Original Research

Primary Hyperparathyroidism with Thyroid Cancer: Clinicopathologic Features

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Abstract

Objectives: Concomitant thyroid disease affects almost half of the primary hyperparathyroidism (PHPT) patients. Pre-operative evaluation of the thyroid gland for the early diagnosis of thyroid carcinoma is essential in PHPT patients. Herein, we aim to investigate the clinicopathologic features that affect the type and extent of surgery in patients having PHPT and concomitant thyroid disease but especially thyroid cancer.

Methods: The files of consecutive patients who underwent parathyroidectomy for PHPT during a 6-year period were retrospectively reviewed. The cases who underwent parathyroidectomy and simultaneous thyroidectomy were enrolled in the study. A total of 84 patients who met the study criteria were divided into two groups as benign thyroid disease (Group 1) and malignant thyroid disease (Group 2) according to the final histopathological examination. The demographic and clinicopathological characteristics were compared between groups.

Results: Concomitant thyroid disease was found in 158 (55.6%) of 284 patients who were operated on for PHPT. Simultaneous total thyroidectomy or lobectomy was performed for 84 (29.6%) patients and thyroid carcinoma was detected in 29 (10.2%) patients. Total thyroidectomy and complication rates were higher in Group 2 (p<0.05). Pre-operative fine-needle aspiration biopsy was obtained in 58.3% of patients and it identified only 26.3% of histopathologically confirmed thyroid carcinoma. Only pre-operative serum phosphorus level was found higher in Group 1 (p<0.05), but none of the study parameters was found as an independent risk factor for thyroid malignancy (p>0.05) in multivariate analysis.

Conclusion: There is no accepted parameter yet to predict the accompanying thyroid carcinoma in PHPT patients. However, a benign biopsy cannot exclude thyroid malignancy in PHPT patients and may cause undiagnosed thyroid carcinoma due to papillary microcarcinoma.

Keywords: Carcinoma; parathyroidectomy; primary hyperparathyroidism; thyroid; thyroidectomy

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Primary hyperparathyroidism (PHPT) is a common endocrine disease that affects 0.1% of the general population.[1] Nodular thyroid disease is very common, especially in endemic regions and prevalence increases with the widespread use of ultrasound (US). The occult nodular disease is estimated to be present in up to 70% of the general population.[2,3] Benign or malignant nodular thyroid disease may accompany PHPT in approximately 20–60% of the patients.[2] The prevalence of thyroid carcinoma was reported to be 2–15% in PHPT patients and this rate seems higher compared to the general population.[4-6] Detection of concomitant thyroid carcinoma preoperatively in PHPT

patients may contribute to decide the extent of surgical intervention and minimize the complications of reoperation and healthcare costs.[3]

Most patients with PHPT undergo a pre-operative neck US to detect the localization of adenoma. The thyroid gland should also be evaluated to detect accompanying benign/malignant thyroid nodules and fine-needle aspiration biopsy (FNAB) should be performed if indicated.[3] Although thyroid FNAB is the most valuable diagnostic method to detect thyroid malignancy, false-negative FNAB results were reported up to a ratio of 40% in PHPT patients.[7]

The objective of this study is to investigate the clinicopathologic features those effect the type or extension of surgery in patients having PHPT and concomittan thyroid disease but especially thyroid cancer.

Methods

The files of the consecutive patients who underwent parathyroidectomy for PHPT in Group B of General Surgery Clinic at Izmir Kâtip Celebi University Ataturk Training and Research Hospital between January 2014 and December 2019 were retrospectively reviewed. The cases who underwent parathyroidectomy and simultaneous thyroidectomy were enrolled on the study. Cases with secondary or tertiary hyperparathyroidism, cases with intrathyroidal parathyroid adenoma or parathyroid carcinoma, cases with multiple endocrine neoplasia syndrome, and cases with a history of previous neck surgery and cases with incomplete data were excluded from the study. The patients had a history of exposure to neck radiation, which were also excluded from the study. The patients who met the study criteria were divided into two groups as benign thyroid disease (Group 1) and malignant thyroid disease (Group 2) according to the final histopathological examination. The demographic characteristics, clinicopathological data, type of surgery, and surgical complications were investigated and compared between groups.

All PHPT patients underwent neck US preoperatively to evaluatethe thyroid gland. Thyroidectomy indications were nodular goiter disease, hyperthyroidism, and thyroid hyperplasia with compression symptoms. FNAB was administered for patients with nodules larger than 1 cm or those with nodules smaller than 1 cm but with sonographic nodule characteristics suggesting thyroid carcinoma or those with risk factors. Some of the patients with large-sized (>4 cm) nodules (low diagnostic accuracy of FNAB) or patients with multiple nodules (non-applicable FNAB for all nodules technically) or patients with hyperthyroidism or those with a thyroid gland with retrosternal/mediastinal extension underwent simultaneous thyroidectomy without pre-operative FNAB. Patients with Hashimoto thyroiditis, patients with nodules smaller than 5 mm, and patients with nodules with low risk of malignancy on US (with/without benign FNAB results) underwent only parathyroidectomy. Cervical lymph node dissection was performed for patients if radiologically or clinically suspicious nodal involvement.

Ethics committee approval for this study was obtained from the Izmir Kâtip Celebi University Ethics Committee (decision number 246, date April 29, 2021). Written informed consents were obtained from the patients/patient relatives who participated in this study. This study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki.

Statistical Analysis

The Statistical Package for the Social Sciences version 22.0 (IBM Corp.; Armonk, NY, USA) was used for statistical analyzes. Mean ± standard deviation and percentage and frequency were calculated for variables. The homogeneity of variances was confirmed by the Levene test. For the comparison of two groups, Student's t-test or Mann–Whitney-U-test was used. The correlation between categorical variables was analyzed by Fisher's exact test and Chi-Square test. P<0.05 was considered statistically significant.

Results

Concomitant thyroid disease was found in 55.6% of (158/284) patients who met the criteria and were operated on for PHPT. Simultaneous lobectomy/total thyroidectomy was performed for 84 (29.6%) patients for various reasons (Table 1). The main indication was nodular goiter disease (69%).

Final thyroid pathology was benign in 55 patients and malignant in 29 patients and those patients were subjected for further analysis (Fig. 1).

The mean age was 57.8±11.9 (24–83). Seventy-five patients (89.3%) were female and 9 (10.7%) were male. The mean duration of hospital stay was calculated as 1.2±0.7 days (1–6). Histopathological examination revealed benign thyroid

Table 1. Thyroidectomy indications in the study group

Indication	n (%)
Nodular goiter	58 (69)
Hyperthyroidism	8 (9.5)
Toxic adenoma	2 (2.4)
Retrosternal goiter	3 (3.6)
Thyroid cancer	5 (5.9)
Indeterminate cytology	8 (9.5)
Total	84 (100)
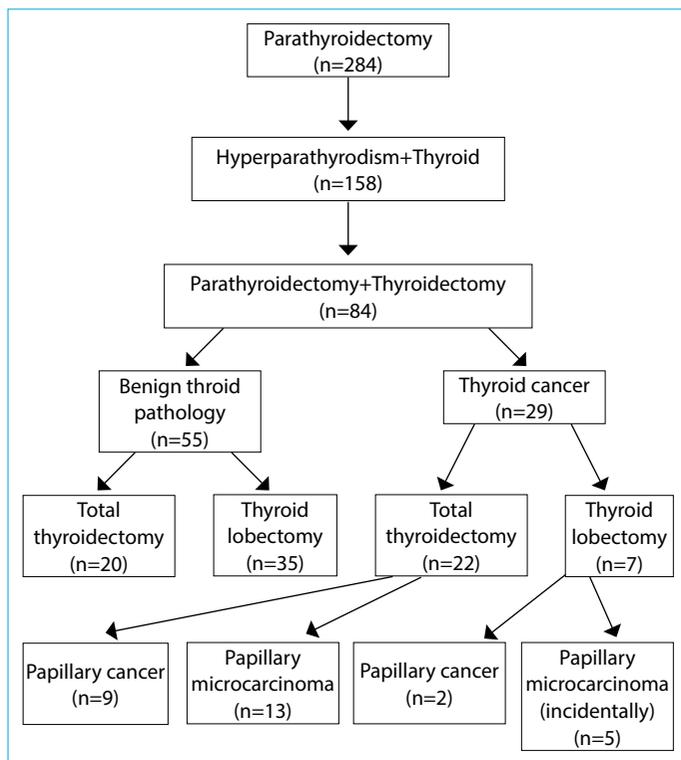
Figure 1. Diagram of surgical and histopathological features of the groups.

disease in 55 (65.5%) patients (Group 1) and malign thyroid disease in 29 (34.5%) patients (Group 2) including papillary carcinoma in 11 (13.1%) and papillary microcarcinoma in 18 (21.4%). Other types of thyroid carcinoma were not detected in any of the patients. Total thyroidectomy was performed for 20 (36.4%) of 55 patients in Group 1 and 22 (75.9%) of 29 patients in Group 2. Two patients who underwent lobectomy were diagnosed with papillary carcinoma in final pathology. These patients did not need completion thyroidectomy due to tumor diameter below 2 cm and favorable microscopic features. Recurrent laryngeal nerve palsy did not occur in the study group. Persistent disease occurred in a patient who was later diagnosed with double adenoma. That patient underwent redo surgery and this operation was successful. Permanent hypocalcemia occurred only in a patient who underwent total thyroidectomy and therapeutic central compartment lymph node dissection in Group 2.

Age, gender, pre-operative calcium and parathormone level, presentation of PHPT, and localization of pathological parathyroid gland were similar between groups (all p>0.05). Pre-operative serum phosphorus value was found to be significantly higher in Group 1 (p=0.041). Total thyroidectomy rate and complication rate were higher in Group 2 (p=0.001 and p=0.015, respectively). The permanent complication rate was found to be comparable be-

tween groups (p=0.345) (Table 2). In multivariate analysis, none of the study parameters was found as an independent risk factor for thyroid malignancy (p>0.05).

Pre-operative thyroid FNAB was administered to 49/84 (58.3%) patients in the whole group, for 30 (54.5%) and 19 (65.5%) patients in Group 1 and 2, respectively (Fig. 2). FNAB results were benign in 25 (83.3%) patients and indeterminate (cells of undetermined significance and follicular neoplasm) in 5 (16.7%) patients in Group 1 (n=30). The diagnosis of thyroid carcinoma or suspicion of carcinoma by FNAB could be established in only seven (36.8%) out of 19 patients. The reasons were false-negative results in seven patients and incidental microcarcinoma foci in five patients with other nodules not subjected to FNAB.

Discussion

The results of this study showed the absence of any independent risk factor to predict thyroid carcinoma preoperatively. Moreover, surgeons should be very carefull in the pre-operative evaluation of the patients with PHPT and concomittant thyroid nodular disease since a thyroid FNAB may miss the diagnosis of cancer in more then half of the cases with multiple nodular disease.

The coincidence of PHPT and medullary thyroid carcinoma is a well-known entity. However, the incidence of non-medullary thyroid carcinoma in PHPT patients has been reported to be 2–15%,[4-6] of which relatively higher rates were obtained in endemic areas.[8,9] The thyroid malignancy rate was found 10.2% in our study, which is consistent with the current literature.

PHPT is reported not to be associated with thyroid carcinoma according to the current guidelines of the American Thyroid Association.[10] On the other hand, PHPT has been
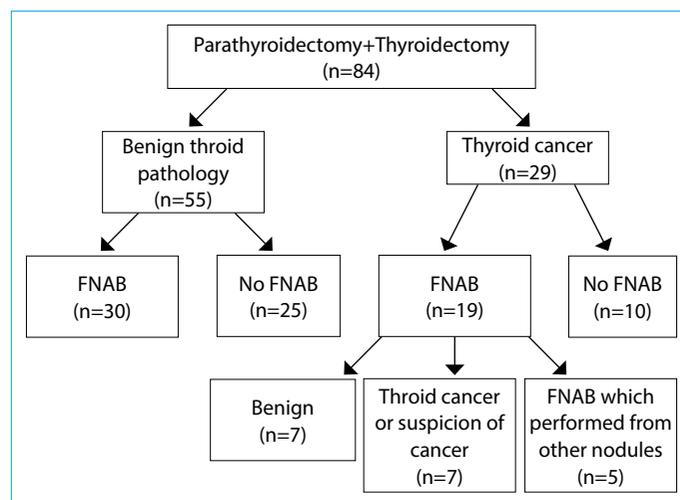
Figure 2. Diagram of the results of fine-needle aspiration biopsy in the study group.

Table 2. Comparison of demographic and clinical characteristics of the groups

	Group 1 (n=55)	Group 2 (n=29) n (%)	All patients (n=84)	p
Gender				0.712
Female	50 (90.9%)	25 (86.2%)	75 (89.3%)	
Male	5 (9.1%)	4 (13.8%)	9 (10.7%)	
Age	58.71±11.16	56.1±13.29	57.81±11.92	0.344
Duration of hospital stay (days)	1.25±0.67	1.28±0.99	1.26±0.79	0.908
Pre-operative parathormone	270.76±226.71	448.07±647.84	331.98±426.86	0.261
Pre-operative calcium	11.4±1.25	11.72±1.59	11.51±1.38	0.315
Pre-operative phosphorus	2.75±0.52	2.51±0.44	2.67±0.51	0.041
Presentation of primary hyperparathyroidism				0.48
Symptomatic	11 (20%)	4 (13.8%)	15 (17.9%)	
Asymptomatic	44 (80%)	25 (86.2%)	69 (82.1%)	
Pathological parathyroid gland side				0.340
Right	29 (52.7%)	11 (37.9%)	40 (47.6%)	
Left	23 (41.8%)	17 (58.6%)	40 (47.6%)	
Bilateral	3 (5.5%)	1 (3.4%)	4 (4.8%)	
Pathological parathyroid gland location				0.704
Upper	21 (38.2%)	13 (44.8%)	34 (40.5%)	
Lower	30 (54.5%)	15 (51.7%)	45 (53.6%)	
Combined	4 (7.3%)	1 (3.4%)	5 (5.9%)	
Operation				0.001
Parathyroidectomy + Lobectomy	35 (63.6%)	7 (24.1%)	42 (50%)	
Parathyroidectomy + Total thyroidectomy	20 (36.4%)	22 (75.9%)	42 (50%)	
Parathyroid pathology				0.863
Single adenoma	51 (92.7%)	27 (93.1%)	78 (92.9%)	
Double adenoma	1 (1.8%)	1 (3.4%)	2 (2.4%)	
Triple adenoma	1 (1.8%)	0	1 (1.2%)	
Hyperplasia	2 (3.7%)	1 (3.4%)	3 (3.5%)	
Complication				0.015
No	50 (90.9%)	20 (69%)	70 (83.3%)	
Yes	5 (9.1%)	9 (31%)	14 (16.7%)	
Transient hypocalcemia	4 (7.3%)	8 (27.6%)	12 (14.2%)	
Permanent hypocalcemia	0	1 (3.4%)	1 (1.2%)	
Persistence	1 (1.8%)	0	1 (1.2%)	
Permanent complication				0.345
Yes	0	1 (3.4%)	1 (1.2%)	
No	55 (100%)	28 (96.6%)	83 (98.8%)	

thought to be related to various types of carcinomas and thyroid carcinoma was found to be the most common type. Some recent studies reported PHPT as a risk factor for thyroid carcinoma.[5,11,12] Some hypotheses have been proposed to explain the high incidence of thyroid carcinoma in PHPT. Neck irradiation during childhood was reported as a risk in the early studies. In addition, high PTH levels, lower levels of vitamin D, and hypercalcemia have been considered to favor thyroid carcinogenesis by inhibiting several immune functions and increasing the release of growth factors.[5,13-15]

Several studies have investigated the risk factors for non-medullary thyroid carcinoma in patients with PHPT.[12,15] High pre-operative parathormone value in patients with symptomatic PHPT was found to be associated with an increased risk of thyroid malignancy.[15] Lower concentrations of albumin-corrected serum calcium and higher levels of serum phosphorus in the patients with PHPT and thyroid malignancy compared to those with PHPT and benign thyroid nodules were reported in another study.[12] The relation of increased risk of thyroid carcinoma with lower serum calcium levels asserted by Xue et al.[12] seems con-

flicted considering the widely accepted hypothesis that hypercalcemia favours thyroid carcinogenesis. The relatively higher serum calcium levels (non-significant) and significantly lower levels of phosphorus were found in PHPT patients with concomitant thyroid carcinoma in our study. However, none of the study parameters was found as an independent risk factor for thyroid malignancy in multivariate analysis, (p>0.05).

Pre-operative evaluation of concomitant thyroid disease is required for PHPT patients to decide the optimal treatment method. The US is the preferred radiological examination for the evaluation of the thyroid gland. FNAB may be required in some cases to detect thyroid malignancy.[3] On the other hand, thyroid FNAB may result in an indeterminate pathology including atypia of undetermined significance/follicular lesion of undetermined significance in 2–18% of nodules, follicular neoplasm/suspicious for follicular neoplasm in 2–25%, and suspicious for malignancy in 1–6%. These indeterminate cytology results are associated with a 5–75% risk of malignancy.[10] We found thyroid carcinoma in 28.6% of patients with indeterminate cytology. In addition, high rates of false-negative results have been reported in the previous studies.[7,11] Similarly, pre-operative evaluation with an FNAB missed 73.7% of cancer cases in patients with thyroid malignancy in the presented study. The reasons for the fact were false nodule biopsy or sampling error in multinodular setting, false-negative pathologic evaluation, malignancy in non-suspicious nodule, and microcarcinoma foci that can not be seen in the US or biopsied.

Many studies related to thyroid nodules in PHPT patients have been reported to date, but the optimal treatment method is still under debate.[5,16] Relevant studies have shown that most PHPT patients with thyroid nodules underwent simultaneous lobectomy or total thyroidectomy.[8,17] Some reliable explanations have been established for this decision. First, concomitant hyperthyroidism or thyroid disease with compression symptoms might be required thyroidectomy. Second, simultaneous thyroidectomy might be preferred to avoid missing cancer in nodular disease, especially in endemic goiter areas and to prevent higher healthcare costs and complication risks of redosurgery.[17] Patients preference or refusal to follow-up of thyroid nodules in multinodular setting may play a role for concomittant thyroidectomy with parathyroidectomy. Cinamon et al.[11] suggested performing an intraoperative frozen section examination for thyroid nodules that have a benign pre-operative FNAB result to decide the extent of surgery and the necessity of lymph node dissection, but its contemporary practical value for nodule evaluation can be arguable.

This study has some limitations including being conducted in a single endocrine surgery clinic, retrospective design, and relatively small sample size.

Conclusion

The results of this study showed the absence of any independent risk factor to predict thyroid carcinoma preoperatively. In addition, pre-operative evaluation with US and FNAB may miss a significant proportion of cancer cases in patients with PHPT. The surgeon should be very carefull during the evaluation of patients with PHPT and nodular thyroid disease to determine the optimal extent of surgery.

Disclosures

Ethics Committee Approval: Ethics committee approval for this study was obtained from the Izmir Kâtip Celebi University Ethics Committee (decision number 246, date April 29, 2021). Written informed consents were obtained from the patients/patient relatives who participated in this study. This study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki.

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