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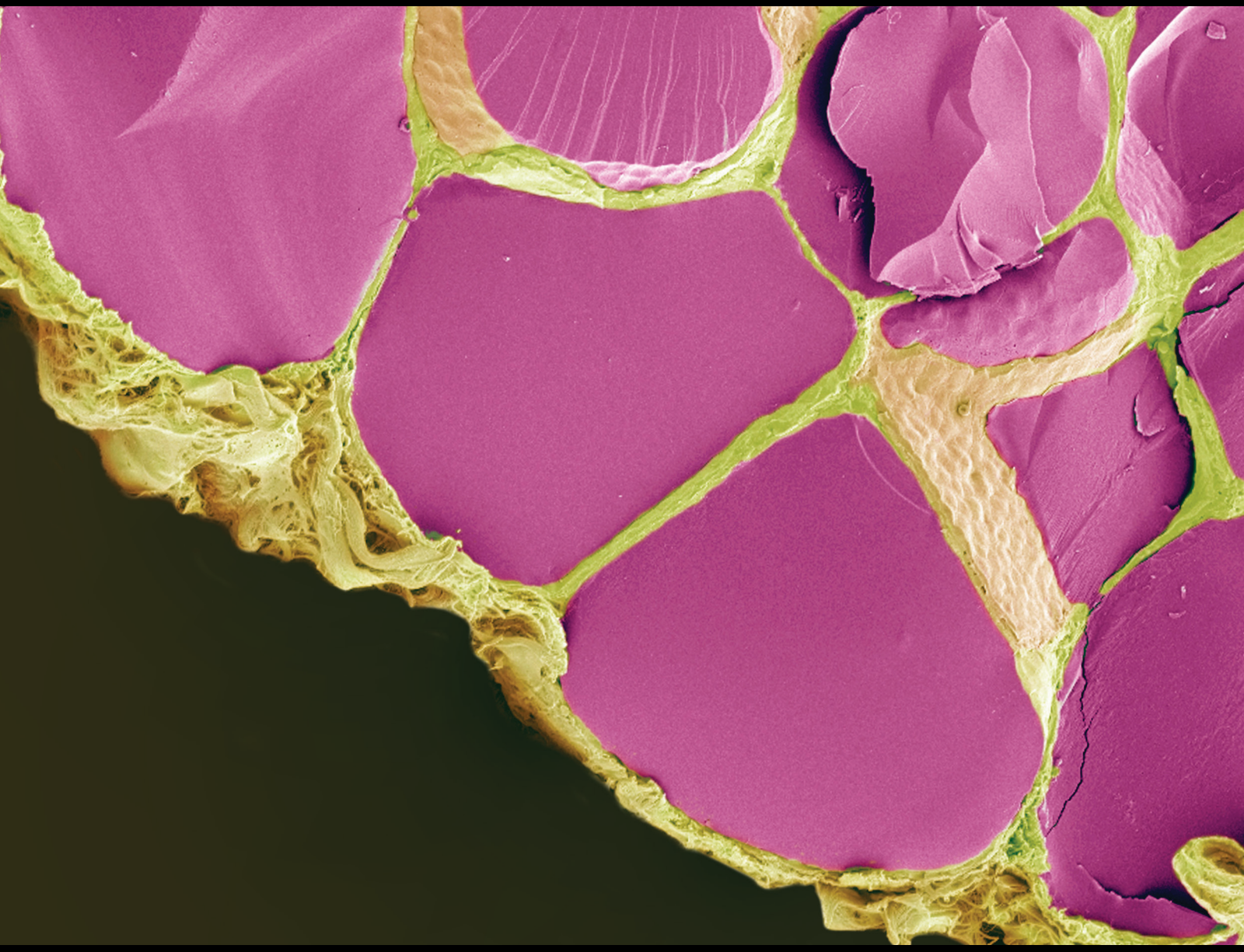
Primary Hyperparathyroidism: Diagnosis, Management, and Therapy 2021

Lead Guest Editor: Maria G. Chiofalo
Guest Editors: Giorgio Borretta, Filomena Cetani, and Loredana De Pasquale



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Research Article

Evaluation of Wisconsin and CaPTHUS Indices Usefulness for Predicting Monoglandular and Multiglandular Disease in Patients with Primary Hyperparathyroidism through the Analysis of a Single-Center Experience

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Background. The main challenge for treating primary hyperparathyroidism (PHPT) is to understand if it is caused by a single adenoma (80–85% of the cases) or by a multiglandular disease (15–20%), both preoperatively and intraoperatively. For this reason, some preoperative scores were proposed in the literature, to perform focused parathyroidectomy, avoiding intraoperative parathormone assay (ioPTH). The most known are the CaPTHUS test and the Wisconsin index. We applied them to our experience. *Methods*. A retrospective cohort study on 462 patients referred for parathyroidectomy to Thyroid and Parathyroid Unit at Santi Paolo e Carlo Hospital, Milan, Italy, from 2011 to 2021. Only patients affected with benign PHPT and neck ultrasound performed at our institution were included. Both patients for whom preoperative imaging agreed with the localization of a single diseased parathyroid and those with only ultrasound or scintigraphy positive for parathyroid localization underwent Mini-Invasive Video-assisted parathyroidectomy. In all cases, ioPTH assay was performed. The conversion to bilateral neck exploration was decided based on the drop in ioPTH. CaPTHUS score and the Wisconsin index (Win) were applied to the series. CaPTHUS score ≥3 and Win index >1600, according to the original studies of the literature, were considered at high probability of monoglandular disease. Outcomes in these two groups were examined. *Results*. 236 patients were eligible for the study. The pathology resulted in multiglandular disease in 24 patients (10.2%). Among these, 18 (75.0%) obtained a CaPTHUS score ≥3, and 20 (83.3%) had a Win index>1600. Intraoperative PTH allowed to identify multiglandular disease in 16 of 18 cases with CaPTHUS ≥3 and in 18 of 20 cases with win >1600, who could have been lost, based only on the results of these 2 tests. *Conclusion*. Based on our experience, CaPTHUS test and Wisconsin index were not so useful in predicting multiglandular disease as ioPTH.

1. Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine pathology with a prevalence of 1 per 1,000 in men and 2–3 per 1,000 in women [1]. PHPT is caused by a single-gland adenoma in 80–85% of the cases. In 15–20%, it is due to the involvement of more parathyroid glands, either in the form of hyperplasia of all glands or in the form of multiple adenomas [2]. Parathyroid carcinoma is rare and accounts for less than 1% of the cases [2]. The only definitive treatment for PHPT is surgical therapy [3]. The ability to correctly identify if the source of the gland's

hyperfunction is a single adenoma or a multiglandular disease is essential for the success of the surgical treatment. The traditional surgical approach involves the identification of all parathyroid glands through bilateral neck exploration (BNE), and the removal of the macroscopically pathological ones [4]. Due to the improvement of localization exams and the addition of intraoperative tests, such as intraoperative parathormone assay (ioPTH) [5], currently focused parathyroidectomy (FP) is the most used approach for the surgical treatment of PHPT. Indications for FP are the accurate preoperative localization of a single pathological gland by imaging investigations, no previous neck interventions, and the absence of associated thyroid pathologies. When performed, success rates comparable to those of the traditional approaches are achieved, while the risk of complications, postoperative pain, operative time, length of hospital stays, and hospital costs are all reduced [6–10]. To perform FP, it is important to verify whether all pathological tissues were removed or not. Intraoperative PTH has proven to be a reliable method in predicting the eradication of the disease [11]. However, ioPTH is not available in all centers, and it increases the cost of treatment and operating time [12, 13]. For these reasons, numerous studies have been conducted to identify a preoperative score that would allow surgeons to predict the presence of multiglandular disease, to establish the most suitable surgical approach. The most frequently examined were CaPTHUS score, described by Kebebew et al. in 2006 [14], and Wisconsin index (Win score), described by Mazeh et al. in 2013 [15]. The aim of our study is to verify the utility of these two preoperative scores in predicting single-gland disease, through the analysis of our center experience.

2. Materials and Methods

This is a retrospective cohort study on 462 consecutive adult patients referred for parathyroidectomy to the Thyroid and Parathyroid Unit at Santi Paolo *e* Carlo Hospital, Milan, Italy, from 2011 to 2021. All cases were retrieved from a Microsoft Access Database (Version 2001, Microsoft Corp, Redmond, WA, US), where patients are registered after discharge. Only patients with benign PHPT were included in the study. Exclusion criteria were as follows: persistent or relapsed primary hyperparathyroidism and follow-up of less than 6 months. The diagnosis of PHPT was made based on calcium, phosphorus, PTH and vitamin D 25-OH blood levels, and 24-hour urine calcium. All patients, after diagnosis, underwent neck ultrasound and ^{99}Tc-labeled sestamibi scintigraphy (MIBI). To eliminate a possible bias, since the accuracy of the ultrasound scans in locating a pathological parathyroid is linked to the expertise of the operator, in this study, we included only patients who underwent ultrasound by an experienced radiologist from our hospital. Both patients for whom preoperative imaging agreed on the localization of a single diseased parathyroid and those with only ultrasound or scintigraphy positive for parathyroid localization underwent parathyroidectomy with the Mini-Invasive Video-assisted Parathyroidectomy (MIVAP) technique; when ultrasound and scintigraphy were discordant, we based upon ultrasounds of the expert radiologist. In all cases, an intraoperative PTH assay was performed. The conversion of the procedure to the traditional bilateral cervical exploration was decided based on the drop in the ioPTH. In all patients, ioPTH was evaluated 10 minutes after parathyroidectomy, and if there was a drop in ioPTH values greater than 50% compared to the baseline (Vienna criteria), the surgery was considered concluded. When the drop in PTH 10 minutes after parathyroidectomy was less than 50%, a second sampling was performed to evaluate the possibility of late drop of the hormone. If the failure to the drop of PTH was confirmed, a traditional bilateral cervical exploration was carried out.

The following data were considered in the evaluation of patients: demographic data (age at surgery and sex), preoperative biochemical data (PTH, calcium, vitamin D, and urinary calcium), preoperative imaging (ultrasound and scintigraphy), ioPTH, histological outcomes, glands weight, and outcome of surgery (follow-up of at least 6 months). PTH values are expressed in pg/mL (normal range 8.7–79.6 pg/mL) and serum calcium values in mg/dL (normal range 8.4–10.2 mg/dL). Persistent hyperparathyroidism was defined as hypercalcemia that develops immediately after surgery or within 6 months of it. Recurrent hyperparathyroidism was defined as the development of hypercalcemia in a patient who was hypocalcemic or normocalcemic for at least 6 months after parathyroidectomy. Patients were followed up by reevaluating calcemia, PTH, and vitamin D-25-OH at 3 months, 6 months, and 1 year after surgery.

The CaPTHUS test and the Wisconsin index (Win) were applied to the series.

The CaPTHUS test is characterized by 5 conditions, each of which is assigned a score of 0 or of 1. The score is 1 if the condition is satisfied; otherwise, it is 0. The sum of each of these scores results in the value of the CaPTHUS score, which can range from a minimum of 0 to a maximum of 5. The conditions considered are described and shown in Table 1.

With a score of 5, the patient possesses all characteristics taken into consideration. With a minimum value of 0, the patient does not have any of the listed values. A CaPTHUS value ≥ 3 should be indicative of single-gland disease.

The Wisconsin index (Win score) takes into consideration the preoperative calcium and parathyroid hormone values, which must be multiplied to obtain the score. Patients are then divided into three classes: Win scores equal or greater than 1600, between 1600 and 800, and equal or less than 800. It is hypothesized that patients with multiglandular disease have significantly low win values. The Win score classes are shown in Table 2.

Sensitivity (Sn), specificity (Sp), positive predictive value (PPV), negative predictive value (VPN), and, finally, accuracy were evaluated for the proposed tests. In addition, confidence intervals (CI) were calculated. Specificity, sensitivity, positive and negative predictive values, and prevalence are expressed in percentages. Confidence intervals for specificity, sensitivity, and accuracy were calculated according to the Clopper–Pearson method.

Table 1: CaPTHUS score.

Total serum calcium	≥12 mg/dL
PTH	≥2 times then the upper limit
Ultrasound	Positive for one enlarged gland
Scintigraphy	Positive for one enlarged gland
Imaging (ultrasound + scintigraphy)	Concordance

Table 2: Win score (Ca x PTH).

≥1600	High
1600–800	Medium
≤800	Low

3. Results

Among the 462 patients, 236 were eligible for analysis. Among these, 184 were female (78.0%) and 52 men (22.0%), and the median age was 64 years (with a range 22–85, average of 61.4, and SD ± 12.3). Of these, 212 patients (89.8%) underwent MIVAP, and the remaining 24 patients (10.2%) underwent bilateral neck exploration. 13 patients also underwent a thyroidectomy during the same operating session.

For each patient, two localization imaging techniques were considered: ultrasound and ^{99}Tc-labeled sestamibi scintigraphy (MIBI).

All 236 patients underwent neck ultrasounds. It revealed only one enlarged gland in 205 cases (86.9%); in the remaining 31 (13.1%), it was not possible to identify any enlarged parathyroid.

All 236 patients underwent scintigraphy; 200 (84.7%) were found positive in locating a single hyperfunctioning gland, and the remaining 36 (15.3%) were negative.

Overall, 200 patients (84.7%) had concordant imaging, while, in 36 cases, ultrasound and scintigraphy did not indicate the same side (15.3%).

Clinical features of the patients are shown in Table 3.

The histological findings were divided as follows: single-gland disease in 212 patients (89.8%) and multiglandular in 24 (10.2%). In particular, the definitive diagnosis was as follows: single adenoma for 212 patients (89.8%), hyperplasia for 21 (8.9%), and double adenoma for 3 (1.3%). MEN1 was diagnosed in 3 patients with hyperplasia.

Patients treated for PHPT caused by parathyroid carcinoma (PC) were excluded, because they showed average calcium and PTH preoperative values higher than patients treated for benign PHPT. Moreover, they always had a preoperative concordant localization, since PC is generally a monoglandular disease, with a larger diameter than adenoma. All these aspects could have been a bias for the study, considering that all above-mentioned parameters are considered in calculating the CaPTHUS score and the Wisconsin index.

Histological features of all patients are shown in Table 4.

Overall, considering the 236 patients enrolled in the study, 6 had a relapse or persistence of disease (2.5%), with an intervention success rate of 97.5%, considering these selected series, which is comparable to 97.8% if we refer to all patients treated at our center for Primary Hyperparathyroidism, in the same period. Of these 6 patients, only the data relating to the first intervention were included for the study, and details about them are reported at the end of the results section.

All patients were followed up after surgery by reevaluating calcium, parathyroid hormone, and vitamin D-25-OH 3 months, 6 months, and 1 year after the intervention.

The patients were then divided into two groups: single-gland disease (adenoma) and multiglandular disease (hyperplasia and double adenoma).

The group of patients with single-gland disease consisted of 212 patients (89.8%); 166 (78.3%) were women, and 46 (21.7%) were men; the average age was 61.6 years.

The group of patients classified as multiglandular disease was made up of 24 subjects (10.2%), of which 18 are females (75.0%) and 6 are males (25.0%); in this group, the average age was 59.3 years. The values of calcemia and parathyroid hormone and, furthermore, the results of the diagnostic imaging are summarized in Table 5 (single-gland) and Table 6 (multiglandular).

Intraoperative PTH assay was performed for all patients. The sampling of peripheral blood was performed at the induction of anaesthesia and 10 minutes after the removal of the pathological parathyroid. Once the gland was removed, any manoeuvres were stopped for 10 minutes before sampling, to avoid artefacts due to local manipulation. The basal sample and the sample 10 minutes after the excision of the gland were sent to the central laboratory for the analysis of the parathyroid hormone. A reduction of more than 50% in parathyroid hormone values was considered as an indication of the success of the intervention. When the parathyroid hormone descent was not significant, a third sampling was performed. If the parathyroid hormone in the third sampling was nondescent, then it was considered indicative of multiglandular disease, and the intervention was converted into a bilateral exploration.

The average of the baseline PTH values was 289.04 ± 304.69; the median of the values was 205.85. For PTH values at 10 minutes, the mean was 55.34 ± 73.05 with a median of 35.55.

The CaPTHUS test was applied to the 236 patients, who entered the study and were then divided into 6 classes, shown in Table 7.

According to the original study of Kebebew, we divided the patients in two groups: patients with a CaPTHUS score ≥3 (highest probability of monoglandular disease) and patients with CaPTHUS score <3 (highest probability of multiglandular disease). For 201 (85.2%) patients, the CaPTHUS score ≥3. Among these, 18 patients had the definitive diagnosis of multiglandular disease. We identified 16/18 of these cases through ioPTH assay and missed the other 2. For 35 (14.8%) patients, the CaPTHUS score <3, with 35 cases of adenoma and 6 of multiglandular disease. Among these 6 cases, 4 were identified by ioPTH, while the other two were missed (Table 8).

Table 3: Clinical features of patients with PHPT ($n = 286$).

Clinical features	Value
Sex n (%)	
Female (F)	184 (78.0%)
Male (M)	52 (22.0%)
Age at surgery	
Mean ± SD	61.4 ± 12.3
Median (range)	64 (22–85)
Preoperative serum calcium (mg/dL)	
Mean ± SD	12.08 ± 1.31
Median (range)	11.9 (9.34–19.24)
Preoperative PTH	
Mean ± SD	311.4 ± 301.93
Median (range)	206.7 (71.4–1910.0)
Ultrasound	
Positive	205 (86.86%)
Negative	31 (13.14%)
Scintigraphy	
Positive	200 (84.7%)
Negative	36 (15.3%)
Concordant imaging	
Yes	200 (84.7%)
No	36 (15.3%)

Table 4: Definitive diagnosis and success of surgery.

Clinical feature	Value
Histological finding n (%)	
Single adenoma	212 (89.8%)
Double adenoma	3 (1.3%)
Hyperplasia	21 (8.9)
Parathyroid weight (mg)	
Mean ± SD	(i) 2011.5 ± 4463
Median (range)	(ii) 1000 (30–56000)
Multiglandular disease *n* (%)	24 (10.2%)
Single-gland disease *n* (%)	212 (89.8)
Persistence or relapse *n* (%)	6 (2.5%)

CaPTHUS score had a sensitivity of 13.68%, a specificity of 75.00%, a PPV of 82.86%, a NPV of 8.96%, and an accuracy of 19.92% (Table 9).

The Win test was applied to the 236 patients recruited, who were thus distributed in 3 classes: 179 (75.8%) patients in the class with a score >1600, 56 (23.8%) in the class with the score 800–1600, and 1 (0.4%) score <800 (Table 10).

Among 179 patients with Win index >1600, considered with high probability of monoglandular disease, according to the original study of Mazeh et al., 20 were multiglandular. Among these, 18/20 (90%) were diagnosed, thanks to ioPTH assay, while 2 were missed (Table 11).

The Win score had a sensitivity of 75.0%, a specificity of 16.7%, a PPV of 88.8%, a NPV of 7.1%, and an accuracy of 69.1% (Table 12).

4. Persistence/Relapse

Among 6 patients with persistence/recurrence of PHPT, 5 showed persistence at blood tests 3 three months after the intervention, and 1 patient developed relapse 8 months after

Table 5: Clinical features of patients with single-gland disease ($n = 212$).

Clinical features	Value
Sex n (%)	
Female (F)	166 (78.3%)
Male (M)	46 (21.7)
Age at surgery	
Mean ± SD	61.65 ± 12.40
Median (range)	64 (22–85)
Preoperative serum calcium (mg/dL)	
Mean ± SD	12,10 ± 1.25
Median (range)	11.97 (9.34–19.24)
Preoperative PTH	
Mean ± SD	304.80 ± 289.12
Median (range)	198.6 (71.4–1878)
Imaging N	
Positive ultrasound	195
Positive scintigraphy	180
Concordant imaging	189
Parathyroid weight (mg)	
Mean ± SD	1578.31 ± 2024.28
Median (range)	1000 (70–20000)

the intervention. This patient had a relapse after inferior left MIVAP, with significative ioPTH drop. This patient was a 62-year-old male, with CaPTHUS >3 and Win score 3. The histological diagnosis was adenoma. After the relapse, neck ultrasound and scintigraphy showed an enlarged inferior right gland. He underwent inferior right parathyroidectomy 12 months after the first intervention, with significative i.o. PTH drop. Histological diagnosis was of adenoma. He has normal serum calcium and PTH 60 months after the second intervention.

2 of the 5 patients with persistence underwent reintervention. 1 of these was a 60-year-old female with severe osteoporosis, CaPTHUS 1 and Win score >3. She had persistence three months after the removal of superior right, inferior right and superior left parathyroid, and thyroidectomy for goiter. Both calcium and PTH levels were in the range at when she was discharged from hospital. Histological diagnosis was hyperplasia of both parathyroid and thyroid. After the diagnosis of persistence neck ultrasounds was negative, scintigraphy was positive, with uptake in the left side of the neck. Because of severe osteoporosis, indication for reoperation was given. She underwent inferior left radioguided parathyroidectomy 9 months after the first intervention, with histological confirmation of hyperplasia. In the immediately postoperative period, she had normal values of PTH and calcium, despite the removal of 3 glands in the first intervention and 1 in the second. Then, a scintigraphy was performed without the evidence of further hyperfunctioning parathyroid tissue. A CT scan of neck and chest was negative for ectopic glands. The patient is in follow-up and 23 months after the reintervention has normal serum calcium and PTH at the upper level.

The other one who underwent reintervention, 6 months after the first operation, was a 32-year-old female with preoperative neck ultrasound and scintigraphy concordant in locating an enlarged inferior left parathyroid. She had

Table 6: Clinical features of patients with multiglandular disease ($n = 24$).

Clinical features	Value
Sex n (%)	
Female (F)	18 (75.0%)
Male (M)	6 (25.0%)
Age at surgery	
Mean ± SD	59.28 ± 11.37
Median (range)	660 (32–76)
Preoperative serum calcium (mg/dL)	
Mean ± SD	12.07 ± 1.82
Median (range)	11.55 (10.4–18.0)
Preoperative PTH	
Mean ± SD	369,77 ± 400.82
Median (range)	236 (99–1910)
Imaging N	
Positive ultrasound	10
Positive scintigraphy	20
Concordant imaging	11
Parathyroid weight (mg)	
Mean ± SD	5838.04 ± 12205.80
Median (range)	1500 (30–56000)

Table 7: CaPTHUS score.

CaPTHUS		Absolute frequency
CaPTHUS 0	Total	7 (2.96%)
	Multiglandular	2
	Single-gland	5
CaPTHUS 1	Total	13 (5.51%)
	Multiglandular	1
	Single-gland	12
CaPTHUS 2	Total	15 (6.35%)
	Multiglandular	3
	Single-gland	12
CaPTHUS 3	Total	58 (24.57)
	Multiglandular	5
	Single-gland	53
CaPTHUS 4	Total	82 (34.75)
	Multiglandular	9
	Single-gland	73
CaPTHUS 5	Total	61 (25.85%)
	Multiglandular	4
	Single-gland	57

Table 8: CaPTHUS score and ioPTH descent after excision of a single gland.

CaPTUS	Disease		ioPTH descent	
			>50%	<50%
0–2	Multiglandular	6	0	6
($n = 35$)	Single-gland	29	27	2
3–5	Multiglandular	18	2	16
($n = 201$)	Single-gland	183	180	3

CaPTHUS >3 and Win 3. At the first intervention, there was the confirmation of an enlarged inferior left gland. It was removed, without a significative ioPTH drop, with histological intraoperative diagnosis of "hypercellular parathyroid." At further exploration, the superior left gland was enlarged. It was removed with a significative ioPTH drop. For this reason, the right side was not explored. Histological definitive diagnosis was double adenoma (inferior and superior left). Calcium and PTH were normal for 3 months after the intervention, and then the patient showed a persistence. Imaging (ultrasounds, scintigraphy, and TC scan of neck and chest) was negative. Because of her age and symptoms, she underwent exploration of the right side of the neck, 6 months after the first intervention. The inferior right parathyroid was enlarged and behind the jugulum, while the superior is in the range of normality. Inferior right parathyroid was removed with significative ioPTH drop. The specimens of the two glands removed at first intervention and the inferior right gland were reviewed together by the same expert pathologist, with the diagnosis of hyperplasia on all the three removed glands. MEN1 was subsequently diagnosed. She has normal calcium and PTH values after 96 months.

Among the 3 patients who did not undergo reintervention, 1 is a 56-year-old woman with osteoporosis, CaPTHUS >3, and Win 3, who underwent inferior left MIVAP with significative ioPTH drop and histological diagnosis of inferior left adenoma. She showed persistence at blood tests 3 months after the intervention. The scintigraphy showed hyperfunctioning tissue in the mediastinum. A CT scan confirmed a lesion in the upper posterior mediastinum, compatible with an ectopic parathyroid gland. The patient refused reintervention.

For the other 2 patients, a 58-year-old male affected with AIDS and a 72 old-year-old female, it was decided to continue with the follow-up, in consideration of comorbidities for the male and the mild hyperparathyroidism for the female. Both showed the persistence 3 months after the intervention, had CaPTHUS >3 and a WIN score 3, and underwent bilateral neck exploration at first intervention, due to the failure of the ioPTH descent, with the removal of three glands and histological diagnosis of hyperplasia.

5. Discussion

Surgery still represents the best treatment for PHPT, compared to observation or medical therapy. It allows to cure the disease definitively, avoiding the possible side effects of drugs and the additional costs that would be necessary, due to the need of clinical follow-up and laboratory tests [16].

The traditional surgical approach involves the median cervicotomy with bilateral cervical exploration, visualization of all four parathyroid glands, removal of the macroscopically pathological one, and the biopsy of the smaller ones, subjected to extemporaneous histological examination [17].

Focused unilateral access involves a mini-cervicotomy with direct access to the pathological gland, identified by imaging and intraoperative dosing of PTH. This approach limits the surgical exploration to only one side in the presence of a single-gland disease, avoiding the devascularization of the nonpathological glands and reducing the risk

Table 9: CaPTHUS.

CaPTHUS	Single-gland		Multiglandular		Total
CaPTHUS 0–2	29		6		35
CaPTHUS 3–5	183		18		201
	212		24		236
	Sensitivity	Specificity	PPV	NPV	Accuracy
	13.68%	75.00%	82.86%	8.96%	19.92%
95% CI	9.36% to 19.05%	53.29% to 90.23%	69.09% to 91.27%	7.20% to 11.09%	15.02% to 25.59%

Table 10: Win index (Ca ∗ PTH).

>1600	Total	179 (75.8%)
	Multiglandular	20
	Single-gland	159
1600–800	Total	56 (23.8%)
	Multiglandular	4
	Single-gland	52
<800	Total	1 (0.4%)
	Multiglandular	0
	Single-gland	1

Table 11: Win score and ioPTH after excision of a single gland.

WIN	Disease		ioPTH descent	
			>50%	<50%
1	Multiglandular	0	0	0
($n = 1$)	Single-gland	1	1	0
2	Multiglandular	4	0	4
($n = 56$)	Single-gland	52	50	2
3	Multiglandular	20	2	18
(179)	Single-gland	159	157	2

Table 12: Win score.

Win	Single-gland		Multiglandular		Total
≥1600	159		20		179
<1600	53		4		57
Tot	212		24		236
	Sensitivity	Specificity	VPP	VPN	Accuracy
	75.00%	16.67%	88.83	7.02%	69.07%
95% CI	68.61% to 80.68%	4.74% to 37.38%	86.74% to 90.62%	2.91% to 15.98%	62.75% to 74.90%

of hypoparathyroidism. It also limits the exposure of the inferior laryngeal nerve to only one side, reduces the operating times, and allows a better aesthetic result, with less postoperative pain [18].

About the treatment, both the traditional and the focused technique had the same results, with a success rate of 98% of cases in highly specialized centers [6, 10], comparable to the 97.5% obtained at our institution. In our experience, the failure of surgery was due in 3 cases to a false drop of IOPTH. In one of these, the patient had the diagnosis of double adenoma, after the second intervention. This is a well-known cause of failure of ioPTH, which may be explained because one of the two adenomas would be more functioning than the other at the time of the first diagnosis. The second adenoma would start functioning within a variable period, only after the removal of the first [19]. A similar mechanism may explain the case of persistence for the patient who refused the reintervention, for whom an adenoma was removed in the neck and after three months showed a persistence. This was due to an ectopic gland, which emerged only after the removal of the gland in the neck. About the other cases of persistence, 1 was due to supernumerary glands, and 2 to an insufficient resection at first intervention. In both cases, the multiglandular disease was correctly diagnosed, and three glands were removed.

The introduction of minimally invasive methods has led to an increasing demand for focused parathyroidectomy in the surgical treatment of PHPT. This approach requires verifying the adequacy of the intervention, which is why the use of intraoperative dosage of PTH has begun since the end

of the 1990s [19]. Since this examination is not available in all centers, especially because of the additional costs, some authors have sought models that would allow the prediction of single-gland pathology, to use minimally invasive surgical procedures, even without having ioPTH available. In 2006, Kebebew et al. proposed the CaPTHUS test [14], which allows to combine biochemical and diagnostic imaging data, to select patients with a high probability of single-gland disease. The study proposed as cut-off score 3: according to this, only in case of a CaPTHUS score test <3, it was indicated to perform ioPTH. In these cases, the test provided a good estimate of the probability of multiglandular disease, with a precision of almost 100%. The original work [14], which proposes the CaPTHUS test, demonstrated the correlation between biochemical and diagnostic imaging tests and single-gland disease but presented some limitations. It was conducted by excluding all subjects who had not performed both imaging methods and considering as curing all patients who had normal calcium levels one week after surgery. The failure to evaluate patients after adequate follow-up did not allow to establish the actual healing of the subjects, classifying even those who have relapsed over time as single-gland diseases.

In 2015, Elfenben et al. [20] and, the following year, Mogollon-Gonzalez et al. [21] conducted two studies with the aim of validating the CaPTHUS score. The first [20] included, in the evaluation of CaPTHUS score, also patients who had undergone only scintigraphy or only neck ultrasound. In this way, with a score of ≥3, the PPV decreased to 91% in predicting single-gland disease. Moreover, without measuring ioPTH for patients with high CaPTHUS scores, the cure rate was 89% at 6 months, compared with 98% when the assay was performed. In the second study, Mogollon-Gonzalez et al. [21] chose a follow-up of at least six months but decided to include only patients who had performed both tests. In this case as well, the CaPTHUS test was found to be a model that even though it accurately predicts multiglandular disease, it does not allow to correctly classify 100% of patients, therefore allowing to reduce the use of ioPTH.

In our study, the pathology showed multiglandular disease in 24 patients (10.2%). Considering the CaPTHUS test, among these 24 patients, 13 (54.2%) had a CaPTHUS >3. If ioPTH had not been performed in patients with CaPTHUS >3, as suggested by Kebebew [14], 54.2% (13/24) of all patients affected with multiglandular disease, instead of 8.3% (2/24) obtained by performing ioPTH assay in this group, would not have been cured. We would have obtained an even worse result if we had used the Win Index: among 24 patients affected with multiglandular disease, 20 (83.3%) achieved a score ≥1600. If ioPTH had not been performed in these patients, 83.3% of all patients affected with multiglandular disease, instead of 8.3% by performing ioPTH, would have not been cured.

The Win score was proposed by Mazeh et al. in 2013 [15], aiming to predict multiglandular disease. It takes into consideration only the biochemical parameters, in particular calcium and parathyroid hormone, to classify patients: subjects with elevated calcium and parathyroid hormone are more likely to present a single-gland disease. In our case series, however, there was no correlation between the levels of calcium and PTH and the underlying disease of PHPT. Similarly, in the literature [15], the win score allows to predict the risk of multiglandular disease only in relation to the weight of the gland removed, although laboratory data alone is not a sufficient indication. In our series, which has the limit of being a retrospective study, the unsatisfactory results in predicting single-gland disease by two scores can be attributed to the fact that both the CaPTHUS test and the win score use the same biochemical data. Only 41.5% of patients had levels of Ca and PTH high enough to satisfy both parameters of the CaPTHUS test. This may be due also to the fact that, in the last years, we observed a change in the presentation of PHPT, from a clinical and biochemical point of view. Normocalcemic hyperparathyroidism with surgical indication is increasingly common [2, 22, 23]. In our series, by comparing the preoperative scores with ioPTH, it can be noticed that the models studied are not as effective in predicting the presence of multiglandular disease as intraoperative monitoring of PTH. Even when selecting subjects with a high score at CaPTHUS test (4 and 5 or only 5) and at Wisconsin index (>1600), the drop in intraoperative PTH has been more reliable, allowing to avoid a greater number of nondefinitive treatments.

6. Conclusion

Based on our experience, the CaPTHUS score and the Wisconsin Index have not been proved preoperatively so useful in distinguishing between mono- and multi-glandular disease, as ioPTH assay. Intraoperative tests confirmed their accuracy in predicting the adequacy of the intervention, and the patient has been cured. For this reason, in cases of a focused approach to parathyroid diseases, it is advisable to perform ioPTH dosage, regardless of the patients' preoperative characteristics.

Data Availability

All data were retrieved from a Microsoft Access Database (version 2001, Microsoft Corp, Redmond, WA, US), where patients are registered after discharge, and are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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Research Article

Management and Outcome of Parathyroid Carcinoma-Induced Primary Hyperparathyroidism: A Single-Centre Experience

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Background. Parathyroid carcinoma (PC) is the rarest endocrine cancer and an infrequent cause of primary hyperparathyroidism (PHPT), responsible for less than 1% of cases. Due to its rarity, treatment is challenging. *Methods*. A retrospective cohort study on 462 patients referred for parathyroidectomy to Thyroid and Parathyroid Unit at Santi Paolo e Carlo Hospital, Milan, Italy, from 2011 to 2021. We identified and individually described the patients affected with PC. Then, we split all patients treated for PHPT into four groups based on the cause: PC, adenoma, atypical adenoma, and hyperplasia. Patients' demographics, preoperative evaluation results, intraoperative findings, and outcomes for the PC group were compared with groups of PHPT due to benign causes. *Results*. Eight cases of PC were identified, five males and three females. Seven cases presented with symptoms of hypercalcemia and one with a neck mass. Five underwent en bloc resections and three local excisions. Histopathological features showed capsular invasion in four patients, capsular and soft tissue invasion in three patients, and vascular invasion in one case. No patients had distant metastasis. One patient was classed as high risk based on the Schulte classification system. All patients treated for PC were alive and disease-free at a mean follow-up of 38.4 months. When compared with other PHPT patients, PC patients were more frequently male and had higher preoperative blood calcium and PTH and lower phosphate levels, larger and heavier parathyroids excised, lower postoperative calcium, and a higher rate of postoperative hypoparathyroidism. *Conclusion*. Our study highlights some aspects valuable to suspect PC and differentiate PHPT-PC from benign causes of PHPT preoperatively. Preoperative suspicion of malignancy is essential to guarantee the best course of treatment for patients. Although limited for size and follow-up, the excellent outcome of our series seems to support the value of both surgery extension and risk class according to the Schulte classification as possible prognostic factors for recurrence.

1. Introduction

Parathyroid carcinoma (PC) is a rare malignancy, accounting for 0.005% of all cancers [1], the rarest endocrine cancer, as well as the rarest cause of primary hyperparathyroidism (PHPT). Less than 1% of PHPT cases are due to PC [2].

Most patients affected with this rare malignant tumour present with either sporadic primary hyperparathyroidism or primary hyperparathyroidism in the context of a genetic endocrine syndrome, namely, Multiple Endocrine Syndrome Type I (MEN I), Multiple Endocrine Syndrome Type II (MEN II), Hyperparathyroidism Jaw Tumour Syndrome (HPT/JT), and Familial Isolated Primary Hyperparathyroidism (FIHP) [3–5].

Only a few cases of PC have normal serum PTH levels [6–8].

Diagnosis is generally confirmed only after surgery by detailed pathological analysis unless there is preoperative evidence of gross local invasion, cervical lymph nodes, or distant metastases.

The surgical approach offers the best disease control rates, while there is no evidence supporting other PC management options.

Since this cancer is rare, a general consensus about the staging system and prognostic factors is lacking. Schulte proposed two types of classification based on histopathological criteria as good predictors of recurrence and survival [9].

This study aims to review our experience with 8 PC patients concerning diagnosis, treatment, and outcomes. In order to provide a more solid reference framework, we shall compare the demographics, preoperative status, complications, and postoperative status of these cases with those of a retrospective cohort of patients affected by primary hyperparathyroidism due to non-PC-related causes (typical and atypical parathyroid adenoma and parathyroid hyperplasia).

2. Materials and Methods

This retrospective cohort study is on 462 consecutive adult patients referred for parathyroidectomy to the Thyroid and Parathyroid Unit at Santi Paolo e Carlo Hospital, Milan, Italy, from 2011 to 2021, focusing on PC cases.

All cases were retrieved from a Microsoft Access Database (Version 2001, Microsoft Corp, Redmond, WA, US), where patients are registered after discharge. This database contains the following information for each patient: sex, age at surgery, clinical presentation, preoperative calcium, parathormone (PTH), vitamin D 25-OH, phosphorus, creatinine, calciuria, preoperative instrumental examinations, description of surgical intervention, intraoperative PTH, pathological description, weight and diameter of the excised glands, postoperative complications, and follow-up.

All patients underwent both neck ultrasound and 99Tc-labeled sestamibi scintigraphy (MIBI) before surgery. Further imaging was performed only in selected cases: patients referred to us for persistent PHPT after previous neck interventions or suspicion of PC with local invasion. No patient underwent fine needle aspiration (FNA). Calcium is expressed in mg/dL (normal range 8.4–10.2 mg/dL), PTH in pg/mL (normal range 8.7–79.6 pg/mL), phosphate in mg/dL (range 2.5–4.5 mg/dL), vitamin D 25-OH in ng/mL (normal range 30–100 ng/mL), creatinine in mg/dL (range 0.84–1.21), and 24-hour calciuria in mg/kg/24 h (normal value < 4 mg/kg/24 h).

The same experienced endocrine surgeon performed all surgical procedures, and surgical samples—both intraoperative and definitive—were analysed every time by the same pathologist, who has in-depth expertise in parathyroid pathologies. The PC diagnosis was based on (i) the presence of invasive growth involving adjacent structures, such as thyroid and soft tissue, (ii) capsular and/or extracapsular blood vessels or perineural spaces, (iii) and/or documented metastases, based on 2017 WHO criteria.

All patients were classified into two different risk classes, according to Schulte: low risk (capsular and adjacent soft tissue invasion) and high risk (vascular and vital organ invasion).

Postoperative hypocalcemia was considered as a serum calcium value lower than 8.4 mg/dL, with normal PTH. Postoperative hypoparathyroidism was considered serum PTH lower than 8.7 pg/mL and with a calcium value lower than 8.4 mg/dL. Both complications were deemed transient if lasting less than six months and definitive if lasting longer. Hungry Bone Syndrome (HBS) was defined as the need for oral calcium supplementation, with normal PTH levels, due to bone resorption.

All patients underwent postoperative laryngoscopy. Inferior Laryngeal Nerve Palsy (ILNP) was defined as transient or definitive, depending on whether it persisted for less or more than six months, respectively. All patients were monitored by an expert endocrine oncologist, with blood and instrumental tests every three months in the first year and every six months afterwards. We considered patients with adequate PTH and calcium serum levels to be cured.

First, we summarised data and outcomes descriptively for every patient affected with PC.

Then, based on the cause of PHPT, we split the patients into four groups: PC, typical adenoma, atypical adenoma, and hyperplasia.

The data that support the findings of this study are available from a Microsoft Access Database (Version 2001, Microsoft Corp, Redmond, WA, US), upon request to the corresponding author.

2.1. Statistical Analysis. We performed a statistical analysis on the data collected to compare patients' demographics, preoperative evaluation results, intraoperative findings, and outcomes among the four study groups.

The Chi-square test was used to assess differences in binomial variables in the four groups. The binomial variables compared were sex distribution, preoperative imaging concordance, overall complication rate, postoperative hypoparathyroidism rate, postoperative haemorrhage rate, recurrent laryngeal nerve lesion rate, and hungry bone syndrome rate.

The Kruskal–Wallis test was used to assess the differences in all other parameters in the four groups. The parameters evaluated via the Kruskal–Wallis test were age at surgery, preoperative blood calcium, preoperative blood phosphate, preoperative blood PTH, preoperative blood creatinine, greatest excised gland weight and diameter, postoperative blood calcium on postoperative days 1 and 2 (POD 1 and 2), and postoperative blood PTH.

All statistical analyses were performed using the SPSS software (PASW Statistics for Windows, version 21.0; SPSS Inc., Chicago, IL). Values of $p < 0.05$ were deemed to be statistically significant.

3. Results

Four hundred sixty-two patients underwent surgery for parathyroid diseases: 419 (90.7%) for primary, 39 (8.4%) for secondary, and 4 (0.9%) for tertiary hyperparathyroidism. We excluded patients with secondary and tertiary HPT. Out of the 419 cases operated on for PHPT, 8 (1.9%) were affected with PC and 411 (98.1%) with benign parathyroid diseases: 330 (78.8%) had a histological diagnosis of adenoma (A), 55 (13.1%) of hyperplasia (H), and 26 (6.2%) of atypical adenoma (AA) (Table 1).

3.1. Clinical Presentation of PC. The eight patients affected with PC were five males and three females, with a mean age of 57.8 years (range 28–78 years). They all had a preoperative diagnosis of PHPT via blood tests.

Patient 1: a 38 y.o. male with a long history of kidney stones

Patient 2: a 73 y.o. male admitted to the Emergency Department for mental confusion with evidence of severe, life-threatening hypercalcemia of 18.0 mg/dL and acute renal failure; he was already known for persistent PHPT after two neck explorations at another hospital

Patient 3: a 74 y.o. female affected with severe osteoporosis

Patient 4: a 50 y.o. female with a neck mass initially interpreted as a thyroid nodule

Patient 5: a 45 y.o. female with leg muscle weakness and tibial and peroneal lesions with suspicious metastasis

Patient 6: a 78 y.o. male admitted to the Emergency Department with mental confusion and evidence of severe life-threatening hypercalcemia of 19.3 mg/dL and acute renal failure

Patient 7: a 76 y.o. male with depression and cognitive decline

Patient 8: a 28 y.o. male with a long history of kidney stones, previous resection of right-hand sarcoma, and partial kidney resection for carcinoma

Median preoperative levels were calcium 13,7 mg/dL (range 12,5–19,3), PTH 736,9 (205.0–4349.0), and phosphorus 2,1 ± 0,425 (0,6–3,3).

A neck ultrasound and a MIBI scintigraphy were performed in all eight cases, which showed evidence of a single enlarged parathyroid gland. In all cases, the two types of imaging confirmed that the lesion was on the same side. Three patients (patients 2, 5, and 6) underwent a CT scan for suspicious PC with adjacent organ invasion—not confirmed in 2 cases—while in 1 (patient 6), the CT scan indicated suspicious oesophagus infiltration. A transoesophageal ultrasound endoscopy ruled out this suspicion. The mean preoperative diameter of the lesion from the neck ultrasound was 25,8 mm (range 15,0–36,0).

3.2. Treatment. All eight patients underwent surgery: 2 mini-invasive video-assisted inferior left parathyroidectomies (MIVAP) (patients 1 and 3); 1 MIVAP converted to traditional neck exploration with the removal of three parathyroid glands for intraoperative detection of multiple gland disease (patient 7).

In 5 cases (patients 2, 4, 5, 6, and 8), an enlarged right inferior parathyroid gland was excised en bloc with the ipsilateral thyroid lobe and the superior parathyroid. In these cases, a strong suspicion for PC arose preoperatively based on the excessively high serum calcium and PTH levels, coupled with the large US diameter of the affected gland. In this group of 5 patients, 3 underwent central node dissection and 2 contralateral thyroid lobe excisions: patient 4 had multinodular goitre, and patient 8 had a histological diagnosis of clinically unsuspected papillary carcinoma of the resected right lobe and radicalisation was advised.

In all cases, intraoperative PTH (IOPTH) dosage was performed, considering significant drop of 50% in PTH value ten minutes after parathyroid excision compared to the preincision value.

In patient 4, who underwent total thyroidectomy as part of the same procedure, IOPTH was measured 10 minutes after en bloc resection of the right side and before commencing surgery on the left side.

Among three patients with no preoperative suspicion of PC, patient 1 underwent reintervention after pathological diagnosis. It consisted of ipsilateral lobectomy and VI-level lymph node removal 45 days from the initial intervention. The other two patients (patients 3 and 7) were not reoperated, one for refusal (patient 3) and the other (patient 7) for comorbidities (Table 2).

3.3. Outcomes. In all cases, the tumour was removed entirely without capsular rupture, and there was no evidence of resection margin invasion.

In 7 cases, we observed a significant IOPTH drop, with a mean drop of 92.3% (range 86.8–99.1%). In 1 case (patient 7), IOPTH did not decrease after MIVAP excision of the enlarged inferior left parathyroid, based on preoperative localisation. Traditional neck exploration showed significantly enlarged inferior right and minimally enlarged superior left parathyroids, not described by the preoperative ultrasound.

In 5 cases, the PTH value was lower than normal on the first postoperative day (cases 1, 3, 4, 6, and 7). Of these patients, 1 underwent total thyroidectomy (case 4) and 1 subtotal parathyroidectomy (case 7). The other 3 patients showed normal PTH levels on day one (patients 2, 5, and 8), with a mean value of 15.3 pg/mL (range 3.4–42.8).

In 4 cases, first postoperative day calcium values were higher than normal (patients 2, 5, 6, and 8), while they were within the range in the other 4 cases (patients 1, 3, 4, and 7), with a mean value of 10.1 mg/dL (range 8.1–12). In all cases, calcaemia reached the lowest value on the third postoperative day, with a mean value of 8.4 mg/dL (range 7.6–9.2).

Table 1: Causes of PHPT in our series.

Benign				Uncertain		Malignant		Total	
Adenoma		Hyperplasia		Atypical adenoma		Carcinoma			
330	78.8%	55	13.1%	26	6.2%	8	1.9%	419	100%

Seven cases developed transient hypocalcemia (patients 2, 3, 4, 5, 6, 7, and 8)—4 with associated transient hypoparathyroidism (patients 3, 4, 6, and 7), which became definitive in 1 case (patient 7). Three cases developed hungry bone syndrome (patients 5, 6, and 8).

One transient ILNP (patient 6) and one definitive ILNP (case 5) were observed, the latter one due to intraoperative findings of nerve involvement, which was not suspected preoperatively because the preoperative laryngoscopy showed normal motility of the vocal cords (Table 3).

Pathological examination showed capsular and soft tissue invasion in 3 cases (patients 2, 7, and 8), only capsular invasion in 4 (patients 1, 3, 4, and 6), and capsular, soft tissue, and vascular invasion in 1 (patient 5). 5 patients presented mitosis (patients 1, 2, 3, 4, and 8), with mean mitosis/HPF 3 (range 1–5). Ki67 label index was present in 7 patients (cases 1, 2, 4, 5, 6, 7, and 8) and was higher in the two younger patients (cases 1 and 8). All had fibrous bands.

Patient 7, who underwent the removal of three glands, was diagnosed with carcinoma of the inferior right parathyroid (diameter 1.3 cm, weight 2,930 mg) and hyperplasia of the inferior left parathyroid (diameter 2.5 cm, weight 1,630) and the superior left parathyroid (diameter 0.6 cm, weight 30 mg).

Parathyroid weight could only be ascertained for 3 patients (cases 1, 3, and 7) because the thyroid lobe and the parathyroid carcinoma were weighed together in the five en bloc resections. Median weight was 2,415 mg (range 1,850.0–2,930.0). Median histological diameter was 2,3 cm (range 1,3–3,6).

In all cases, histological examination confirmed that the tumour did not involve resection margins. All cases were metastasis-free. The patient with tibia and fibula lesions had a diagnosis of "brown tumours."

Patient 8 underwent genetic tests because of suspicious HPT/JT syndrome due to previous sarcoma and kidney carcinoma: CDC73, AIP, CDKN1B, GNAS, HRAS, MEN1, NF1, VHL, MAX, GPR101, PRKAR1a, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, TMEM127, EPAS1. All tests were negative for mutations.

Based on the Schulte classification, only one patient was high risk, presenting vascular and recurrent laryngeal nerve invasion: pT4N0M0 (patient 5). All other patients were low risk, presenting only capsular and soft tissue invasion: 3 pT1NxM0 (patients 1, 3, and 7), 1 pT1N0M0 (patient 4), two pT2N0M0 (patients 6 and 8), and 1 pT2NxM0 (patient 2).

At a mean follow-up of 38.4 months (range 13–109), all patients were alive and had no recurrence evidence. All patients had normal calcium and PTH levels, with a mean value of 9.3 mg/dL (range 8.5–10.4) and 34.7 pg/mL (range 6.3–88), respectively, and negative neck ultrasound (Table 4).

3.4. Comparison between PC and Other Causes of PHPT. Compared with other PHPT patients, PC patients were more frequently male, had higher preoperative blood calcium and PTH and lower phosphate, had larger and heavier parathyroids excised, had lower postoperative calcium levels, and showed a higher rate of postoperative hypoparathyroidism (Table 5).

The Chi-square test showed statistically significant differences between the 4 groups in terms of sex distribution (p 0.012), overall complication rate (p 0.007), and postoperative hypoparathyroidism rate ($p < 0.001$). There was no statistically significant difference in terms of concordant preoperative imaging rate (p 0.168), postoperative haemorrhage rate (p 0.573), recurrent laryngeal nerve lesion rate (p 0.48), and hungry bone syndrome rate (p 0.671).

The Kruskal–Wallis test showed statistically significant differences in terms of preoperative blood calcium ($p < 0.001$), preoperative blood phosphate (p 0.015), preoperative blood PTH ($p < 0.001$), greatest excised gland weight and diameter (respectively, $p < 0.001$ and 0.007), and postoperative blood calcium on POD 1 (p 0.033). There was no statistically significant difference in terms of age at surgery (p 0.429), preoperative blood creatinine (p 0.313), postoperative blood calcium on POD 2 (p 0.894), and postoperative blood PTH (p 0.128) (Table 5).

4. Discussion

PC is a rare carcinoma and an infrequent cause of PHPT. The incidence of PC as a primary cause of PHPT is around 1%, ranging from 0.2 to 5.0% in the literature [10–16], 1.9% in our series.

Typically, patients affected with PC present with symptoms and complications of PHPT, such as bone and kidney disease, depression, anxiety, weakness, and gastroenteric symptoms (abdominal pain, nausea, vomiting, pancreatitis, and peptic ulcer). At presentation, 50% of patients show renal and bone manifestations, with different degrees of severity, osteopenia, osteoporosis, osteofibrosis, osteitis fibrosa cystica, and pathologic fractures [1, 10, 17, 18]. Some may present with hypercalcemic crisis [19, 20], 2 in our cohort.

About 10% of cases of PC are not functioning [6–8]. Because of the absence of PTH secretion, they usually present at a more advanced stage, with symptoms of local and adjacent structure invasion [7, 8, 21–23], hoarseness, and/or dyspnea and/or neck mass.

Completely asymptomatic PC has been described [11, 24–26]. In our cohort, seven patients presented with symptoms, which led to PHPT diagnosis, and 1 with a neck mass.

Table 2: Clinical data and treatment of 8 patients affected with PC.

No.	Sex	Age	Clinical presentation	Preoperative calcium	Preoperative PTH	Preoperative localisation	Ultrasound diameter (mm)	Sestamibi scan	Suspicion of PC	Operation	IOPTH decrease (%)
1	M	38	Kidney stones	12.5	289.0	Yes	15.0	+	No	MIVAP	94.8
2	M	73	Mental confusion—acute renal failure	18.0	2160.0	Yes	36.0	+	Yes	En bloc resection	99.1
3	F	74	Osteoporosis	12.7	391.1	Yes	14.0	+	No	MIVAP	86.8
4	F	50	Neck mass	13.2	1055.0	Yes	28.0	+	Yes	En bloc resection	90.7
5	F	45	Tibial and peroneal lesions suspected of metastasis	13.7	4349.0	Yes	30.0	+	Yes	En bloc resection	92.0
6	M	78	Mental confusion—acute renal failure	19.3	2146.0	Yes	31	+	Yes	En bloc resection	91.0
7	M	76	Depression—cognitive decline	12.5	205	Yes	Not found	−	No	Subtotal parathyroidectomy	—
8	M	28	Kidney stones	13.9	772	Yes	23	+	Yes	En bloc resection	92.3

Table 3: Postoperative complications of 8 patients affected with PC.

No.	Transient hypoparathyroidism	Definitive hypoparathyroidism	Transient hypocalcemia	Definitive hypocalcemia	Hungry bone syndrome	Transient recurrent laryngeal nerve palsy	Definitive recurrent laryngeal nerve palsy
1	Yes	No	No	No	No	No	No
2	No	No	Yes	No	No	No	No
3	Yes	No	Yes	No	No	No	No
4	Yes	No	Yes	No	No	No	No
5	No	No	Yes	No	Yes	Yes	Yes
6	Yes	No	Yes	No	Yes	Yes	No
7	Yes	Yes	Yes	Yes	No	No	No
8	No	No	Yes	No	Yes	No	No

Table 4: Pathological results, risk class, and outcomes of 8 patients affected with PC.

No.	Histologic diameter (mm)	Weight (mg)	Ki67 (%)	Mithosis/ HPF	TNM	Risk	Follow-up (months)	Outcomes	Persistence	Recurrence	Death
1	15	1760	20	4	PT1NXM0	Low	109	Cured	No	No	No
2	36	—	3	2	pT2NxM0	Low	68	Cured	No	No	No
3	18	1850	1	5	pT1NxM0	Low	54	Cured	No	No	No
4	28	—	1	1	pT1N0M0	Low	18	Cured	No	No	No
5	30	—	2	0	pT4N0M0	High	16	Cured	No	No	No
6	32	—	2	0	pT2N0Mo	Low	15	Cured	No	No	No
7	13	2930	2	0	pT1NxM0	Low	14	Cured	No	No	No
8	21	—	30	3	pT2N0M0	Low	13	Cured	No	No	No

Table 5: Patients' characteristics according to final histology.

	Hyperplasia		Adenoma		Atypical adenoma		Carcinoma		Whole sample	
	Demographics, comorbidities, and preoperative evaluations									
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Sex distribution	18 (33%)	37 (67%)	70 (22%)	246 (78%)	9 (35%)	17 (65%)	5 (63%)	3 (38%)	102 (25%)	303 (75%)
Age (years)	58 ± 16,5 (29–79)		62 ± 16,25 (22–85)		65 ± 26 (20–85)		61,5 ± 32,5 (28–78)		62 ± 17 (20–85)	
Hyperparathyroidism symptoms	14 (25%)	41 (75%)	86 (27%)	230 (73%)	8 (31%)	18 (69%)	2 (25%)	6 (75%)	110 (27,16%)	295 (73%)
Hypertension	0 (0%)	55 (100%)	9 (3%)	307 (97%)	0 (0%)	26 (100%)	0 (0%)	8 (100%)	9 (2,22%)	396 (98%)
Kidney failure	21 (38%)	34 (62%)	100 (32%)	216 (68%)	11 (42%)	15 (58%)	2 (25%)	6 (75%)	134 (33,09%)	271 (67%)
Bone symptoms	13 (24%)	42 (76%)	77 (24%)	239 (76%)	4 (15%)	22 (85%)	1 (13%)	7 (88%)	95 (23,46%)	310 (77%)
Neurological symptoms	0 (0%)	55 (100%)	27 (9%)	289 (91%)	3 (12%)	23 (88%)	2 (25%)	6 (75%)	32 (7,9%)	373 (92%)
Thyroid	6 (11%)	49 (89%)	48 (15%)	268 (85%)	4 (15%)	22 (85%)	2 (25%)	6 (75%)	60 (14,81%)	345 (85%)
Gastrointestinal symptoms	3 (5%)	52 (95%)	23 (7%)	293 (93%)	0 (0%)	26 (100%)	0 (0%)	8 (100%)	26 (6,42%)	379 (94%)
Systemic symptoms	3 (5%)	52(95%)	24 (8%)	292 (92%)	1 (4%)	25 (96%)	0 (0%)	8 (100%)	28 (6,91%)	377 (93%)
Other symptoms	13 (24%)	42 (76%)	45 (14%)	271 (86%)	2 (8%)	24 (92%)	1 (13%)	7 (88%)	61 (15,6%)	344 (85%)
Concordant preoperative imaging	25 (45%)	30 (55%)	184 (58%)	132 (42%)	20 (77%)	6 (23%)	5 (63%)	3 (38%)	234 (58%)	171 (42%)
Preoperative serum Ca (mg)	11 ± 1,135 (9,3–18)		11,3 ± 0,8 (8,9–1213)		12,15 ± 0,975 (10,3–14,8)		13,705 ± 2,5375 (12,5–19,29)		11,3 ± 1,29 (8,9–1213)	
Preoperative serum P (mg)	2,7 ± 0,4 (1,8–3,7)		2,5 ± 0,4225 (0,76–4,5)		2,45 ± 0,675 (1,6–3,9)		2,1 ± 0,425 (0,6–3,3)		2,5 ± 0,5 (0,6–4,5)	
Preoperative serum PTH (mg)	157,15 ± 151,55 (70–2000)		181 ± 156,9 (10–1878)		408,4 ± 283,95 (112–1514)		736,95 ± 1271,25 (205–4349)		183 ± 197 (10–2160)	

Table 5: Continued.

	Hyperplasia	Adenoma	Atypical adenoma	Carcinoma	Whole sample
Preoperative serum creatinine (mg)	0,8 ± 0,18 (0,59–2,4)	0,8 ± 0,2 (0,42–3,85)	0,8 ± 0,4 (0,59–2,2)	0,9 ± 0,375 (0,6–2,68)	0,9 ± 0,2 (0,42–3,85)
Intra- and postoperative evaluations					
Greatest excised gland weight (mg)	570 ± 1745 (30–30000)	800 ± 1062,38 (6–32000)	1700 ± 2126 (60–9000)	2415 ± 257,5 (1760–2930)	845 ± 1072,38 (6–32000)
Greatest excised gland diameter (cm)	2 ± 0 (1,2–27)	1,5 ± 0,2 (0,008–5,5)	2,3 ± 1 (0,7–5)	2,05 ± 0,775 (1,5–3,6)	1,7 ± 0,2 (0,008–27)
Intraoperative serum PTH (mg)	177 ± 117,7 (48–2733)	175,5 ± 116,6 (2–1550)	433,6 ± 569,85 (107,3–1486)	759,75 ± 701,925 (250–2257)	190 ± 144 (2–2733)
One-day postoperative serum PTH (mg)	72,6 ± 55 (9–640,6)	36 ± 27,5 (2–350)	38 ± 62,85 (11,1–151)	69,5 ± 116,85 (16,6–250)	38 ± 32,6775 (2–640,6)
One-day postoperative serum Ca (mg)	9,185 ± 1,5 (7,4–12,7)	9,1 ± 0,9675 (6,79–13,3)	9,4 ± 1,075 (8,3–11,5)	10,25 ± 0,975 (8,1–12)	9,17 ± 1 (6,79–13,3)
Two-day postoperative serum Ca (mg)	8,74 ± 1,02 (7–11,4)	8,7 ± 0,625 (6,98–13,9)	8,55 ± 0,775 (7,5–10)	8,95 ± 0,55 (7,6–9,7)	8,7 ± 0,71 (6,98–13,9)
Postoperative serum PTH (mg)	18,85 ± 24,765 (3,6–400)	20,2 ± 20,09 (1–581)	16,3 ± 16,05 (5,9–75,1)	10 ± 11,075 (3,4–42,8)	19,2 ± 21,2 (1–581)
Complications and recurrences					

	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Surgical complications	18 (33%)	37 (67%)	81 (26%)	235 (74%)	12 (46%)	14 (54%)	5 (63%)	3 (38%)	116 (29%)	289 (71%)
Transient hypoparathyroidism	8 (15%)	47 (85%)	26 (8%)	290 (92%)	6 (23%)	22 (85%)	4 (50%)	4 (50%)	44 (11%)	361 (89%)
Definitive hypoparathyroidism	2 (4%)	53 (96%)	1 (0%)	315 (100%)	0 (0%)	26 (100%)	0 (0%)	8 (100%)	3 (1%)	402 (99%)
Haemorrhage	0 (0%)	55 (100%)	8 (3%)	308 (97%)	1 (4%)	25 (96%)	0 (0%)	8 (100%)	9 (2%)	396 (98%)
Transient recurrent laryngeal nerve lesions	1 (2%)	54 (98%)	9 (3%)	307 (97%)	1 (4%)	25 (96%)	0 (0%)	8 (100%)	11 (3%)	394 (97%)
Definitive recurrent laryngeal nerve lesions	2 (4%)	53 (96%)	6 (2%)	310 (98%)	0 (0%)	26 (100%)	1 (13%)	7 (88%)	9 (2%)	396 (98%)
Hungry bone syndrome	2 (4%)	53 (96%)	21 (7%)	295 (93%)	2 (8%)	24 (92%)	1 (13%)	7 (88%)	26 (6%)	379 (94%)
Hyperparathyroidism persistence	6 (11%)	49 (89%)	3 (1%)	313 (99%)	0 (0%)	26 (100%)	0 (0%)	8 (100%)	9 (2%)	396 (98%)
Hyperparathyroidism recurrence	1 (2%)	54 (98%)	3 (1%)	313 (99%)	0 (0%)	26 (100%)	0 (0%)	8 (100%)	4 (1%)	401 (99%)

According to other studies, preoperative calcium and PTH values were significantly higher, while phosphate levels were lower than in benign PHPT [3, 5, 24, 27–29]. However, the criteria to define a threshold of malignancy is still under debate.

In our cohort imaging, ultrasound scans and MIBI scintigraphy proved useful in localising the lesion, in that they always identified the same diseased gland, but they did not distinguish between benign and malignant lesions. Only in one case was there the suspicion of extracapsular extension of parathyroid lesion, which CT scan confirmed. In such situations, characterised by an invasion of the surrounding structures, ultrasound scans may anticipate malignancy, as well as in cases of enlarged lymph nodes and/or very enlarged parathyroids: a diameter >3 cm has been reported as suspicious for PC [30–32]. CT and MRI may be useful in PC with the invasion of surrounding tissue and adjacent organs or distant metastases [32, 33].

We had never performed fine needle aspiration on parathyroids, especially when we suspected PC. Fine needle aspiration on parathyroid glands should not be performed preoperatively to prevent capsular rupture and tumour dissemination along the needle tract and the related risk of recurrence [33–36].

Considering the above, the challenge for clinicians is to differentiate between PC-induced PHPT and PHPT due to benign diseases. This issue is the key to guaranteeing the best course of treatment for patients: complete tumour resection with microscopically negative margins and intact tumour capsule, at first intervention, is the best chance of cure.

En bloc resection is the gold-standard treatment. It consists of removing the parathyroid tumour, the surrounding soft tissue, the ipsilateral thyroid lobe, the VI-level lymph nodes, and the adjacent structures (if involved by the carcinoma), avoiding the spillage of tumour cells into the surgical field [33, 37, 38]. En bloc resection seems to reduce the risk of recurrence, compared to simple excision of the diseased parathyroid (8% for the former against 51% for the latter) [39].

However, as PC diagnosis often takes place after surgery, local excision of the affected gland along the border of the peritumoral capsule is the most often performed first-line surgical procedure [40–44]. According to some authors, the prognosis of these patients may improve in terms of local recurrence, with additional surgery consisting of en bloc resection of the ipsilateral thyroid lobe and the central compartment lymph nodes within one month [33, 38, 41, 45]. However, the benefits of reintervention are not clear for patients with local extracapsular excision, and other authors suggest close follow-up for them [21, 44, 46].

There are conflicting views regarding the extent of the intervention as an important predictor of recurrence and death. In some studies, local excision of PC showed to be an adverse prognostic factor compared with more extensive resections [9, 41, 47]. According to other authors, there is no link between radical excision and improved survival [21, 44].

In our cohort, based on the clinical presentation of PHPT, particularly with very high preoperative levels of calcium and PTH and large gland size at imaging, we suspected PC in 5 out of 8 cases (62.5%). This diagnosis led us to performing en bloc resection in all these cases, and pathology confirmed the diagnosis. In the remaining 3 cases, no preoperative elements led us to suspect PC, and simple local excision was the choice. There was no suspicion of malignancy during the intervention in any of these 3 cases since the pathological glands were easily cleaved from the surrounding tissue and were smaller than 2 cm.

In addition to preoperative features, the intraoperative presentation may lead to suspecting malignancy, first, the diameter of the lesion. Many authors cite a median maximum PC diameter ranging from 3.0 and 3.5 cm to be larger than that of simple parathyroid adenoma [1, 14, 48, 49]: our cohort confirms this statement.

PC usually consists of lobulate, solid, hard-consistence tumours, with a cystic component in 21% of cases [33, 45], a dense fibrous capsule, ranging in colour from greyish to white, while adenoma is soft, smaller, and reddish-brown [45, 49]. Adhesions to surrounding tissue and/or invasion of adjacent organs are signs of malignancy [49–52].

The definitive diagnosis, however, is only possible with a histological examination after surgical excision. Schantz and Castleman first reported pathological criteria to define parathyroid carcinoma in 1973: fibrous bands, capsular invasion, vascular invasion, and mitotic activity [53–56].

According to the WHO classification, revised in 2017 [57–59], the diagnosis of malignancy should be restricted to those tumours showing evidence of invasive growth and involving adjacent structures, such as thyroid and soft tissue, capsular and/or extracapsular blood vessels, or perineural spaces and those with documented metastases. Vascular invasion occurs when a tumour invades capsular vessels or vessels of the surrounding soft tissues. Tumour's cellularity is variable: broad bands of fibrous connective tissue extending from the peritumoral capsule often divide cell clusters. These bands are present in 90% and mitotic figures in 80% of PC cases, but both characteristics are not specific for malignancy [59], even if atypical mitoses strongly favour PC diagnosis.

The Ki67 proliferation index is the most studied marker: it is higher in carcinomas (6–8%) than in adenomas (<4%), and a percentage greater than 5% generally suggests PC [60–63]. CDC73, also called parafibromin, is another marker: many parathyroid carcinomas are negative [64]. Conclusions from the literature on genetic profiling require cautious interpretation because studies can differ in the criteria used for diagnosis and selecting cases.

Among the cases selected using rigorous criteria, inactivation of the tumour suppressor gene CDC73 is the major known molecular driver in the pathogenesis of PC. Somatic mutation of CDC73 is present in 70% of PCs [65] and rarely in benign sporadic adenomas (0.8%) [66–69]. Germline mutations are present in one-third of patients [70], suggesting HPT-JT syndrome in a subgroup of patients and occasionally in FIHP [23, 67, 68, 71–80]. The presence of CDC73 mutation with negative parafibromin increases the probability of malignancy [81–90], but it is not pathognomonic. Other genes or their protein products, such as BRCA2, Rb, *p*53, and PRAD 1 [7, 49, 91–94], have been studied in PC pathogenesis, but none has proven useful in distinguishing PCs from benign adenomas.

All patients showed unequivocally WHO histological malignancy criteria in our series, and only one showed vascular invasion. In addition, all had fibrosis bands, 5 had mitosis, and 2 had a very high Ki67 index. Only in 1 case was the CDC73 mutation studied, but it was negative.

There is no universally recognised staging system for PC [95]. A large retrospective cohort study proposed a former staging system [9, 14], which proved insufficient to achieve meaningful outcome prediction in terms of prognosis.

Talat and Schulte proposed a staging system based on histopathological criteria. It includes two risk classes: low risk (capsular and adjacent soft tissue invasion) and high risk (vascular and vital organ invasion). This system seems to have a great power to predict survival and recurrence [9, 95]: patients categorised as high risk carried a higher risk of recurrence and death than those in the low-risk category. According to the Schulte classification, only one patient in our series met the high-risk criteria. All three patients who underwent local excision were low risk. For this reason, we radicalised only the younger patient because one refused reintervention, and the other was an elderly subject with comorbidities.

Our experience, albeit limited to a small number of cases, seems to confirm the validity of the Schulte staging system concerning prognosis. The positive outcomes of our cohort can be explained mainly by the fact that 7 of 8 patients affected with PC were low risk. Furthermore, most of them (5/8), including the high-risk patient, underwent en bloc resection and one radicalisation after the first procedure. This supports our previous arguments about the value of

surgery extension as a prognostic factor. Finally, the high-risk patient had a relatively short follow-up period of 16 months.

According to other studies [7, 8, 96, 97], patients affected with PC relapsed within 2 to 5 years from the initial intervention, usually presenting increasing serum and PTH calcium. Distant metastases occur in about 25% of patients during follow-up [27, 98], with a disease-free period of up to 20 years [82, 98, 99]. The most reported metastasis sites are lungs (40%), liver (10%), and, in a few cases, bones, pleura, and pancreas [45, 100]. The clinical course is usually indolent, and some patients survive for many years after diagnosis of metastatic disease.

The main clinical manifestation of recurrence is hypercalcemia and related complications [45]. In some cases, the metastatic disease can detect a misunderstood PC diagnosis in a patient who previously had been operated on for PHPT [25]. In about two-thirds of cases, the main site of recurrence is local in the neck [27] and is difficult to detect because it is small and/or multifocal and/or located in the scar left by the previous surgery. Half of these patients also have distant metastasis [98].

The best treatment, if possible, is reintervention [1, 24, 48, 97, 101–103], with an increase in long-term survival of up to 30% [97, 101]. Even if reintervention is not radical, it can be useful for palliation by reducing serum calcium levels for a period ranging from months to years [1, 12, 24, 27, 82, 99, 101, 102]. In local recurrences, percutaneous US-guided alcohol injections have been reported in the literature, but with short-term improvements in calcium serum levels [104] and RLN injuries associated with ethanol toxicity [105]. For liver and lung metastasis, radiofrequency ablation (alone or with arterial embolisation) has been reported as having a good chance to improve calcium and PTH levels [106, 107]. Therapies other than surgery, such as chemotherapy and radiotherapy, both as alternative and adjuvant therapies, have shown poor results [24, 96]. Few studies report on novel therapies, such as anti-PTH immunotherapies and biological agents [108, 109].

The lack of a universally recognised staging system for PC does not allow clinicians to formulate a precise prognosis. Studies report overall survival rates between 76 and 85% and 49 and 77% at five and ten years, respectively [1, 14, 21, 25, 96]. In patients treated with complete tumour resection during the initial surgical procedure, survival rates improve to 90% and 67% at five and ten years, respectively [110].

In our series, all patients are alive and disease-free, but only two among these have a follow-up period longer than five years: this is a limit of the present study.

The prognosis of nonfunctional PC is worse since diagnosis is always made at an advanced stage [28, 111].

5. Conclusions

Although limited by a short follow-up and the small size, our study highlights some valuable aspects to suspect PC and differentiate PHPT-PC from PHPT due to benign causes preoperatively. Suspecting this rare cancer is essential to offer patients the best treatment options at the time of diagnosis.

According to Schulte classification, our series seems to support both the value of surgery extension at first intervention and risk class as prognostic factors for recurrence in patients affected with PC.

The rarity of this tumour and the ability to recognise it among other causes of PHPT requires in-depth expertise. The implicit consequence is that preferably the referral centres should treat these patients.

Due to the rarity of this cancer, there is the need for multicentre studies collating cases from referral centres.

Data Availability

The data that support the findings of this study are available from a Microsoft Access Database (version 2001, Microsoft Corp, Redmond, WA, US) upon request to the corresponding author.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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