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ORIGINAL SCIENTIFIC REPORT

Does Primary Hyperparathyroidism Have an Association with Thyroid Papillary Cancer? A Retrospective Cohort Study

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Abstract

Background To investigate the relationship between primary hyperparathyroidism (pHPT) and papillary thyroid cancer (PTC).

Methods The perioperative findings of 275 patients with pHPT who underwent surgery between January 2014 and December 2017 were retrospectively reviewed. Thirty-one patients were diagnosed with pHPT and PTC concurrently. Pathology results and demographic findings of these patients were compared with 186 patients who underwent thyroidectomy and diagnosed with PTC at the same time interval.

Results The co-occurrence of pHPT and PTC was 11.3% (31/275). The median ages of the pHPT, pHPT + PTC, and PTC groups were 55, 57, and 50 years old, respectively ($p < 0.001$). The diameter of tumor was smaller in the pHPT + PTC group [median 7 mm (range 0.5–25 mm) vs. 15 mm (range 1–100 mm)], with higher rates of microcarcinomas ($p < 0.001$), than the patients in the PTC group. Examination of tumor morphology showed higher rates of tumor capsule invasion and multicentricity in the pHPT + PTC group than those in the isolated PTC group ($p = 0.02$, $p = 0.04$, respectively).

Conclusion The pHPT + PTC group had significantly smaller tumor diameter than the PTC group. This result may support the idea that pHPT leads to overdiagnosis of PTC. However, observation of high rates of tumor capsule invasion and multicentricity in the pHPT + PTC group may suggest an associative etiology with more aggressive PTC.

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Introduction

Primary hyperparathyroidism (pHPT) is a common endocrine disorder that affects 0.1–0.4% of the general population [1]. A solitary parathyroid adenoma is responsible for most of the cases, and surgical excision is the choice of treatment in case of primary hyperparathyroidism [2]. Patients undergoing parathyroidectomy should have preoperative thyroid evaluation because of the high rate of concomitant disease [3]. As a natural consequence, preoperative imaging studies for diagnosis and localization of parathyroid adenomas may result with the detection of thyroid incidentalomas and most of these thyroid nodules should be evaluated by fine-needle aspiration biopsy (FNAB) before parathyroid surgery [4].

Papillary thyroid cancer (PTC) is the most common thyroid cancer with a rate of 85–90%, and the incidence has increased worldwide in the last few decades [5, 6]. Small papillary cancers comprised most of these cases which could be related to the overdiagnosis of PTC [7, 8]. However, it has been reported that the incidence of advanced-stage PTC is also rising which could not be explained solely by the result of overdiagnosis, in recent studies [4, 9]. Also, thyroid cancer mortality in the USA increased significantly between 1992 and 2012, with an average annual percent change of 0.8% per year [10]. Therefore, associations should be evaluated to determine whether they cause overdiagnosis of PTC or they have a role in the occurrence of PTC.

For the first time, in 1956, Ogburn et al. reported a small series consisting of four cases with the co-occurrence of pHPT and PTC [11]. Since then, this co-occurrence has been reported as case series with a range of 2–13% in the literature [12–17]. However, the mechanism of this relationship remains undefined. Several published studies emphasize the association between pHPT and PTC as coincidental, whereas others claim the goitrogenic and carcinogenic effects of hyperparathyroidism on thyroid glands; nevertheless, no evidence is available for the related pathogenesis.

In this study, we aimed to evaluate whether pHPT is a possible risk factor for PTC or increased number of imaging methods for localization of parathyroid adenomas has an association with overdiagnosis of PTC.

Method

Subjects

The preoperative imaging and biopsy findings of 275 patients with pHPT, admitted to Kartal Dr. Lutfi Kirdar Training and Research Hospital, a tertiary referral center for thyroid and parathyroid diseases, between January 2014 and December 2017 were retrospectively reviewed. Patients with secondary and tertiary hyperparathyroidism, multiple endocrine neoplasia, or thyroid cancer except papillary type were excluded. Study protocol was approved by institutional review board (reg. 2018/s14/138/5), and an informed consent was not obtained due to the retrospective design of the study. Thirty-one of the patients were diagnosed pHPT and PTC concurrently (pHPT + PTC group). The clinical findings of 186 patients who underwent thyroidectomy and diagnosed with PTC in our clinic (PTC group) between the same time intervals were compared. Characteristics of the patients and pathological findings of tumor morphology (tumor diameter, tumor subtype, total number of foci, presence of multicentricity, presence of calcification in the tumor; vascular, perineural, and tumor capsule invasion; and extrathyroidal spread) were evaluated.

Surgical approach to primary hyperparathyroidism and thyroid nodules in our clinic

The surgical treatment of pHPT in our clinic is as follows: All patients were evaluated with US. Tc99 m sestamibi parathyroid scintigraphy ± single-photon emission computed tomography (CT) are frequently used for preoperative localization of parathyroid adenomas. Parathormone (PTH) washout is performed in case of suspicious or incoherent results. CT or magnetic resonance imaging (MRI) scan of neck is performed when the parathyroid adenoma could not be localized preoperatively or due the presence of suspicion for the disease of multiple glands. The adenomas are preoperatively localized and subsequently excised under general or local anesthesia with <3-cm lateral incisions. Intra-operative frozen sections are often used as quick PTH is not available in our hospital.

The evaluation of thyroid nodules by FNAB is applied according to American Thyroid Association (ATA) 2009 and 2015 guideline recommendations. FNAB is applied to thyroid nodules <1 cm in the case of a high malignancy risk in the US findings, to all hypoechoic solid >1 cm, and isoechoic solid >1.5 cm or partial cystic nodules. Lobectomy/total thyroidectomy is recommended if the cytological results are recurrent atypia of undetermined significance (AUS), follicular lesion of undetermined significance (FLUS), follicular neoplasm, malignancy suspicion, or malign. Surgery is also recommended to patients with benign nodules with a diameter ≥4 cm [4].

Statistical analyses

Statistical analysis was carried out using IBM SPSS v22.0 (IBM Co., Armonk, NY, USA). The data are expressed as mean ± standard deviation (SD) for continuous variables or median (min–max) for non-normally distributed variables. The normality of data distribution was assessed by the Kolmogorov–Smirnov test. Statistical significance was evaluated using the Mann–Whitney *U* test due to our non-normally distributed variables and Chi-square test for the categorical variables. Kruskal–Wallis test was used to compare non-normally distributed data in three or more independent groups. A 5% type 1 error level indicated statistical significance.

Results

A total of 275 patients with pHPT underwent parathyroidectomy between January 2014 and December 2017. Concurrent thyroid nodules were detected in 116 (42%) of the patients during preoperative examination with US. Thirty-three patients with thyroid nodules underwent thyroidectomy due to FNAB cytological results [recurrent AUS or FLUS (n = 11), suspicious for a follicular neoplasm (n = 9), suspicious for malignancy (n = 10), and malignant (n = 3)]. In addition, 16 patients underwent thyroidectomy due to large thyroid nodules (>4 cm). Pathological examination showed PTC in 25 of these patients. PTC was also detected in five out of 23 patients who underwent frozen section evaluation due to the suspicious appearance of thyroid nodules during parathyroidectomy, and thyroidectomy was also performed at the same session. Lymph node (LN) excision was performed in ten patients during parathyroidectomy due to the suspicious appearance of LNs. Pathological examination has revealed PTC metastasis in one patient, and total thyroidectomy with central LN dissection was performed in a separate session. Eventually, 31 (11.3%) of the 275 patients who underwent surgery for pHPT were concurrently diagnosed as PTC (Fig. 1). Sixty (32.3%) of the patients in PTC group were incidentally diagnosed following thyroidectomy, whereas 126 (67.7%) of the patients underwent surgery for malignancy or suspected malignancy. The indications for thyroidectomy in PTC group are depicted in Table 1.

The median age of patients with pHPT + PTC (n = 31) was 57 years (min: 26–max: 74), those in with pHPT

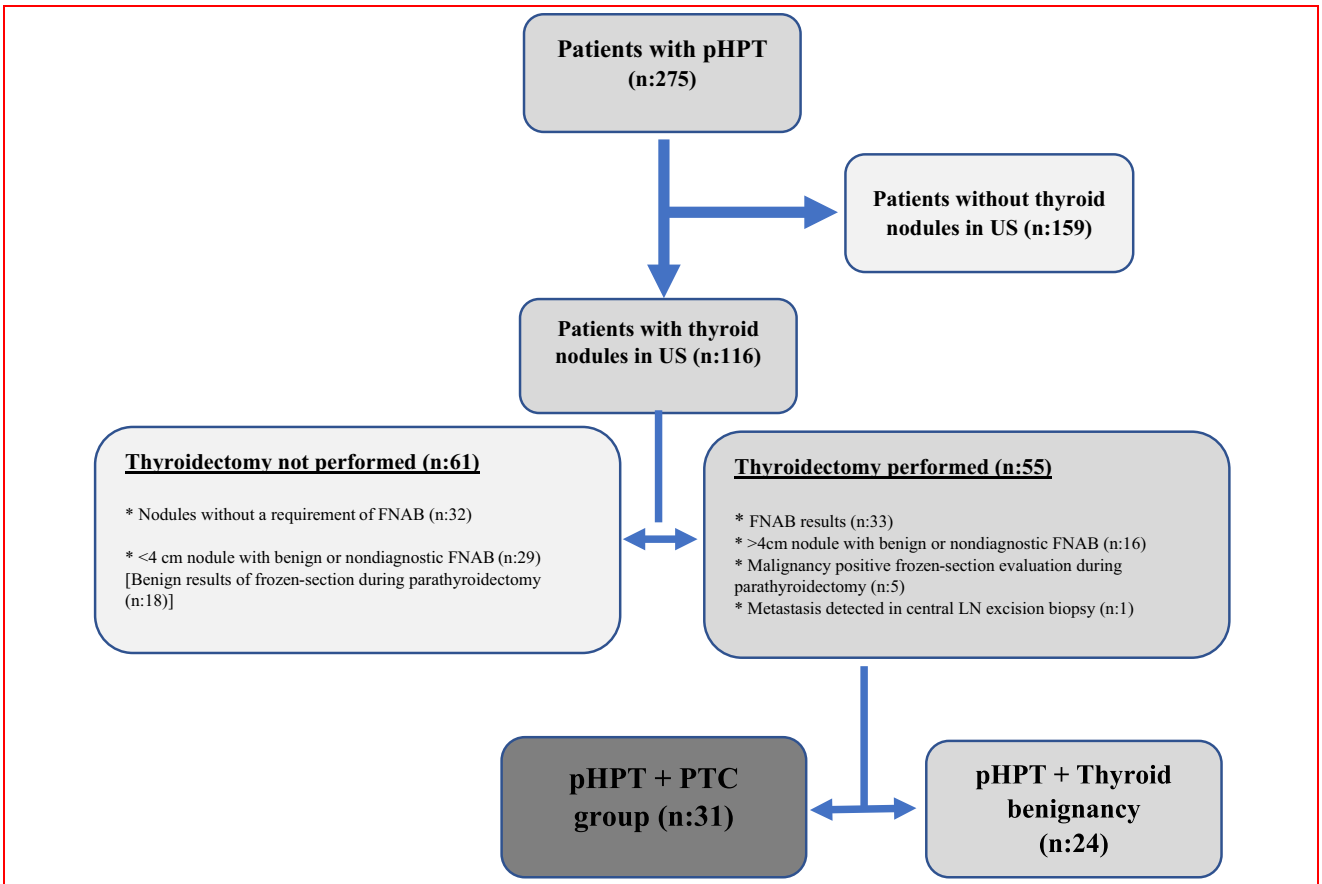

Fig. 1 Flow diagram of patients with PTC presenting with primary hyperparathyroidism

Table 1 Indications for thyroidectomy in PTC group

Indications for thyroidectomy	*n*	Percent
Patients who underwent surgery due to FNAB	126	67.7
Malignant	45	24.2
Suspicious for malignancy	40	21.5
Recurrent AUS	23	12.4
Suspicious for a follicular neoplasm	7	3.8
Suspicious for Hurthle cell neoplasm	9	4.8
Recurrent non-diagnostic	2	1.1
Patients diagnosed with incidental PTC	60	32.3
Nodules >4 cm with benign cytology	42	22.6
Toxic multinodular goiter	13	7.0
Graves disease	3	1.6
Toxic adenoma	2	1.1
Total	186	100

Table 2 Comparison of age and gender among groups

	pHPT (n = 244)	pHPT + PTC (n = 31)	PTC (n = 186)	p
Age[a]	55 (18–84)	57 (26–74)	50 (17–78)	<0.001
Female (%)	210 (86)	25 (81)	147 (79)	0.15

[a]Median (min–max)

Kruskal–Wallis and Chi-square tests were used

(n = 244) was 55 years (min: 18–max: 84), and in those with PTC (n = 186) was 50 years (min: 17–max: 78). Distribution of the age among these groups showed statistically significant difference ($p < 0.001$). Overall, 86%, 81%, and 79% of the patients in the pHPT, pHPT + PTC, and PTC groups were women, respectively, and there was no statistically significant difference between the groups for gender (p = 0.15) (Table 2).

Morphological comparison of the tumor in the PTC and pHPT + PTC groups is shown in Table 3. PTC group presented with larger tumors [median diameter 15 mm (min: 1–max: 100 mm)] than the the pHPT + PTC group [median diameter 7 mm (min: 0.5–max: 25 mm)] (p = 0.001). There was statistically significant difference between the pHPT + PTC and PTC groups when compared for the tumor presence with a diameter of less than 1 cm [64.5% (20/31) vs. 31.7% (59/186)] ($p < 0.001$). Tumor multicentricity and tumor capsule invasion frequency were higher in the pHPT + PTC group than in the PTC group (p = 0.04; p = 0.02, respectively).

Five of the patients in pHPT + PTC group underwent central LN dissection, and two patients had PTC metastases. Twenty-two patients in PTC group underwent central LN dissection, and in ten patients LN metastases were detected. Fourteen patients in PTC group underwent central + lateral neck dissection who had LN metastasis findings at the initial evaluation, and all of 14 patients had LN metastasis. LN metastasis rates were similar in pHPT + PTC and PTC groups (p = 0.95).

There was no patient with incidental parathyroid adenoma during the evaluation of primary PTC or LN metastasis.

Discussion

Co-occurrence of pHPT and PTC has been reported in the literature since 1956. Depending on the rising advanced-stage PTC and thyroid cancer mortality rate, factors affecting the thyroid papillary cancer should be evaluated for an association. The lack of large series concerning the association in the literature led us to evaluate the relationship between pHPT and PTC. pHPT and PTC are more common in women [1]. Considering the gender, observed rates were similar in pHPT, PTC, and pHPT + PTC groups in our study. Regarding the literature, pHPT incidence increases with age and PTC is frequently observed in younger population [18, 19]. Age of the patients in PTC group was lower than pHPT and pHPT + PTC groups in accordance with the literature. Although the patients in pHPT + PTC group were older than PTC group, they could have an earlier diagnosis of more aggressive PTC.

The presence of concomitant thyroid nodule, as a possible cause of preoperative localization difficulty in pHPT, has been reported at a high rate of 12–52% in the literature [17, 20, 21]. Examination with US for localization of parathyroid adenoma in the preoperative period has revealed thyroid nodules with a ratio of 42% in our study. The incidence of the presence of nodule has also been reported to reach 37–57% in the autopsy and thyroid US series [22]; therefore, we believe that the presence of concomitant thyroid nodule could not be associated with the pathophysiology of hyperparathyroidism.

pHPT has been associated with various cancer types in the past, and it has been emphasized as a risk factor for PTC in recent years [23–26]. The relationship is based on the fact that the same genes and transcription factors are involved in the development of both organs owing to their common embryological origins [26]. In addition, studies have suggested that high PTH levels, low level of vitamin D, and hypercalcemia contribute to thyroid carcinogenesis by promoting the release of growth factors such as fibroblast growth factor and vascular endothelial growth factor which may show mitogenic and differential effects on thyroid follicles and angiogenic effects on endothelial cells [26–28]. However, there is no evidence available in the literature for the related pathogenesis.

Conversely, according to the report of the International Agency for Research on Cancer, the unnecessary diagnosis is attributed to the increase in the frequency of thyroid

Table 3 Comparison of tumor morphologies of pHPT + PTC and PTC groups

Morphological findings of Tm	pHPT + PTC (n = 31)	PTC (n = 186)	p
Tm diameter[a] (mm)	7 (0.5–25)	15 (1–100)	0.001
Tm diameter <1 cm (%)	20 (64.5)	59 (31.7)	<0.001
Number of total foci[a]	1 (1–6)	1 (1–8)	0.16
Side (right–left–bilateral) (n)	13–6–12	70–58–58	0.38
Multicentricity (+/%)	14/45.2	51/27.4	0.04
Tm calcification (+/%)	15/48.4	90/48.4	0.99
Vascular invasion (+/%)	3/9.7	19/10.2	0.98
Perineural invasion (+/%)	0/0	9/4.8	0.24
Presence of Tm capsule (+/%)	18/58.1	109/58.6	0.96
Tm capsule invasion (+/%)	14/77.8	52/47.7	0.02
Intra-thyroidal spread (+/%)	6/19.4	26/14	0.45
Extrathyroidal spread (+/%)	5/16.1	21/11.3	0.43
LN metastasis (+/the number of the patients LN dissected)	2/5	24/36	0.95
Variants (n/%)			0.95
Undetermined	6/19.4	32/17.2	
Follicular	7/22.6	58/31.2	
Classical	10/32.3	59/31.7	
Follicular + classical	4/12.9	13/7	
Oncocytic	2/6.5	16/8.6	
Classical + oncocytic	1/3.2	4/2.2	
Follicular + oncocytic	1/3.2	4/2.2	

Mann–Whitney U test and Chi-square tests were used

Tm tumor, *LN* lymph node

[a]Median (min–max)

cancer observed in recent years [29]. Both increased medical monitoring opportunities and the widespread use of diagnostic tools, such as US and FNAB in conjunction with US, have led to the detection of small (<1 cm) and silent PTCs in healthy individuals. Thyroid US is the first imaging technique used in the preoperative localization of pHPT. While the detection of thyroid nodules during examination with US has forced radiologists and endocrinologists to perform FNAB, it draws the attention of surgeons to thyroid during parathyroid surgery. PTC cases were diagnosed during the preoperative localization of parathyroid adenoma by performing FNAB on suspicious nodules, performing frozen section for suspicious nodules during surgery or excisional biopsy on suspicious LNs in our study. On the other hand, there was no patient with a diagnosis of incidental parathyroid adenoma during primary PTC or LN evaluation for metastasis. In our study, examination of tumor morphology showed higher rates of tumor capsule invasion and multicentricity in the pHPT + PTC group, whereas PTC group had higher diameter of tumor ($p < 0.05$). Smaller diameter of tumor and higher rate of microcarcinoma (64.5% vs. 31.7%) in pHPT + PTC group could be suggestive for an overdiagnosis of PTC. However, high rates of tumor capsule invasion and multicentricity with an older age in pHPT + PTC group could be suggestive for an early detection of advanced-stage PTC. Based on the results of our study, further prospective studies should be designed for patients with pHPT with a long-term follow-up to evaluate advanced-stage PTC occurrence.

Retrospective design was the major limitation of our study. The patients were evaluated and operated by different clinicians. Also, the isolated PTC group is a heterogeneous group as it includes patients incidentally diagnosed with PTC and those diagnosed with LN metastasis. In addition, prophylactic central LN dissection is performed when the tumor is >4 cm in our clinic as recommended in ATA guideline. Thus, we believe that we cannot statistically evaluate the effect of pHPT on LN metastasis in PTC because of the low number of patients with prophylactic dissection in both groups.

In conclusion, there was statistically significant difference regarding the diameter of tumor and pHPT + PTC group has smaller diameter than PTC group, which may support the idea that pHPT leads to overdiagnosis of PTC, whereas high rates of tumor capsule invasion and multicentricity were unexpectedly observed and it may suggest an associative etiology with more aggressive PTC.

Compliance with ethical standards

Conflict of interest None of the authors have any financial or other relationship leading to a conflict of interest.

Ethical approval All procedures performed in studies involving human participant were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Study protocol was approved by Dr. Lutfi Kirdar Kartal Research and Training Hospital in affiliation with University of Medical Sciences' ethics committee.

Informed consent Informed consent was not obtained from participants due to retrospective design of the study.

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