy in patients with PHPT and thyroid nodules is a matter of debate, and inflammatory indices have attracted great interest among researchers focusing on this issue. In tumor biology, inflammation assumes a significant role, impacting not just the immediate tumor microenvironment but also exerting systemic effects that shape tumor advancement or reappearance. This process encourages the proliferation of tumor cells, angiogenesis, invasion, and metastasis [5]. The body's reaction to systemic inflammation involves changes in hematopoiesis and the release of acute-phase proteins, cytokines, growth factors, and hormones. Various serum-based inflammation indicators, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII), can provide insights into the extent of systemic inflammation. Additionally, these indicators can predict the clinical outcomes and prognosis for cancer patients [6]. In cases of concurrent pathologies, thyroid surgery could be performed simultaneously with parathyroid surgery to avoid increased surgical complications due to postoperative adhesions in secondary interventions. Concomitant thyroidectomy and parathyroidectomy have been reported to be safe and equally effective, except for prolonged hospital stay, long operative time, and higher frequency of transient hypocalcemia [7]. The primary aim of this study was to assess the accompanying malignant thyroid pathologies in PHPT and the value of inflammatory indices in predicting malignancy in patients in an endemic region of nodular thyroid disease. The secondary aim was to examine the efficacy of ultrasound, sestamibi scanning, and the combination of both techniques in accurate localization, complication rates, hospitalization durations of concurrent surgery, and serum phosphate levels to predict cancer in concomitant thyroid and parathyroid disease.

METHODS

The Ethics Committee of Zonguldak Bülent Ecevit University approved this study (No.2022/01-4). It was performed in accordance with the Declaration of Helsinki and written informed consent was waived due to its retrospective nature.

The prospectively maintained hospital database was reviewed to identify PHPT patients who underwent surgery at our institution between April 2015 and June 2021. Patients who were younger than 18 years of age, those with a history of previous thyroid or parathyroid surgery, those with secondary/tertiary hyperparathyroidism, those who had previous head and neck radiation, those who did not undergo imaging tests, and those whose medical records were incomplete or could not be obtained were excluded from the study. Ultrasound evaluations were performed by a designated radiologist and endocrine surgeon preoperatively and intraoperatively. Thyroid nodules were classified according to the American Thyroid Association (ATA) classification system [8], and FNA cytology indications were determined. The Bethesda classification system [9] was used for pathological categorization. Size-independent FNA cytology was performed in patients with a thyroid pathology accompanied by parathyroid adenoma. All cases had been discussed by multidisciplinary endocrine boards, including endocrine surgeons, endocrinologists, radiologists, and nuclear medicine specialists, before surgery as the standard of routine clinical practice. Scintigraphic imaging is the standard approach in patients with parathyroid disease concomitant with thyroid nodules. Permanent pathological reports were used as the gold standard for identifying adenomas and the nature of thyroid diseases. Ultrasound and sestamibi scan reports were used systematically as the preoperative examination method and were defined as true positives by determining the localization of the affected parathyroid adenoma in the presence of thyroid disease, at least unilaterally (right-left), concordant with the surgical pathology report. Age, sex, pre- and postoperative serum calcium, PTH, phosphate, vitamin D 25-OH, and thyroid-stimulating hormone (TSH) levels were evaluated. Permanent histopathological results of the removed parathyroid and thyroid tissues were examined. Neutrophil, lymphocyte, platelet, and monocyte ratios were obtained based on preoperative complete blood count test data from the patient registry. The NLR and PLR were calculated by dividing the neutrophil and platelet counts by the absolute lymphocyte count. The lymphocyte-to-monocyte ratio (LMR) was calculated by dividing the lymphocyte count by the absolute monocyte count. The SII was obtained by multiplying the neutrophil count by the PLR as described by Feng et al. [10]. The NLR, PLR, LMR, and SII were calculated to assess their value in predicting concomitant PHPT and thyroid cancer. Postoperative complications and the duration of hospitalization were also reviewed. Routine nerve monitoring was performed for each patient as a standard of care. Preoperative and postoperative vocal cord examinations were performed using indirect laryngoscopy. Calcium replacement therapy was initiated in all patients during the early postoperative period as a standard protocol.

Statistical analysis

The Jamovi 2.2.5. software was used for statistical analyses. Quantitative data are presented as frequency and percentage values, while quantitative data are presented as median, minimum, and maximum values. The Shapiro-Wilk test was used to test the normality of the quantitative variables. The Mann-Whitney U-test was used for independent group comparisons. All statistical comparisons with a P-value of <0.05 were assumed statistically significant.

RESULTS

Two hundred thirty-five patients who underwent surgery for PHPT were included in the study; 200 (85.1%) were female, and 35 (14.9%) were male. The mean age of the patients was 53.7 ± 11.6 years. Parathyroidectomy and concurrent thyroidectomy were performed in 50 patients (21.3%), whereas isolated parathyroidectomy was performed in 185 patients (78.7%) (Table 1). The ATA classification was applied to 50 patients who underwent concurrent thyroidectomy. The isolated parathyroidectomy group displayed no accompanying thyroid nodules on preoperative evaluation. In the concurrent surgery group, there were multiple thyroid nodules on the side with parathyroid gland pathology in 22 patients (44.0%) and both thyroid lobes in 28 (56.0%). Fifty patients who underwent concurrent parathyroid and thyroid surgery in accordance with the decisions of the multidisciplinary endocrine board were included in the case group. Forty-two of these patients (84.0%) were female, and 8 (16.0%) were male. The median age of the patients was 58 years (range, 40–75 years). Neck ultrasound and sestamibi scans accurately localized parathyroid adenoma in 45 (90.0%) and 44 patients (88.0%), respectively. Among the 5 cases (10.0%) for which intraoperative real-time ultrasound was performed by the surgeon, with the detection of sono-scintigraphic discordance, accurate localization was revealed after thyroid gland removal in 4 patients (8.0%). For the last discordant case, scintigraphic data were found to be accurate. In addition to parathyroidectomy, 22 patients (44.0%) underwent lobo-isthmectomy and 28 (56.0%) underwent total thyroidectomy. Thyroid FNA biopsy results were nondiagnostic (Bethesda I) in 6 patients (12.0%), benign (Bethesda II) in 16 (32.0%), atypia/follicular lesions of undetermined significance (Bethesda III) in 20 (40.0%), follicular neoplasia (Bethesda IV) in 4 (8.0%), and suspicious for malignancy (Bethesda V) in 4 (8.0%). Permanent pathological evaluation revealed thyroid malignancy accompanying PHPT in 13 (26.0%) out of 50 patients, 8 of which (16.0%) were papillary microcarcinoma, 4 (8.0%) were reported to be papillary carcinoma, and Hurthle cell carcinoma was detected in 1 case (2.0%). Benign thyroid diseases were detected in the remaining 37 patients (74.0%), including lymphocytic thyroiditis in 7 (14%) and nodular hyperplasia and cystic changes in 30 (60.0%). Analysis of parathyroid pathologies in the case group revealed adenoma in 46 patients (92.0%) and hyperplasia in 4 (8.0%). Analysis of inflammatory indices in patients with PHPT revealed no significant relationship between thyroid cancer and preoperative peripheral blood NLR, PLR, LMR, SII, serum phosphate, TSH, vitamin D 25-OH, or PTH

Table 1. Demographics and operative data

Characteristic	Isolated parathyroidectomy	Concurrent surgery
No. of patients	185	50
Sex		
Male	27 (14.6)	8 (16.0)
Female	158 (85.4)	42 (84.0)
Age (yr)	52 (18–78)	58 (40–75)
Localization accuracy		
Neck ultrasound	153 (85.0)	45 (90.0)
Sestamibi	142 (79.0)	44 (88.0)
Neck ultrasound + sestamibi	175 (94.0)	50 (100)
Hospital stay (day)	3.05 ± 0.93	4.28 ± 0.86
Postoperative complication		
Transient hypocalcemia	41 (22.2)	9 (18.0)
Neuropraxia	0 (0)	1 (2.0)
Hypocalcemia	0 (0)	0 (0)
Hematoma	0 (0)	0 (0)
Parathyroid pathology results		
Parathyroid adenoma	171 (92.4)	46 (92.0)
Hyperplasia	13 (7.0)	4 (8.0)
Carcinoma	1 (0.6)	0 (0)

Values are presented as number only, number (%), median (range), or mean ± standard deviation.

Table 2. Comparison of inflammatory indices and blood biochemistry in concurrent surgery

Variable	Benign	Malignant	P-value[a]
NLR	1.79 (0.80–3.95)	1.71 (0.89–2.93)	0.877
PLR	113.53 (29.41–22.31)	116.67 (62.96–197.78)	0.472
LMR	4.25 (2.00–11.00)	4.25 (2.80–5.50)	0.658
SII	418.38 (82.35–868.25)	483.84 (151.11–972.57)	0.588
Preoperative laboratory parameter			
Calcium	11.10 (10.60–14.80)	10.80 (10.60–12.50)	0.213
Vitamin D 25-OH	20.10 (5.10–46.50)	22.40 (2.00–43.30)	0.791
TSH	1.00 (0.02–7.77)	2.24 (0.08–4.25)	0.293
PTH	178.80 (3.70–860)	118.00 (2.24–301.50)	0.073
Phosphate	2.60 (1.00–3.80)	2.90 (1.30–4.00)	0.180

NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; SII, systemic immune-inflammation index (neutrophil × PLR); TSH, thyroid-stimulating hormone; PTH, parathyroid hormone.
[a]Mann-Whitney U-test. Statistical significance at $P < 0.05$.

values ($P > 0.05$) (Table 2). In the isolated parathyroidectomy group, 158 patients (85.4%) were female, and 27 (14.6%) were male. The median age of the patients was 52 years (range, 18–78 years). Histopathological examination revealed 171 adenoma (92.4%) and 13 hyperplasia cases (7.0%), in addition to 1 parathyroid carcinoma case (0.5%) (Table 3). The evaluation of complications in the present cohort revealed symptomatic transient hypocalcemia requiring an additional intravenous dose despite early postoperative calcium replacement in 41 (22.2%) and 9 patients (18.0%) in the isolated parathyroidectomy and concurrent surgery groups, respectively. In the isolated parathyroidectomy patients, no hematoma or recurrent laryngeal nerve (RLN) injury was detected, and the mean hospital stay duration of the patients was found to be 3.05 ± 0.93 days. In the concurrent surgery group, recurrent nerve neuropraxia was observed in 1 patient (2.0%) who returned to normal after 6 months of follow-up, and hematoma or infection was not detected with a mean hospital stay duration of 4.28 ± 0.86 days (Table 1).

Table 3. Histopathological Data

Concurrent surgery group (n = 50)	No. (%)
ATA nodule sonographic pattern risk of malignancy	
High suspicion	17 (34.0)
Intermediate suspicion	16 (32.0)
Low suspicion	5 (10.0)
Very low suspicion	6 (12.0)
Benign	6 (12.0)
Thyroid FNA biopsy	
Bethesda I	6 (12.0)
Bethesda II	16 (32.0)
Bethesda III	20 (40.0)
Bethesda IV	4 (8.0)
Bethesda V	4 (8.0)
Type of surgery	
Parathyroidectomy + lobo-isthmectomy	22 (44.0)
Parathyroidectomy + total thyroidectomy	28 (56.0)
Thyroid pathology accompanying PHPT	
Papillary microcarcinoma	8 (16.0)
Papillary carcinoma	4 (8.0)
Hurthle cell follicular neoplasia	1 (2.0)
Lymphocytic thyroiditis	7 (14.0)
Nodular hyperplasia and cystic changes	30 (60.0)

ATA, American Thyroid Association; FNA, fine-needle aspiration; PHPT, primary hyperparathyroidism.

DISCUSSION

In this study, the rate of thyroid malignancy accompanying PHPT in an endemic region of nodular thyroid disease was 26.0%. The incidence of thyroid cancer accompanying PHPT has been reported to range between 6% and 48.7% in Turkey [1,11-16] (Table 4), while the global rate is between 2.1% and 18.2% [17,18].

The establishment of a surgical algorithm for this relationship has become the primary goal of endocrine surgeons, not only for a cure but also for lower morbidity rates since higher complication rates have been reported in reoperations than in initial surgeries [19]. Therefore, it is crucial to investigate whether a thyroid nodule carries a risk of malignancy in PHPT before surgery. Concurrent surgery is cost-effective and routine preoperative PHPT assessment is rational. Ultrasonography and ^{99m}technetium-sestamibi scintigraphy are widely used in the preoperative localization of parathyroid adenomas, enabling the detection of thyroid pathologies (Fig. 1). Sidhu and Campbell [20] recommended sonographic evaluation of the thyroid gland and FNA of identifiable thyroid nodules >1 cm in all patients scheduled for minimally invasive parathyroidectomy. Accordingly, Castellano et al. [21] reported that nodular thyroid disease and the localization of the nodule on the same side as the parathyroid adenoma before surgery influenced the decision

Table 4. Frequency of thyroid cancer in patients who underwent parathyroidectomy in Turkey

Study	Year	No. of patients with thyroid pathologies concomitant with PHPT	Thyroid cancer concomitant with PHPT (n)	No. (%)
Kosem et al. [15]	2004	51	Papillary microcarcinoma (2) Papillary carcinoma (6) Multicentric papillary carcinoma + bilateral medullary microcarcinoma (1)	9 (17.6)
Kutluturk et al. [1]	2014	35	Papillary microcarcinoma (5)	5 (14.2)
Emirikçi et al. [11]	2015	83	Papillary microcarcinoma (4) Papillary carcinoma (1)	5 (6)
Yazici et al. [13]	2015	86	Papillary microcarcinoma (4) Papillary carcinoma (2)	6 (6.9)
Cuhaci et al. [16]	2017	106	Papillary carcinoma (2) Papillary microcarcinoma (20)	22 (20.8)
Celik et al. [12]	2017	41	Papillary carcinoma (papillary microcarcinoma?) (20)	20 (48.7)
Ozden et al. [14]	2019	50	Papillary microcarcinoma (11) Papillary carcinoma (2)	13 (26)

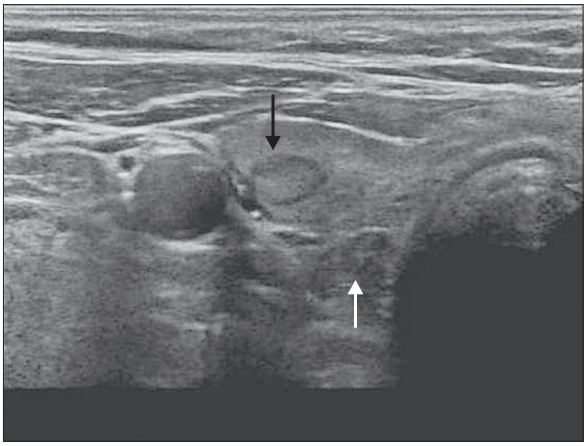

Fig. 1. Preoperative neck ultrasound. Black arrow, thyroid adenoma; white arrow, parathyroid adenoma.

to perform simultaneous thyroidectomy [21]. In the presence of parathyroid adenoma with a thyroid nodule, accurate adenoma localization is invaluable for surgical success because the sensitivity and specificity of preoperative adenoma localization are limited in concomitant thyroid diseases [22].

This study employed ultrasound (preoperative and intraoperative) and sestamibi scans to localize parathyroid adenomas. The comparison of surgical pathology revealed that the accuracy of localizing parathyroid adenomas was 90.0% and 88.0% for ultrasound and sestamibi scans, respectively, without statistical significance ($P > 0.05$). Moreover, for discordant cases, intraoperative sonography performed by the surgeon after thyroid gland removal was of paramount importance in that it confirmed localization in 4 out of 5 patients in the present series.

Another issue to be emphasized is the extensive use of ultrasound for neck pathologies leading to the incidental identification of thyroid nodules, questioning the value of concurrent surgery for both pathologies. To answer this question, Kiernan et al. [7] noted more frequent transient hypocalcemia, longer operation times, and prolonged hospital stays for patients who underwent simultaneous surgery than for those who underwent parathyroidectomy alone. According to Pradhan et al. [23], patients who underwent both parathyroid and thyroid surgeries were 8 times more likely to have short-term complications than those who underwent parathyroid surgery only [23]. Likewise, Castellano et al. [21] reported similar cure and complication rates for simultaneous surgery, while on the other hand, the duration of surgery and hospital stay was found to be prolonged [21].

Various other studies have shown a significant increase in the rates of RLN injury and hypocalcemia in cases of reoperation and concluded that simultaneous operations should be performed if a patient for whom parathyroidectomy is planned has a thyroid pathology requiring surgery [24]. In the presented series, surgical indications were determined based on ATA sonographic classification and FNA results, and a shared decision for surveillance versus surgery was made in collaboration with patients for appropriate cases. The low complication rates could be attributed to the fact that all operations were performed by highly experienced endocrine surgeons who were highly active in terms of performing operations in an experienced center using routine neuromonitoring. Nevertheless, the hospitalization period was longer in the concurrent surgery group, emphasizing the importance of preoperative patient information.

Another important issue that is underscored by supporters of concurrent surgery is the argument that thyroid malignancy is associated with PHPT. Various studies have evaluated different factors with the potential to predict malignancy in specific patient populations. Inflammatory indices have long been the subject of interest for the prediction of aggressiveness, malignancy, and metastasis in various types of cancer [25-27]. Seretis et al. [28] found significantly higher NLRs in patients with both incidental papillary thyroid microcarcinoma (PTMC) and thyroid cancer and stated that this might be a possible marker of thyroid cancer. Similarly, Kocer et al. [29] reported that the NLR could be a potential marker for differentiating benign and malignant thyroid disorders. Moreover, prognostic significance of inflammatory markers in intermediate and high-risk papillary, medullary, and anaplastic thyroid carcinoma has been reported [30-32]. The preoperative inflammatory markers have been proposed to be used as predictors of parathyroid cancer in patients with PHPT [33]. However, there is no data regarding systemic inflammatory markers in patients with both PHPT and thyroid malignancy.

No statistically significant difference was found in the preoperative peripheral blood NLR, PLR, LMR, and SII values in PHPT patients with PTMC or benign thyroid pathology in this study ($P > 0.05$). Kutluturk et al. [1] reported higher serum phosphate levels in PHPT patients with PTMC. In contrast, no statistically significant difference was observed in the preoperative serum phosphate levels between patients with PTMC ($P > 0.05$).

Thyroid malignancy accompanying PHPT was found in 26.0% of patients (13 of 50) in the concurrent surgery group; 16.0% of whom (8 patients) had PTMC. Surgeons perform preoperative and intraoperative neck ultrasounds, and FNA biopsies are routinely performed in all patients who would undergo concurrent surgery at our clinic, regardless of nodule size. The higher rate of thyroid malignancy in patients with PHPT than in the normal population in our endemic region might be attributed to the extensive utilization of sonographic evaluation allowing the detection of small nodules with malignant potential which turned out to be PTMC, suggesting

that active surveillance might be appropriate. Nevertheless, patients' preferences were surgical intervention in each case. In geographical regions where molecular tests are not available and multinodular goiter is endemic, such as Turkey, this approach may provide a higher detection rate of nodules with sonographic features of malignant potential. Concurrent operation of malignant or potentially malignant nodules with parathyroidectomy has the potential to prevent secondary surgeries and treat thyroid malignancies at the point of microcarcinoma with a low rate of complications. Nonetheless, it is imperative to emphasize that morbidity is a function of the surgeon's experience, and the decision should be made after discussion with the patient.

This study had various limitations, including a small sample size, single-center experience, and the fact that the number of inflammatory cells in the peripheral blood can be affected by many independent factors such as the patient's physical condition, diet, and lifestyle. Therefore, making an accurate comment was not possible. Multicentric trials including more comprehensive analysis with a larger sample size are required to support the value of inflammatory markers to be accepted as predictors of thyroid malignancy in patients with PHPT in real-world practice.

In regions endemic to nodular thyroid disease, detailed neck ultrasonography is invaluable for patients with PHPT in the design of surgical algorithms. The use of sestamibi scans with preoperative ultrasound accurately predicted the localization of adenomas in most cases. However, intraoperative sonography merits consideration in discordant cases. Concurrent thyroidectomy can be performed with low complication rates in experienced endocrine centers to protect patients from the burden of morbidity associated with secondary interventions. However, patients should be informed about the longer hospital stay. Additionally, the value of inflammatory indices in the prediction of thyroid malignancy in PHPT is controversial, and these indices should not be employed in the surgical decision-making process in regions endemic to nodular goiter. In the era of precision medicine, the priority is to evaluate each entity independently to create an individualized treatment plan.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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