Primary hyperparathyroidism: a retrospective study over 18 years in an oncology center

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Aim: To study primary hyperparathyroidism (pHPT) in an oncology center, including its possible association with malignancy and ionizing radiation. **Methods:** Retrospective analysis of 188 patients with sporadic pHPT treated with parathyroidectomy between 2000 and 2018. We studied the etiology, clinical and biochemical features of pHPT, history of malignancies and exposure to radiotherapy. **Results:** pHPT was caused by parathyroid adenoma in 90.4%, hyperplasia in 5.3% and carcinoma in 4.3%. Cure and recurrence rates of pHPT were 99 and 4.3%, respectively. Median follow-up time was 19 months. Prevalence of malignancies was 30%, mostly thyroid and breast cancer. Radiotherapy of the head, neck or thorax (8.5%) was not associated with worse hypercalcaemia or recurrence. Males had larger adenomas, higher calcium and parathyroid hormone ($p < 0.01$). **Conclusion:** Prevalence of parathyroid carcinoma and other malignancies was higher than reported in other studies. Ionizing radiation exposure was unrelated with pHPT severity. Men had more severe pHPT. High cure and low recurrence rates were achieved.

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Primary hyperparathyroidism (pHPT) is characterized by hypercalcemia, resulting from inappropriately high parathyroid hormone (PTH) secretion [1]. It has an incidence of 66 cases per 100,000 persons per year among women and 25 per 100,000 persons per year among men, with an estimated prevalence of 0.1% in the general population [2–5]. Most cases of pHPT are sporadic and generally caused by a parathyroid adenoma (85%), while parathyroid hyperplasia occurs in 15% of cases and parathyroid carcinoma in <1% [1,2]. The only curative treatment is parathyroidectomy, with rates of cure >95%, when performed by experienced surgeons [1].

Physiopathology of pHPT comprises multiple mechanisms. In syndromic or hereditary pHPT, as in hyperparathyroidism jaw-tumor syndrome and multiple endocrine neoplasia types 1, 2A and 4, a single genetic mutation is responsible for the disease. In nonsyndromic pHPT, although the genetic basis is not yet fully understood, several molecular pathways involved in parathyroid tumorigenesis have been investigated [1,6–8]. Growth factors including VEGF, TGF β and IGF-1 have been found to be increased in pHPT [1,7]. These proteins stimulate cell proliferation and differentiation, and are thought to be implicated in growth regulation of parathyroid tumors. Cyclins are regulators of the cell cycle and cyclin D1, encoded by the gene *CCND1*, promotes cell-cycle progression [1]. Overexpression of *CCND1* has been found in 20–40% of parathyroid adenomas and in parathyroid carcinomas [7]. Mutations of the *RB* gene, an inhibitor of the cell-cycle progression, have also been observed in parathyroid carcinomas [7]. Moreover, sporadic parathyroid tumors may harbor somatic mutations in the *MEN1* gene [1]. In whole exome sequencing studies, *PRUNE2* was found to be recurrently mutated on a germline and somatic manner in a subset of parathyroid carcinomas [8]. In the same study, the *APOBEC* mutational signature was found to be dominant in another subset of parathyroid carcinoma patients with high mutational burden and early age onset of disease [8].

Beyond genetic alterations, risk factors for pHPT include female sex and exposure to ionizing radiation [6,9–12]. Irradiation has been associated with pHPT especially in patients who received radiation treatment of the head and neck region in childhood [9,10]. In a prospective study of 2923 patients exposed to radiotherapy in childhood,

the incidence of pHPT was 2.9-times greater than in the general population [9]. An increased risk of pHPT was also observed in Hiroshima (Japan) atomic bomb survivors and in workers at the Chernobyl Nuclear Power Plant (Pripyat, Ukraine) [13,14]. Radiation-associated hyperparathyroidism seems to occur after a long period of time after exposure to radiation [12].

Classical manifestations of pHPT are related to kidney and skeletal damage, including nephrolithiasis, nephrocalcinosis, decreased renal function, low bone mineral density, bone cysts and brown tumors. In developed countries, however, the clinical presentation of pHPT has changed over the years and is now, in most cases, diagnosed in asymptomatic patients [15–17].

Besides the classical presentation, pHPT has been linked to neurocognitive changes, cardiovascular dysfunction and malignancy [15,17–20]. In fact, an increased risk of cancer-related death in patients with pHPT has been reported [21,22] and pHPT has been associated with a number of malignancies, such as breast, colon, kidney, thyroid and skin cancer [19,20,23–25]. A possible antiapoptotic effect of parathyroid hormone could contribute to an increased risk of cancer; however, such risk seems to persist after parathyroidectomy, suggesting that common etiologic factors may exist for pHPT and some malignancies [24,25].

In this study, we retrospectively reviewed a series of patients with sporadic pHPT, who were treated with parathyroidectomy between 1 January 2000 and 30 June 2018. We studied associations between pHPT and malignancies, and tried to understand the role of previous exposure to ionizing radiation in pHPT and its manifestations.

Materials & methods

A total of 196 parathyroidectomies performed between 1 January 2000 and 30 June 2018 were identified and clinical records, pathology reports, biochemical and imaging studies of the patients were reviewed. Based on this information, we excluded cases of tertiary hyperparathyroidism ($n = 3$), familial primary hyperparathyroidism ($n = 4$) and multiple endocrine neoplasia ($n = 1$). All the patients with diagnosis of sporadic pHPT who had parathyroidectomy in the above-mentioned period were included in the study ($n = 188$).

We have documented for each patient the concentrations of total serum calcium, phosphate, intact PTH, magnesium, calcifediol, creatinine and 24-h urine calcium and phosphate. Serum calcium, phosphate and PTH from the last follow-up appointment were also recorded. Serum intact PTH was determined using a third-generation PTH assay (PTH1–34 and 44–84). Information regarding the reason that led to diagnosis, symptoms attributable to pHPT, history of previous fragility fractures, personal and family history of malignancies and previous exposure to ionizing radiation was obtained from the clinical records. Pathology reports from parathyroidectomies were reviewed for histological diagnosis, location and dimensions of parathyroid adenomas and carcinomas. Imaging studies were also reviewed for the presence of nephrolithiasis or calcinosis, bone mineral density, presence or absence of enlarged parathyroid glands and concordance of localization.

The study was approved by the Institutional Ethics Committee

Statistical analysis

Statistical analysis of the results was performed with Microsoft Excel® and IBM SPSS®. Data are presented as means and standard deviations, or as medians and intervals, as appropriate. A one-sample Kolmogorov–Smirnov was performed to test for normality of quantitative variables. We used the Mann–Whitney test to compare differences and the Spearman coefficient for correlations between variables, considering data as statistically significant if $p < 0.05$.

Results

We studied 188 patients with sporadic pHPT, including 151 females (80%) and 37 males (20%). At diagnosis, mean age was 59 ± 14.7 years (median 61 years, range 14–93).

In most cases (59%), pHPT was diagnosed through routine laboratory tests. Symptoms attributable to pHPT occurred in 23.4%, with the most common being bone pain and fatigue (Table 1).

Table 2 shows the laboratory profile of patients at diagnosis.

Target organ lesions were present in 134 patients (71.3%), the most common being nephrolithiasis, which was documented in 66.4%. The prevalence of target organ lesions at diagnosis was significantly higher in the first years of the studied period (2000–2004) when compared with the last years (2014–2018) – 86.8 versus 51.4%, respectively ($p < 0.01$). Table 3 shows the full frequency of target organ lesions.

Table 1. Motive for diagnosis of primary hyperparathyroidism.

Motive for diagnosis	Frequency (%)
Routine laboratory tests	111 (59)
Symptoms:	44 (23.4)
– Bone pain	16
– Fatigue	12
– Abdominal pain/vomiting	8
– Dizziness	4
– Renal colic	2
– Mental confusion	2
Nephrolithiasis	17 (9)
Palpable nodule of the neck	8 (4.3)
Osteoporosis	4 (2.1)
Maxillary brown tumor	2 (1.1)
Incidental in thyroidectomy	2 (1.1)

Table 2. Initial laboratorial evaluation in patients with primary hyperparathyroidism.

Biochemical features	Median (interval)	Normal range
Total calcium (mg/dl) – n = 187	11.5 (9.2–20)	8.4–10.2
Phosphate (mg/dl) – n = 183	2.5 (0.9–4.1)	2.3–4.7
Magnesium (mg/dl) – n = 116	2.1 (1.1–2.7)	1.6–2.6
Serum intact PTH [†] (pg/ml) – n = 187	186 (53.1–3150)	12–65
25(OH)vitamin D [‡] (ng/ml) – n = 82	17.5 (8–79)	9–45
24-h urine calcium (mg/24 h) – n = 83	313 (59–994)	100–300
24-h urine phosphate (mg/24 h) – n = 62	794 (138–2293)	400–1300

[†] Parathyroid hormone.
[‡] Calcifediol.

Table 3. Target organ lesions in patients with primary hyperparathyroidism.

Target organ lesion	Frequency (%)			p-value
	Total	pHPT diagnosed 2000–2004	pHPT diagnosed 2014–2018	
Nephrolithiasis/nephrocalcinosis	97 (66.4), n = 146	24 (66.7), n = 36	11 (40.7), n = 27	0.04
Renal dysfunction [†]	29 (15.5), n = 187	8 (21), n = 38	7 (18.9), n = 37	0.82
Osteoporosis [‡]	48 (58.5), n = 82	16 (61.5), n = 26	7 (31.8), n = 22	0.04
Fragility fracture (reported)	15 (8), n = 188	5 (13.2), n = 38	2 (5.4), n = 37	0.25
No. of patients with any target organ lesion	134 (71.3), n = 188	33 (86.8), n = 38	19 (51.4), n = 37	0.001

[†] Serum creatinine >1.11 mg/dl.
[‡] Documented in osteodensitometry
pHPT: Primary hyperparathyroidism.

Each patient had an average of two imaging studies for localization of enlarged parathyroid glands. Neck ultrasound and ^{99m}Tc-Sestamibi parathyroid scintigraphy were the most commonly used imaging methods, in 88.3 and 75%, respectively, whereas neck CT scan was performed in 21.8% and MRI in 17.6%. In 86.7% of the cases the location of abnormal parathyroid glands, as seen in the imaging studies, was concordant with the surgical report.

Time between diagnosis and surgery was <1 year for 75.5%, between 1 and 2 years for 14.9% and over 2 years for 9.6%. A parathyroid adenoma was identified in 170 cases (90.4%), parathyroid hyperplasia in 10 (5.3%) and carcinoma in 8 (4.3%). The largest tumor diameter was 21.4 ± 9 mm in parathyroid adenomas and 32.1 ± 20 mm in carcinomas. Most adenomas were located at the right inferior (41.2%) and left inferior (32.9%) parathyroid glands. There were two ectopic adenomas (retroesophageal and mediastinal).

Table 4. Malignancies in patients with primary hyperparathyroidism.

Malignancies	Frequency (%)
Papillary thyroid carcinoma	26 (13.8)
Breast carcinoma	14 (7.4)
Hematological malignancies:	7 (3.7)
– Non-Hodgkin's lymphoma	3
– Chronic lymphocytic leukemia	2
– Acute lymphoblastic leukemia	1
– Multiple myeloma	1
Head and neck basal cell carcinoma	4 (2.1)
Prostate adenocarcinoma	3 (1.6)
Other	8 (4.3)

The cure rate was 99% (186/188). Median follow-up time was 19 months (0–214 months). Recurrence of pHPT occurred in eight patients (4.3%), between 1 and 10 years after parathyroidectomy (median 6.5 years).

pHPT & malignancy

Prevalence of malignancies was 30.3%, the most frequent being papillary thyroid carcinoma (13.8%), followed by breast cancer (7.4%). See Table 4 for summary of malignancies. Seven patients had two malignancies and one had four malignancies.

Among 26 patients with papillary thyroid carcinoma, only four had been treated with radioiodine before the diagnosis of pHPT.

Known family history of malignancy was present in 15 patients (8%), in at least one first or second-degree relative. The most frequently reported malignancies were from the GI tract (seven cases), breast (three cases) and kidney (three cases). The age at diagnosis of pHPT was significantly lower in patients with a family history of malignancy (median age 53 vs 62 years, $p < 0.05$); however, serum calcium, adenoma size and recurrence rate were similar between the two groups.

pHPT & radiotherapy exposure

Sixteen patients (8.5%) had been exposed to radiotherapy of the head, neck or thorax, between 1 and 19 years before the diagnosis of pHPT (median 5 years). Among these, ten patients had radiotherapy for breast carcinoma, three for head and neck cancer, two for non-Hodgkin's lymphoma and one for acute lymphoblastic leukemia (CNS-directed radiotherapy).

There were no significant differences in serum calcium, histological diagnosis, adenoma size or recurrence rate between patients exposed and nonexposed to ionizing radiation (Table 5).

Gender differences in pHPT

In this series, 151 patients were females, with a female-to-male ratio of approximately 4:1. Women, compared with men, were more frequently diagnosed through routine laboratory tests, although this was also the main route of diagnosis in men. Male patients had higher median serum concentrations of total calcium and PTH and larger adenomas. Nevertheless, the rates of target organ lesions, such as nephrolithiasis and osteoporosis, and the recurrence rate of pHPT, were not significantly different between males and females. Table 6 shows full breakdown of gender differences.

Discussion

We describe a large series of patients with pHPT and their clinical evolution over time. Consistent with other series [17,26], we have obtained high cure (99%) and low recurrence (4.3%) rates. This study shows recurrences occurred with a median of 6.5 years after parathyroidectomy, whereas other studies have reported recurrence rates between 0 and 5%, but most have shorter follow-up times [26,27].

In the majority of cases, pHPT was caused by a parathyroid adenoma. However, compared with other series [28–30], there was a relatively higher prevalence of parathyroid carcinoma (4.3%) and a lower than expected prevalence of hyperplasia (5.3%). In the first case, this might be due to the study taking place in an oncology center and, in

Table 5. Features of primary hyperparathyroidism in patients previously exposed and not exposed to radiotherapy of the head, neck or thorax.

Features of primary hyperparathyroidism	Patients exposed to RT	Patients not exposed to RT	p-value
Total serum calcium (mg/dl) – median (interval)	11.6 (10.5–12.5)	11.5 (9.2–20)	0.52
Histological diagnosis:			
– Parathyroid adenoma – n (%)	15 (94)	155 (90.1)	
– Parathyroid hyperplasia – n (%)	1 (6)	9 (5.2)	
– Parathyroid carcinoma – n (%)	0	8 (4.7)	
– Largest diameter of parathyroid adenoma (mm) – median (interval)	20 (8–25)	20 (6–70)	0.57
Age at diagnosis (years) – median (interval)	61.2 (17–79)	60.6 (14–93)	0.59
Target organ lesions:			
– Nephrolithiasis/nephrocalcinosis – n (%)	7 (58), n = 12	90 (67), n = 134	0.54
– Renal dysfunction [†] – n (%)	1 (7), n = 15	28 (16), n = 172	0.33
– Osteoporosis [‡] – n (%)	4 (67), n = 6	44 (58), n = 76	0.68
– Fragility fracture (reported) – n (%)	2 (13), n = 16	13 (8), n = 172	0.49
– Any target organ lesion – n (%)	9 (56), n = 16	125 (73), n = 172	0.17
Cure after parathyroidectomy – n (%)	16 (100)	170 (99)	0.67
Recurrence – n (%)	1 (6)	7 (4)	0.68

[†] Serum creatinine >1.11 mg/dl.
[‡] Documented in osteodensitometry.
RT: Radiotherapy.

Table 6. Gender differences in primary hyperparathyroidism.

Features of primary hyperparathyroidism	Males	Females	p-value
Total serum calcium (mg/dl); median (interval)	12.5 (10.3–20)	11.4 (9.2–16.5)	< 0.001
Total serum phosphate (mg/dl); median (interval)	2.25 (0.9–3.9)	2.5 (1.2–4.1)	0.005
Serum intact PTH [†] (pg/ml); median (interval)	255 (70–2091)	164 (53–3150)	0.001
25(OH)vitamin D [‡] (ng/ml); median (interval)	22 (8–45)	16 (8–79)	0.46
24-h urine calcium (mg/24h); median (interval)	545 (63–994)	302 (59–883)	0.02
Largest diameter of parathyroid adenoma (mm); median (interval)	25 (10–70)	20 (6–55)	0.003
Age at diagnosis (years); median (interval)	58 (14–93)	61 (15–87)	0.12
Motive for diagnosis:			
– Routine laboratory tests; n (%)	16 (43)	95 (63)	0.03
– Symptoms; n (%)	11 (30)	33 (22)	0.31
– Nephrolithiasis; n (%)	5 (14)	12 (8)	0.29
– Other; n (%)	5 (14)	11 (7)	0.23
Nephrolithiasis/nephrocalcinosis; n (%)	20 (65)	77 (67)	0.8
Renal dysfunction [§] ; n (%)	8 (22)	21 (14)	0.25
Osteoporosis [#] ; n (%)	10 (59)	38 (59)	0.98
Fragility fracture (reported); n (%)	3 (8)	12 (8)	0.97
Any target organ lesion; n (%)	29 (78)	105 (70)	0.29
Cure after parathyroidectomy; n (%)	37 (100)	149 (99)	0.48
Recurrence; n (%)	0	8 (5)	0.15

[†] Parathyroid hormone.
[‡] Calcifediol.
[§] Serum creatinine >1.11 mg/dl.
[#] Documented in osteodensitometry

the second, because familial cases of pHPT, in which parathyroid hyperplasia is a frequent cause of pHPT, were excluded.

The overall prevalence of target organ lesions was considerable, especially for nephrolithiasis, reaching 66.7% in the first years of the studied period (2000–2004) and declining to 40.7% in the latest (2014–2018). Similar rates

have been reported in other series [15,31,32]. At present, renal stones may be found in 25–55% of systematically screened patients [31].

Imaging studies, mostly ultrasound and parathyroid scintigraphy, were able to correctly locate the abnormal parathyroid glands in almost 90% cases. In a recent meta-analysis, sensitivity/specificity was 80/77% for ultrasound and 84/87% for scintigraphy [33]. Moreover, when used in combination, the two methods perform better than each does individually [34]. Parathyroid adenoma size is also an important factor when evaluating the accuracy of imaging studies; in our study, the largest diameter of adenoma was relatively high (21.4 ± 9 mm) and this was even higher in carcinomas (32.1 ± 20 mm).

Several types of malignancies have been described in association with pHPT [21]. In our study, the prevalence of malignancies (30.3%) was higher than reported in literature, which varies from 12 to 18% [19–21]. In a Swedish cohort including 9782 cases of surgically treated pHPT, an increased risk of kidney, intestinal and squamous cell skin cancer was observed in both genders, as well as of breast cancer in women [20]. Another study, conducted in Denmark, found an increased incidence of hematopoietic malignancies, particularly multiple myeloma, among 2425 patients with pHPT [19]. In our series, papillary thyroid carcinoma and breast cancer were the most frequently observed malignancies, with prevalence of 13.8 and 7.4%, respectively.

The association between pHPT and breast cancer has been previously reported in case series [35,36] and pHPT has been related to the risk of breast cancer in a cohort study in Sweden [37]. Moreover, Palmieri *et al.* reported breast cancer prevalence of 12.2% in pHPT patients [25]. In our series, most patients with breast carcinoma had been previously treated with radiotherapy and, although this is a known risk factor for pHPT, it probably does not solely account for the relatively high frequency of this malignancy in our study population. Notably, radiotherapy exposure did not seem to affect recurrence rates of pHPT, nor its severity.

Thyroid disease is a common finding in patients with pHPT [38,39]. The estimated incidence of papillary thyroid carcinoma in patients with pHPT is 2–4.3% [2,39]. In a retrospective study, the prevalence of thyroid cancer in patients with pHPT who had parathyroidectomy and thyroid surgery was 12.9%, similar to that found in our series [40]. The simultaneous presence of these two disorders, if not recognized, may complicate patient management, particularly surgical approach; hence, routine neck imaging to evaluate concurrent thyroid nodules in patients with pHPT has been proposed [39]. While the best approach is not yet defined in these cases, tailored management based on multidisciplinary team discussion should be warranted.

In this study, we have also found interesting differences in pHPT between males and females. Similar findings were previously reported in other studies, although not consistently [41,42]. Even though it is recognized that pHPT is more common in women, the 4:1 female-to-male ratio in our series is slightly higher than previously reported [41,43,44]. The causes for the gender difference in the incidence of pHPT are still not well known but may result, at least in part, from women's tendency to seek medical attention more often than men [45]. In fact, we have found that women were more frequently diagnosed with pHPT through routine laboratory tests than men. Interestingly, in an autopsy study [46], parathyroid adenomas and hyperplasia were found in approximately equal numbers of male and female subjects. In agreement with the observations by Mazeh *et al.* [41], in our series of male patients we observed higher concentrations of serum calcium, PTH and urinary calcium, as well as larger parathyroid adenomas than in females. However, this does not seem to have a negative effect on target organs, including renal stones, or on recurrence rates.

There are a few limitations to our study. The retrospective nature of the study and the relatively small number of patients from a single center may give rise to selection bias and some findings cannot be generalized to a wider population with pHPT. Moreover, as a significant amount of data was obtained from clinical records, some information was unavailable and therefore could not be included in the study.

Conclusion

This study describes a population with surgically treated pHPT in a cancer center. Cure and recurrence rates were, however, similar to those reported in nononcological hospitals. The gender differences in biochemical presentation of pHPT found in our series, and previously described in some but not all studies, are an interesting but still unexplained finding. The higher prevalence of associated malignancies in our series compared with other publications, particularly papillary thyroid carcinoma and breast carcinoma, may provide some insight into the relation between pHPT and these malignancies and would be worth investigating in larger series.

Summary points

- The connections between primary hyperparathyroidism and malignancy, for which common etiologic factors may exist, are still not completely understood.
- Our findings support the association between primary hyperparathyroidism and breast carcinoma, observed in previous studies.
- Radiotherapy exposure does not seem to influence the severity or the recurrence of primary hyperparathyroidism.
- Thyroid disease, particularly, papillary thyroid carcinoma, is frequently associated with primary hyperparathyroidism, which has important clinical implications.
- Gender differences in the presentation of primary hyperparathyroidism may exist, but do not seem to result in different outcomes.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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