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Previous, simultaneous, or subsequent occurrence of malignant tumours in patients with primary hyperparathyroidism: a closer look at the single-tertiary-centre cases

Hava Sezer¹, Hande Bulut Canbaz², Serdar Tezelman³, Tarık Terzioğlu³, Eda Nur Çilingiroğlu², Bülent Çolakoğlu⁴, Dilek Yazıcı¹, Oğuzhan Deyneli¹, Mehmet Onur Demirkol⁵, Adnan Batman¹, Seçil Özışık¹, Yersu Kapran⁶, Faruk Alagöl¹

¹Department of Internal Medicine, Division of Endocrinology, Koç University School of Medicine, Istanbul, Türkiye

²Department of Medical Nursing, Koç University School of Nursing, Istanbul, Türkiye

³Department of General Surgery, American Hospital, Istanbul, Türkiye

⁴Department of Radiology, American Hospital, Istanbul, Türkiye

⁵Department of Nuclear Medicine, Koç University School of Medicine, Istanbul, Türkiye

⁶Department of Pathology, Koç University School of Medicine, Istanbul, Türkiye

Abstract

Introduction: Our aims were to explore the relationship between primary hyperparathyroidism (pHPT) and malignant tumour development, to determine the frequency and the time of occurrence of malignant tumours in patients with pHPT, and to evaluate the characteristics of pHPT in these patients.

Material and methods: This retrospective cohort study included consecutive individuals who were diagnosed with pHPT aged 18 years or older in a university hospital during a 7-year period. A total of 198 patients with pHPT were reviewed retrospectively. Demographic, clinical, biochemical, radiologic findings, and histopathological diagnosis were collected from the electronic medical records of the hospital system.

Results: The mean age of the study population was 58 ± 13 years and was predominantly female (female/male: 162/36). There were 42 (21.2%) patients with malignant tumours. Five (12%) out of 42 patients had metachronous double malignancies. The most common 2 concurrent malignancies were breast (36.1%) and thyroid (17.0%). Sixty-eight per cent of the malignant tumours occurred before the diagnosis of pHPT. A higher percentage (87.5%) of simultaneous tumours was seen in the thyroid gland. No statistically significant differences were observed between patients with and without malignant tumours in terms of demographic, clinical, biochemical, radiological, and histopathological features. The median follow-up duration was 24 months after parathyroid surgery.

Conclusion: The results of this study revealed that pHPT was associated with various tumour types. The frequency of malignant tumours was 21.2%. Breast and thyroid cancers were the most common 2 cancers coexisting with pHPT. A large percentage of malignant tumours occurred before the diagnosis of pHPT. A higher percentage of simultaneous tumours was seen in the thyroid gland. pHPT patients with and without malignant tumours seemed to have similar characteristics. (*Endokrynol Pol* 2023; 74 (4): 372–379)

Key words: malignant tumour; hypercalcaemia; primary hyperparathyroidism

Introduction

Primary hyperparathyroidism (pHPT) is defined as elevated serum calcium concentration and elevated or inappropriately normal serum parathyroid hormone (PTH) levels due to excessive PTH secretion from the one or more abnormal parathyroid glands [1]. It is a common endocrine disorder with a higher prevalence in females and in the elderly population. The majority of pHPT patients (~85%) have a single parathyroid adenoma [1]. Multiglandular disease including hyperplasia and multiple adenomas is observed in approximately 15% of cases [1]. Parathyroid carcinoma is an extremely rare malignancy, accounting for less

than 1% of cases [1]. While parathyroid carcinoma is often associated with several clinical manifestations and significant mortality, most patients with pHPT are asymptomatic. Symptomatic patients present with kidney and skeletal complications as well as nonspecific signs and symptoms of calcium excess [1].

pHPT is a genetically heterogeneous disease with either sporadic or inherited presentation. pHPT is mostly sporadic [2–5]. In about 15% of all cases, pHPT occurs as part of an inherited disorder, most of which are caused by germline mutations of known HPT-susceptibility genes [2–5]. The most common hereditary syndromes associated with HPT are multiple endocrine neoplasia types 1 (MEN1), 2A (MEN2A), 4 (MEN4), and hyper-



Hava Sezer, M.D., Department of Endocrinology, Koç University School of Medicine, Topkapı Davutpaşa Cad, No: 4, 34010, Zeytinburnu/Istanbul, Turkey, tel: 0 505 492 69 28, e-mail: hasezer@kuh.ku.edu.tr

parathyroidism-jaw tumour syndrome (HPTJT). Some of the genes responsible for inherited forms of pHPT also contribute to sporadic pHPT. Two genes: cyclin D1 (CCND1) proto-oncogene which was initially named parathyroid adenomatosis 1 (PRAD1) and MEN1 tumour suppressor gene, are the most well-established primary drivers of sporadic parathyroid neoplasms [6–9]. Acquired mutations in the MEN1 tumour suppressor gene have been frequently found in benign parathyroid adenomas. Alterations in the CCND1 proto-oncogene also play a role in sporadic pHPT [6–9]. Loss-of-function mutation of the cell division cycle 73/hyperparathyroidism 2 (CDC73/HRPT2) tumour suppressor gene has been rarely shown in sporadic parathyroid adenomas [3–9]. This gene encodes the protein parafibromin. Loss of parafibromin expression caused by germline mutations is strongly associated with parathyroid carcinomas or atypical parathyroid adenomas. It is detected in cystic and large adenomas and in recurrent cases. Additional several gene mutations have been identified as a genetic driver of sporadic parathyroid adenomas such as cyclin-dependent kinase inhibitor (CDKN1B) and other members of the CDKI family [3–9].

Although there is conflicting evidence, the incidence of malignant tumours has been increasing in patients with pHPT [10]. Various types of malignancies such as breast, colon, prostate, lung, thyroid, skin, bladder, and haematopoietic cancers are more common in this disorder [10–17]. The underlying mechanisms of the coexistence of various neoplasms and pHPT is not clear yet. Activation of proto-oncogenes and inactivation of tumour suppressor genes stimulate mitogenic signals [3–5]. Most human cancers, parathyroid adenomas, and carcinomas derive from the clonal proliferation of a single progenitor cell [6, 7]. Certain malignancies such as ossifying fibromas of the mandible or maxilla, renal tumours, uterine tumours, and ovarian tumours have been observed within pHPT patients with similar genetic backgrounds [18–20]. Common molecular pathways may play a role in the development of parathyroid neoplasia and malignancy in another location. CCND1 mutation was first established in parathyroid adenomas, but its importance was recognized in many additional tumour types [6, 7, 21]. Environmental factors contribute to the possible aetiological risk factors relevant to coexistence of these 2 diseases [4, 22, 23]. Hypercalcaemia may also induce cell proliferation and cause defective apoptosis [24].

Our aims were to explore the relationship between pHPT and malignant tumour development, to determine the frequency and the time of occurrence of malignant tumours in patients with pHPT, and to evaluate the characteristics of pHPT in these patients.

Material and methods

This was a retrospective cohort study conducted in a single tertiary referral hospital. The study was approved by the Institutional Ethics Review Board (Ethical approval number: 2022.173.IRB1.065). Consecutive patients attending to outpatient clinic of the endocrine division of a tertiary centre between the years of 2015 and 2022 who met the following criteria were included in this study.

We included consecutive patients with a diagnosis of pHPT after the age of 18 years. A total of 198 patients with pHPT were reviewed retrospectively. Baseline clinical characteristics of the patients, including the following: age at diagnosis of pHPT, gender, neoplasm types, the time of occurrence of malignant neoplasms, presence of comorbid diseases, laboratory findings (serum levels of albumin-corrected calcium, phosphate, PTH, 25-hydroxyvitamin D, creatinine, and 24-hour urine calcium), pHPT complications (osteoporosis, nephrolithiasis), radiological findings, histopathological findings, bisphosphonate use, and postoperative follow-up data collection of the patients, were obtained from the hospital records. The diagnosis of pHPT was confirmed with elevated serum calcium along with elevated (defined in this study as > 65 pg/mL) or unsuppressed serum PTH levels. Hypercalcaemia was categorized either as mild when the calcium levels were between 10 and 12 mg/dL, moderate when the levels were between 12 and 14 mg/dL, or severe when the levels were more than 14 mg/dL [1]. Vitamin D deficiency was defined in patients having a 25-hydroxyvitamin D level of < 30 ng/mL [1]. The estimated glomerular filtration (eGFR) rate was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [25]. Neck ultrasonographic evaluation was performed using a GE Healthcare LOGIQ E9 XDclear (GE Healthcare, United States) sonographic device with 6–15 MHz linear-array transducer. Technetium-99m (Tc) labelled sestamibi scintigraphy scan imaging with the single-photon emission computed tomography (SPECT) technique was used for the localization of the hyperfunctioning adenoma. Bone mineral density (BMD) values were determined by dual-energy X-ray absorptiometry with a dual-photon X-ray system (Hologic device).

These patients were operated by experienced surgeons of a tertiary university hospital. Patients with and without malignant tumours were compared according to their demographic, clinical, biochemical, radiological, and histopathological features. Biochemical evaluations were performed every 3 months for a year, and every 6 months after parathyroid surgery.

Assays

Serum intact PTH and 25-hydroxyvitamin D levels were measured using an electrochemiluminescence immunoassay. Serum calcium concentration, serum phosphate concentration, and 24-hour urinary excretion of calcium were measured by spectrophotometric assay. A colorimetric assay system was used to measure the albumin serum concentration. The serum calcium level was corrected for measurement of the albumin serum concentration. An enzymatic colorimetric test was used for serum creatinine concentration and 24-hour urinary creatinine excretion determination (Roche Cobas 6000 device, Mannheim, Germany).

Statistical analysis

IBM SPSS Statistics (version 28, Chicago, USA) software was used for data analysis. Descriptive analyses of variables were expressed as percentage, median, and mean \pm standard deviation. The distribution of variables was evaluated by Kolmogorov-Smirnov test. In the analysis of quantitative independent data, independent sample t test and Mann-Whitney U test were used. The chi-square test was used in the analysis of qualitative independent data. When the chi-square test did not meet the conditions, Fisher's Exact test was used. The level of statistical significance was defined as $p < 0.05$.

Results

A total of 198 patients were analysed in this study. The mean age was 56.3 ± 14.6 years at the time of the diagnosis of pHPT. Of the 198 patients 162 (81.8%) were female and 36 (18.2%) were male.

The mean serum albumin-corrected calcium was 11.4 ± 0.8 mg/dL, phosphorus was 2.7 ± 0.5 mg/dL, PTH was 172.9 ± 136.9 pg/mL, and 25-hydroxyvitamin D was 29.1 ± 18.4 ng/mL. Mean measured 24-hour urinary calcium excretion was 326.5 ± 164.4 mg/day, and eGFR was 100.7 ± 28.3 mL/min/1.73 m². The base-

line characteristics of the whole study population are described in Table 1.

The 2 most prevalent comorbidities were hypertension (41.4%) and thyroid nodules (35.9%). Of the 198 patients, 88 (44.4%) had osteoporosis and 71 (35.9%) had nephrolithiasis. We detected 42 (21.2%) patients diagnosed with malignant tumours. There were metachronous double malignancies in 5 patients (12%). A total of 47 malignant tumours were found. In terms of malignant tumours, 17 (36.1%) of 47 tumours were breast cancers. Eleven of 17 (~65%) patients with breast cancer were found to have invasive carcinoma

Table 1. Demographic, clinical, biochemical, radiological, and histopathological characteristics of the study population

Parameters	Total (n = 198)
Age at pHPT diagnosis (years), mean \pm SD	56.3 \pm 14.6
Gender, n (%)	
Female	162 (81.8)
Male	36 (18.2)
Comorbid conditions, n (%)	
HT	82 (41.4)
Thyroid nodules	71 (35.9)
T2DM	34 (17.2)
Malignancy, n (%)	42 (21.2)
PTH (reference 15-65 pg/mL), mean \pm SD	172.9 \pm 136.9
Albumin-corrected calcium (reference 8.6-10.2 mg/dL), mean \pm SD	11.4 \pm 0.8
Hypercalcaemia, n (%)	
Mild	161 (81.3)
Moderate	33 (16.7)
Severe	4 (2.0)
Phosphorus (reference 2.5-4.5 mg/dL), mean \pm SD	2.7 \pm 0.5
25(OH)D [ng/mL], mean \pm SD	29.1 \pm 18.4
25(OH)D deficiency, n (%)	108 (54.5)
eGFR (mL/min/1.73 m²), mean \pm SD	100.7 \pm 28.3
24-h urinary calcium excretion (reference 100-300 mg/24 h), mean \pm SD	326.5 \pm 164.4
Complications of pHPT, n (%)	
Hypercalciuria	87 (50.9)
Nephrolithiasis	71 (35.9)
Osteoporosis	88 (44.4)
Fracture	19 (9.6)
Bisphosphonate use, n (%)	46 (23.2)
Localization of abnormal parathyroid gland (n, %)	
Neck	176 (88.9)
Ectopic	22 (11.1)
Neck localization of abnormal parathyroid gland, n (%)	
Right	78 (44.3)
Left	98 (55.7)



Table 1. Demographic, clinical, biochemical, radiological, and histopathological characteristics of the study population

Parameters	Total (n = 198)
Parathyroid lesion size [mm], mean ± SD	14.0 ± 6.1
Surgical approach, n (%) (n = 178)	
MIPS	172 (96.6)
Thoracostomy	6 (3.4)
Postoperative complication, n (%) (n = 178)	20 (11.2)
Postoperative complication, n (%) (n = 178)	
Temporary hypocalcaemia	16 (80.0)
Permanent hypocalcaemia	3 (15.0)
Hungry bone syndrome	1 (5.0)
Pathology report, n (%) (n = 178)	
Adenoma	162 (91.0)
Hyperplasia	9 (5.1)
Atypical adenoma	7 (3.9)
Follow-up time [months], median	24.0
Current PTH (reference 15–65 pg/mL), mean ± SD	50.5 ± 23.4
Current albumin-corrected calcium (reference 8.6–10.2 mg/dL), mean ± SD	9.6 ± 0.4

n — number of patients; % — percentage of patients; pHPT — primary hyperparathyroidism; SD — standard deviation; BMI — body mass index; HT — hypertension; T2DM — type 2 diabetes mellitus; HL — hyperlipidaemia; CAD — coronary artery disease; PTH — parathyroid hormone; 25(OH)D — 25-hydroxyvitamin D; eGFR — estimated glomerular filtration rate; h — hour; MIPS — minimally invasive parathyroid surgery

(10 patients had invasive ductal carcinoma, one patient had invasive papillary carcinoma). Breast cancer was followed by thyroid cancer (17.0%). All tumours of the thyroid were reported as papillary thyroid carcinoma. The types of malignant tumours are shown in Table 2. Of the 47 malignant tumours, 32 (68.1%) were diagnosed before pHPT and 6 (12.8%) after pHPT. Simultaneous occurrence of malignant tumours and pHPT were detected in the remaining 9 tumours (19.1%). A higher percentage of simultaneous tumours was seen in the thyroid gland (87.5%). The time of occurrence of malignant tumours is shown in Table 3.

Patients with malignancy were compared to those with no malignancy. No statistically significant differences were observed in terms of demographic, clinical, biochemical, radiological, and histopathological findings between the 2 groups. The mean 25-hydroxyvitamin D level was lower in the non-malignancy group than in the malignancy group, but this difference did not reach statistical significance ($p = 0.058$). The median follow-up was 35 months for the malignancy group and 20.5 months for the non-malignancy group. Comparisons of the patients with and without malignant tumours are shown in Table 4.

A group of 178 patients were operated for pHPT (36 patients with malignancy, 142 patients without malignancy). The remaining 20 patients were lost to follow-up. Six patients were operated with thoracostomy and 172 patients with minimally invasive parathyroid

Table 2. Types of cancer in patients with primary hyperparathyroidism (pHPT)

Locations	47 malignant tumours in 42 patients, n (%)
Breast	17 (36.1)
Thyroid	8 (17.0)
Prostate	4 (8.5)
Colon	3 (6.4)
Stomach	3 (6.4)
Lung	2 (4.3)
Lymphoma	2 (4.3)
Ovarian	2 (4.3)
Kidney	2 (4.3)
Cervix	1 (2.1)
Multiple myeloma	1 (2.1)
Skin (malign melanoma)	1 (2.1)
Endometrial	1 (2.1)

n — number of patients; % — percentage of patients

surgery. The most common location of abnormal parathyroid lesions was the left side of the neck (55.7%). The mean parathyroid lesion size was 14.0 ± 6.1 mm. The permanent hypocalcaemia rate was 1.7% in this cohort.

Biochemical parameters were performed every 3 months for a year, and every 6 months thereafter.

Table 3. Time of occurrence of malignant tumours according to the diagnosis of primary hyperparathyroidism (pHPT)

Locations	47 malignant tumours in 42 patients		
	Before, n (%)	After, n (%)	Simultaneous, n (%)
Breast	13	3	1
Thyroid	1	–	7
Prostate	2	2	–
Colon	3	–	–
Stomach	3	–	–
Lung	1	–	1
Lymphoma	2	–	–
Ovarian	2	–	–
Kidney	1	1	–
Cervix	1	–	–
Multiple myeloma	1	–	–
Skin	1	–	–
Endometrial	1	–	–
Total	32 (68.1)	6 (12.8)	9 (19.1)

n — number of patients, % — percentage of patients

Table 4. Demographic, clinical, biochemical, radiological, and histopathological characteristics of the primary hyperparathyroidism (pHPT) patients with and without malignancy

Parameters	Malignancy group (n = 42)	Non-malignancy group (n = 156)	p-value
Age at pHPT diagnosis (years), mean ± SD	60.3 ± 11.3	55.3 ± 15.2	0.070 ^m
Gender, n (%)			
Female	32 (76.2)	130 (83.3)	0.287 ^{x2}
Male	10 (23.8)	26 (16.7)	
PTH (reference 15–65 pg/mL), mean ± SD	176.6 ± 144.0	171.9 ± 135.3	0.962 ^m
Albumin-corrected calcium (reference 8.6–10.2 mg/dL), mean ± SD	11.4 ± 0.9	11.4 ± 0.8	0.621 ^m
Hypercalcaemia, n (%)			
Mild	33 (78.6)	128 (82.0)	0.563 ^{x2}
Moderate	9 (21.4)	24 (15.4)	
Severe	0 (0.0)	4 (2.6)	
Phosphorus (reference 2.5–4.5 mg/dL), mean ± SD	2.7 ± 0.5	2.7 ± 0.5	0.912 ^m
25(OH)D [ng/mL], mean ± SD	37.1 ± 27.3	26.9 ± 14.4	0.058 ^m
eGFR [mL/min/1.73 m²], mean ± SD	97.9 ± 28.9	101.5 ± 28.2	0.559 ^t
24-h urinary calcium excretion (reference 100–300 mg/24h), mean ± SD	287.7 ± 129.6	336.8 ± 171.3	0.163 ^m
Complications of pHPT, n (%)			
Hypercalciuria	15 (35.7)	72 (46.1)	0.213 ^{x2}
Nephrolithiasis	15 (35.7)	56 (35.9)	0.982 ^{x2}
Osteoporosis	20 (47.6)	68 (43.6)	0.714 ^{x2}
Fracture	5 (11.9)	14 (9.0)	0.585 ^{x2}
Bisphosphonate use, n (%)	12 (28.6)	34 (21.8)	0.356 ^{x2}
Localization of abnormal parathyroid gland, n (%)			
Neck	35 (83.3)	141 (90.4)	0.188 ^{x2}
Ectopic	7 (16.7)	15 (9.6)	



Table 4. Demographic, clinical, biochemical, radiological, and histopathological characteristics of the primary hyperparathyroidism (pHPT) patients with and without malignancy

Parameters	Malignancy group (n = 42)	Non-malignancy group (n = 156)	p-value
Neck localization of abnormal parathyroid gland, n (%)			
Right	20 (57.1)	58 (41.1)	0.081 ^{x2}
Left	15 (42.9)	83 (58.9)	
Parathyroid lesion size (mm), mean ± SD	14.1 ± 5.2	14.0 ± 6.3	0.542 ^m
Surgical approach, n (%) (n = 178)			
MIPS	35 (97.2)	137 (96.5)	1.000 ^{x2}
Thoracostomy	1 (2.8)	5 (3.5)	
Postoperative complication, n (%)	4 (9.5)	16 (10.2)	0.979 ^{x2}
Pathology report, n (%) (n=178)			
Adenoma	32 (88.9)	130 (91.6)	0.618 ^{x2}
Hyperplasia	3 (8.3)	6 (4.2)	0.389 ^{x2}
Atypical adenoma	1 (2.8)	6 (4.2)	1.000 ^{x2}
Follow-up time (months), median	35.0	20.5	0.096 ^m
Current PTH (reference 15–65 pg/mL), mean ± SD	57.0 ± 21.0	48.9 ± 23.8	0.090 ^m
Current albumin-corrected calcium (reference 8.6–10.2 mg/dL), mean ± SD	9.6 ± 0.5	9.6 ± 0.4	0.406 ^m

n — number of patients; % — percentage of patients; pHPT — primary hyperparathyroidism; SD — standard deviation; BMI — body mass index HT — hypertension; T2DM — type 2 diabetes mellitus; HL — hyperlipidaemia; CAD — coronary artery disease; PTH — parathyroid hormone; 25(OH)D — 25-hydroxyvitamin D; eGFR — estimated glomerular filtration rate; h — hour; MIPS — minimally invasive parathyroid surgery. ⁱindependent sample t test; ^mMann-Whitney U test; ^{x2}χ² test (Fisher's test)

The median follow-up was 24 months after parathyroid surgery.

Discussion

This present study is one of the few studies in the literature that describes the frequency and the time of occurrence of malignant tumours in patients with pHPT. The results of this study revealed that pHPT was associated with various tumour types. The frequency of malignant tumours was 21.2%. The 2 most common concurrent malignancies were breast and thyroid. A large percentage of malignant tumours occurred before the diagnosis of pHPT. A higher percentage of simultaneous tumours was seen in the thyroid gland. pHPT patients with and without malignant tumours seemed to have similar characteristics.

There is conflicting evidence of the association between HPT and malignant tumours [26]. When cases with pHPT were followed over a 28-year period, malignancies were lower than expected in patients with pHPT [26]. However, studies have found an association between pHPT and malignancies [10–17, 27–31]. It has been reported that haematopoietic, urinary tract, and thyroid gland malignancies were increased significantly in patients with HPT [12]. Strodel et al. demonstrated patients with concomitant malignant tumours and pHPT [11]. In this study, the most common

accompanying neoplasm types were breast, lymphoma, and thyroid [11]. Minisola et al. showed that the rate of coexistence of prostate cancer and pHPT was 13% [15]. Some authors described cases of lung cancer coexisting with pHPT [11,16]. There are case reports of pHPT associated with non-Hodgkin lymphoma [28]. The coexistence of multiple myeloma and pHPT was also described [29]. A study found that the occurrence of breast, kidney, and skin cancer was significantly higher in patients with pHPT than in patients without pHPT [30]. pHPT was diagnosed in 2.8% of the patients with breast cancer, which was higher than expected [14]. The coexistence of pHPT and thyroid cancer has been demonstrated in 20.8% of cases [31]. The coexistence of malignant tumours and pHPT was found to be 21.2% in our study population. Our study results demonstrated increased occurrence of malignancy risk in patients with pHPT. Palmieri et al. showed that the occurrence of all cancer types (21.5%) was significantly higher in patients with pHPT than in patients without pHPT [30]. A study found 16.5% of pHPT patients had an accompanying malignant tumour [10]. Most accompanying neoplasm types were breast, thyroid, prostate, and colon in our study, as in the literature. They are also the most common cancers according to worldwide cancer data [32]. Breast, prostate, and colon were the most common causes of cancer deaths in males and females [33]. Based on the literature and our study results dealing

with the coexistence of these 2 diseases, we suggest screening pHPT patients for malignant tumours. About two-thirds of patients with breast cancer had invasive cancer. Thus, screening may provide an opportunity to detect possible early-stage cancers in pHPT patients.

There are some studies related to hyperparathyroidism and subsequent cancer risk [10, 12–14]. Several malignant tumours were found before the diagnosis of pHPT [10]. A study from Italy reported increased malignancy risk during the 10 years before the diagnosis of pHPT [30]. Some patients had diagnoses of malignant tumours and pHPT simultaneously [10]. In our study, 68% of the malignant tumours occurred before the diagnosis of pHPT. This result could be due to the diagnostic delay of pHPT in cancer patients. We could not reach calcium and PTH levels at the time of diagnosis of malignancy in most of the patients. Hence, we suggest monitoring cancer patients for pHPT. In our cohort, nearly 19% of malignant tumours had simultaneous presentation with pHPT. Especially, we observed simultaneous diagnosis of parathyroid adenoma and papillary thyroid carcinoma. pHPT is usually the primary pathology, and thyroid cancer is usually diagnosed incidentally, as in our study results [34–36]. Current literature data recommend evaluation of patients for thyroid cancer before parathyroid surgery [37]. We found that 12.8% of the malignant tumours occurred after the diagnosis of pHPT. The increased risk of malignancy in pHPT patients persists after parathyroid surgery [12]. Hence, screening for the most common cancers may be continued after parathyroid surgery. The optimal screening approach could be with gold standard methods by following the current evidence-based clinical practice guidelines [38].

The underlying mechanisms of coexistence of malignant tumours in patients with pHPT are still not understood. To find out whether there is a distinctive feature to predict malignancy in patients with pHPT, we compared the 2 groups. Additionally, we followed up patients after parathyroid surgery for recurrent hyperparathyroidism. There was no significant difference between malignancy and non-malignancy groups with respect to patients' demographics, clinical presentation, laboratory, radiological, histopathological findings, and surgical cure. Similar study results to ours have been reported [10].

This present study has several limitations. The first is that it is a single-centre study with a small sample size and a shorter follow-up duration after parathyroid surgery. If we had a longer follow-up, the number of patients diagnosed with malignancy could have increased. Future multicentre prospective trials with larger sample size and longer follow-up period are needed. Secondly, approximately two-thirds of malignant tu-

mours occurred before the diagnosis of pHPT. These patients may have had pHPT at the time of diagnosis of malignancy. However, we could not obtain the laboratory findings of the patients at that time. Thirdly, a small number of patients underwent genetic testing. They showed positive mutation for MEN1. Each patient should be screened by genetic study in the presence of hereditary disease suspicion such as an earlier age of onset, multiglandular involvement, family history, recurrent pHPT, parathyroid carcinoma, and/or atypical parathyroid adenoma. Although we had suggested genetic analysis, there were patients who could not do this due to the high financial cost. Future studies may be planned to provide evidence of a genetic association in patients with pHPT and coexisting cancer. Lastly, we did not have an age- and gender-matched control group. Comparing the general population with pHPT patients in terms of cancer development would have made the study significantly stronger.

In conclusion, the results of this study stress the need for clinical awareness of concomitant pHPT and certain malignant tumours. Breast and thyroid cancers were the 2 most common cancers coexisting with pHPT. A large percentage of malignant tumours occurred before the diagnosis of pHPT. A higher percentage of simultaneous tumours was seen in the thyroid gland. We suggest screening pHPT patients for malignant tumours or monitoring cancer patients for pHPT.

Conflict of interest disclosure

No conflict of interest was declared by the authors.

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