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Primary Hyperparathyroidism: Can Parathyroid Carcinoma Be Anticipated on Clinical and Biochemical Grounds? Report of Nine Cases and Review of the Literature

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Background: Parathyroid carcinoma (PC) mimics benign primary hyperparathyroidism (PHP), but the diagnosis of PC is seldom available at the time of the first operation. Because PC is plagued by recurrences usually beyond cure, one may wonder whether some of these could be prevented by more extensive resections initially, i.e., if the diagnosis of PC were available at that time.

Methods: Over a 25-year period, 311 consecutive patients with PHP underwent operation in our department: 302 had benign disease (adenomas or hyperplasias), and 9 had PC. Several clinical parameters, serum calcium and parathyroid hormone (PTH) levels, and the weight of the parathyroid tumor removed were compared in both groups. Receiver operating characteristic curves and logistical regression analyses were used to distinguish PC from benign PHP.

Results: Eight of 9 patients with PC had symptoms, versus 238 (79%) of 302 with benign PHP (not significant). In the PC subgroup, serum calcium and PTH levels and the tumor weights of the parathyroid glands removed were significantly higher than in the benign PHP cohort, even if these three parameters were regularly flawed by low positive predictive values (14%, 20%, and 15%, respectively).

Conclusions: Serum calcium, PTH levels, and tumor weights were significantly greater in the PC subgroup, even if not invariably in a discriminatory way. However, when PTH is < 4 times the upper limit of normal and tumor weight is < 1.9 g, the probability of PC is nil.

Key Words: Primary hyperparathyroidism—Parathyroid cancer—Diagnosis—Tumor weight—Parathyroid hormone

Primary hyperparathyroidism (PHP) is caused in the vast majority of cases by parathyroid adenomas or hyperplasias, but occasionally it is caused by parathyroid carcinomas (PC). In all three instances, the clinical and biological picture may be strikingly similar.[1] Because of the lack of specific clinical features and because percutaneous aspiration biopsies are rightly contraindicated,[2] a diagnosis of PC is difficult to establish[3] and is seldom available at the time of the first operation.[1,4-9] The similarity in clinical presentation is unfortunate, because PC may be plagued by recurrences—one of the hallmarks of this tenacious tumor[10,11]—and because recurrences sel-

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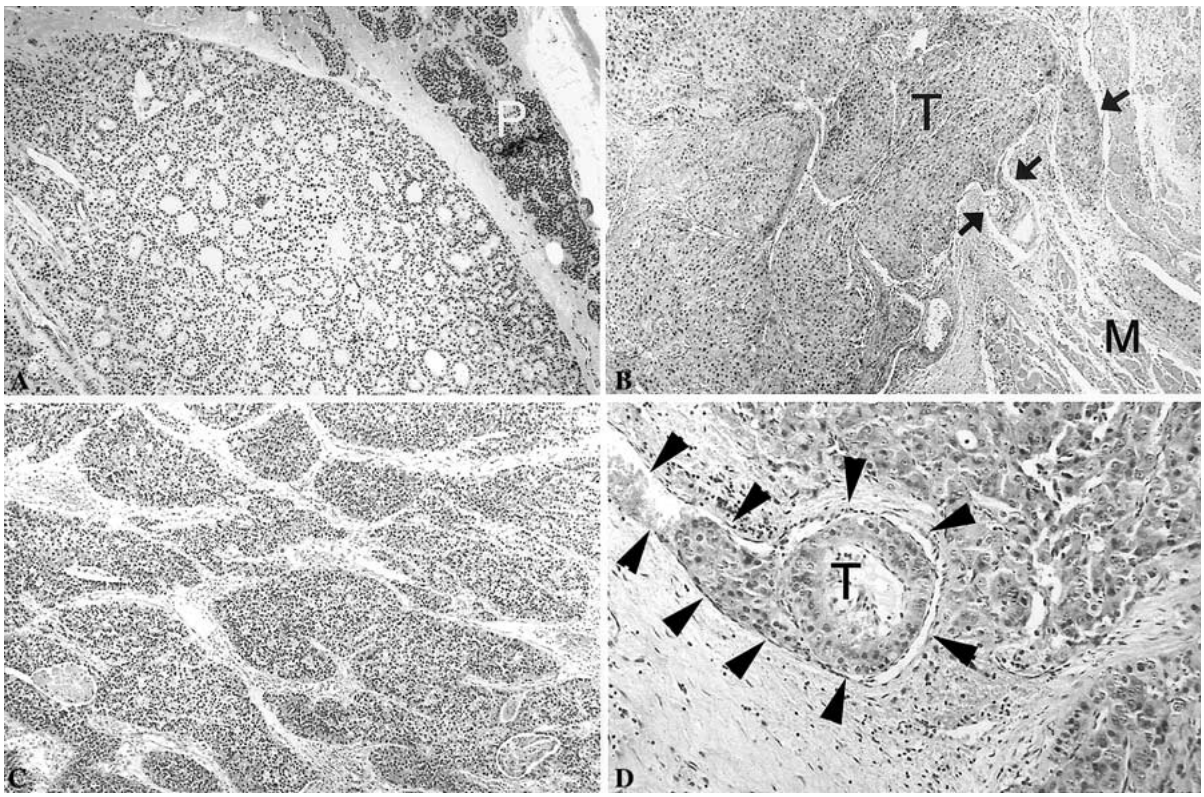

FIG. 1. Histological appearance of parathyroid adenoma (**A**) and carcinoma (**B–D**). (**A**) Adenoma is lined by a capsule, and nontumorous glandular parenchyma is compressed (upper right corner; stain, hematoxylin and eosin; original magnification, ×100). (**B**) Parathyroid carcinoma: tumor (T) invades the capsule (*black arrows*). M, muscle (stain, hematoxylin and eosin; original magnification, ×20). (**C**) Carcinomatous cells are separated by thick fibrous bands (stain, hematoxylin and eosin; original magnification, ×100). (**D**) Tumor invasion (T) is seen within a blood vessel (*arrowheads*; stain, hematoxylin and eosin; original magnification, ×200).

dom lend themselves to curative therapies, be they surgical or conservative.[2,6,11–14]

Recurrences are frequently cervical (up to two thirds of cases[4] and usually within 3 years[11]), and one wonders whether some of these cases could have been prevented had the diagnosis of PC been ascertained and, accordingly, more generous excisions had been performed at the time of the first operation (for instance, on the contiguous thyroid lobe[12] or on enlarged nodes[15]).

The purpose of this study was to reevaluate the clinical and biochemical parameters that have been used to differentiate PC from benign PHP at the time of the first operation. To achieve this, patients with benign PHP were compared retrospectively with patients with PC who underwent operation in the same department during the same period of time. Parameters studied included the age and sex of the patients, the presence and type of symptoms, preoperative levels of serum calcium and parathyroid hormone (PTH), and the tumor weight of the parathyroid glands removed. Comparing two groups of such uneven sizes entails certain statistical precautions, which are discussed below.

MATERIALS AND METHODS

Over a 25-year period (June 1976 to December 2001), 311 consecutive patients (82 men and 229 women, aged 16–92 years; mean ± SD, 60.5 ± 15.2 years) underwent operation in the Department of Surgery of Geneva University Hospital for PHP: 242 had adenomas (78%), 60 had hyperplasias (19%), and 9 had PC (3%). In the PC subgroup, there were seven women and two men, aged 35 to 67 years (mean ± SD, 54.9 ± 9.9 years); none of them had a family history of PC. PC was defined by Schantz and Castelman's criteria,[16] which include any of the following: (1) local invasion of contiguous structures; (2) nodal or distant metastases; and (3) capsular or vascular invasion, thick fibrous bands, pleiomorphic cells in a trabecular pattern, or mitoses (Fig. 1).

TABLE 1. *Characteristics of patients with parathyroid carcinoma (n = 9)*

Patient no.	Sex/age (y)	Symptoms	*s*-Ca	*s*-P	*s*-PTH	OP	Time of diagnosis	Follow-up (y)
1	M/35	U, T, pancreatitis	3.93	↓	19.4	IR + R thyroid lobectomy	After OP	NED 25.2
2	F/62	O, U, T	5.99	1.70	6.9	IL	After OP	NED 21.3
3	F/51	O, U	2.4–2.8	1.9–3.5	12.8	SR	During OP	DOC 3.0 (myocardial infarct)
4	F/57	O, U, T	2.71	↓	4.6	IR	After OP	NED 16.6
5	F/45	None	3.60	.40	4.1	IL	During OP	DOC 5.0 (alcohol abuse)
6	M/56	O, U	3.28	.79	6.4	SR + R thyroid lobectomy + LN	During OP	NED 8.6
7	F/63	O, palpable cervical mass	3.27	.66	20.0	Lx2 + L thyroid lobectomy	During OP	NED 3.8
8	F/67	T	2.91	.52	4.0	IL+ L thyroid lobectomy	After OP	NED 2.0
9	F/58	O, U	3.02	.59	13.8	IL + total thyroidectomy	During OP	NED 1.3

OP, operation; U, urinary symptoms; T, thymic disorders; IR, inferior right; R, right; NED, no evidence of disease; O, osteoarticular symptoms; IL, inferior left; SR, superior right; DOC, dead of other cause; LN, lymph node; L, left; *s*-Ca, calcium in serum; *s*-*P*, phosphorus in serum; *s*-PTH, parathyroid hormone in serum; Lx2, bilateral thyroid lobectomy (total thyroidectomy).
Reference values: *p*-Ca, 2.20 to 2.52 mmol/L; *p*-P, .80 to 1.40 mmol/L.

TABLE 2. *Cases of parathyroid cancer (PC) compared with all cases of benign primary hyperparathyroidism (PHP) operated on during the same period*

Variable	PC	Benign PHP	*P* value
No. of cases	9	302	–
Age (y)			NS
Mean ± SD (range)	54.9 ± 9.9 (35–67)	60.7 ± 15.4 (16–92)	
Median (IQR)	57 (11)	62 (21)	
Sex, M/F (% men)	2/7	80/222 (26%)	NS
Patients with symptoms	8	238 (79%)	NS
General symptoms	4	68 (23%)	NS
Skeletal involvement	5	84 (28%)	< .003
Renal involvement	5	84 (28%)	NS
Renal and skeletal involvement	5	13 (4%)	< .0001
Thymic disorders	3	47 (16%)	NS
GI symptoms	1	39 (13%)	NS
Hypertension	0	52 (13%)	NS
s-Ca (mmol/L)			.04
Mean ± SD (range)	3.4 ± 1.1 (2.6–6.0)	2.9 ± .3 (2.0-4.8)	
Median (IQR)	3.3 (.8)	2.8 (.4)	
s-PTH (× upper range of normal value)			$< 10^{-5}$
Mean ± SD (range)	10.3 ± 6.5 (4.0–20.0)	2.6 ± 2.2 (.5–24.1)	
Median (IQR)	6.9 (9.3)	2.0 (1.5)	
Tumor weight (g)			$< 10^{-5}$
Mean ± SD (range)	4.9 ± 2.1 (1.9–8.0)	1.3 ± 2.2 (.015–14.9)	
Median (IQR)	5.3 (3.2)	.6 (1.0)	

NS, not significant; IQR, interquartile range; GI, gastrointestinal; *s*-Ca, calcium in serum; *s*-PTH, parathyroid hormone in serum.
Continuous variables were compared by using the Mann-Whitney test, and proportions were compared by using Fisher's exact test. Symptoms are detailed in the text (see Materials and Methods). Reference values for *p*-Ca are 2.20 to 2.52 mmol/L.

Symptoms were looked for in the entire PHP group and allocated to six possible categories: general (fatigue, weight loss, and anorexia), articular and/or skeletal (osteopenia or osteoporosis as measured by dual-energy x-ray absorptiometry, according to the World Health Organization criteria[17]), renal (nephrolithiasis, nephrocalcinosis, or impaired renal function in the absence of any other etiology), gastrointestinal (anorexia, nausea, vomiting, dyspepsia, vague abdominal complaints, and constipation[18]), hypertensive, and

TABLE 3. *Weight of parathyroid glands and microscopic features of malignancy according to Schantz and Castleman[16] found in nine patients with PC*

Patient no.	Sex/age (y)	Weight of gland removed (g)	Capsular or vascular invasion	Thick fibrous bands	Pleiomorphic cells, trabecular pattern, or mitoses
1	M/35	6.0	Vascular invasion	–	Trabecular pattern
2	F/62	2.2	Capsular + vascular invasion	–	–
3	F/51	5.0	Vascular invasion	+	–
4	F/57	6.5	Capsular invasion	+	–
5	F/45	8.0	Capsular + vascular invasion	–	–
6	M/56	4.0	Capsular + vascular invasion	+	–
7	F/63	NA	–	+	Mitoses
8	F/67	1.9	Vascular invasion	+	Mitoses
9	F/58	5.7	Capsular invasion	–	Trabecular pattern

PC, parathyroid carcinoma; NA, not available.

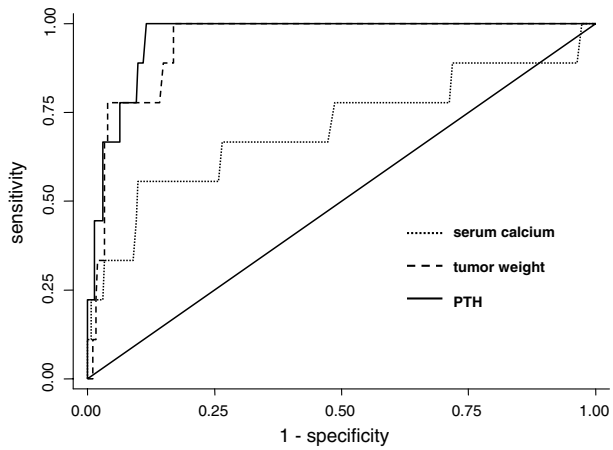

FIG. 2. Box plots for tumor weight and serum calcium and parathyroid hormone (PTH) determinations in the benign primary hyperparathyroidism (PHP) and carcinomatous cohorts. Tumor weights are provided in grams, serum calcium levels in millimoles per liter, and PTH values as multiples of the upper range of normal values.

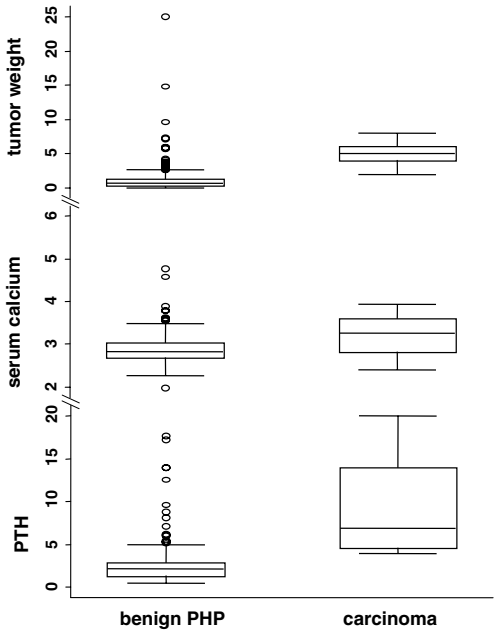

FIG. 3. Receiver operating characteristic (ROC) curves achieved by tumor weights, serum calcium, and parathyroid hormone (PTH) determinations. Areas under ROC curves measure .7051 for serum calcium determinations, .9446 for tumor weights, and .9601 for PTH determinations. PHP, primary hyperparathyroidism.

thymic (or mood disorders). Starting in February 1986, all patients who underwent operation (5 with PC and 251 with benign PHP) received methylene blue in the hour preceding surgery to facilitate identification of the parathyroid gland involved.[19]

Summary results are given as mean ± SD. Comparisons between two groups for continuous variables were performed with a Mann-Whitney test. Fisher's exact test was used for comparing proportions.

Receiver operating characteristic curves were used to determine the performance of two serum parameters (calcium and PTH) and the weight of the parathyroid tumor removed to evaluate their ability to predict PC before surgery. Logistical regression was used to estimate the probability of diagnosing a PC based on serum calcium and PTH levels and the weight of the tumor. The effect of predictive variables was assessed by odds ratio (OR) and 95% confidence intervals. The significance levels for two-sided *P* values was .05 in all tests. The data were analyzed with Stata software, release 7.0 (StataCorp LP, College Station, TX).

RESULTS

Characteristic features of patients with PC are listed in Table 1 and are compared in Table 2 with those

TABLE 4. *Ability of serum calcium, PTH levels, and tumor weight to differentiate PC from benign PHP*

Variable	Cutoff value	Sensitivity	Specificity	PPV	NPV
Ca (mmol/L)	3.27	56 (21–86)	90 (76–93)	14	99
PTH (pmol/L or nmol/L)	4 × N	100 (66–100)	88 (83–91)	20	100
Tumor weight (g)	1.9	100 (66–100)	81 (76–86)	15	100

Except for cutoff values, all figures are percentages; numbers in parentheses are 95% confidence levels.
PTH, parathyroid hormone; PC, parathyroid carcinoma; PHP, primary hyperparathyroidism; PPV, positive predictive value; NPV, negative predictive value; N, upper range of normal value.

TABLE 5. *Odds ratio (OR) estimate of parathyroid cancer compared with benign primary hyperparathyroidism*

Variable	Crude OR	95% CI	*P* value	Adjusted[a] OR	95% CI	*P* value
Tumor weight	1.28	1.07–1.52	.006	.97	.78–1.19	.743
Serum calcium	5.51	1.86–16.35	.002	2.29	.73–7.18	.156
PTH	1.39	1.22–1.59	.000	1.37	1.16–1.61	.000

CI, confidence interval; PTH, parathyroid hormone.
[a]Adjusted variables were tumor weight, serum calcium, and PTH; all variables were mutually adjusted.

of all patients who underwent operation for benign PHP during the same period. Eight of the nine patients with PC had symptoms, versus 238 of 302 in the benign PHP group (not significant). Compared with patients who had adenomas and hyperplasias, patients with PC were more likely to have bone disease ($P < .003$) or concomitant bone and renal disease ($P < .0001$). However, for a given level of increased PTH, symptoms as a whole were evenly distributed whether patients had PC or benign PHP. Within the PC subgroup, one patient presented with a palpable neck mass, but none had preoperative (or postoperative) vocal cord paralysis, and none had regional (lymph nodes) or distant metastases at the time of diagnosis.

The nine patients with PC had their pathologic gland removed, and frozen sections were performed. The gland removed was described as firm in one case, dark in another, and adherent or "in continuity" with the thyroid (in three) or the esophagus (in one). Microscopic criteria for malignancy according to Schantz and Castleman[16] are listed in Table 3. Carcinomatous glands were significantly bigger than adenomatous and hyperplastic glands (4.9 ± 2.1 g vs. 1.3 ± 2.2 g, respectively; $P < .00001$).

Frozen sections were unable to prove cancer in four patients. Excision of the thyroid lobe adjacent to PC was performed in five patients (three times in a second step upon receipt of the definite diagnosis) because definite slides had shown the surgical section to be invaded. In none of these three cases, however, did histology confirm invasion of the thyroid tissue removed. In two instances, thyroidectomy was added because of intrinsic benign thyroid pathologies, irrespective of PC. In addition to thyroid lobectomy, one patient had benign-looking internal jugular lymph nodes removed, and these also proved benign. No adjuvant treatment was proposed for any of the PC patients.

Two patients with PC died of unrelated causes 3 and 5 years after surgery. The remaining seven patients with PC are alive after a median follow-up period of 8 years (range, 3 months to 20 years), and yearly serum calcium determinations are so far within the normal range.

The ability of increased PTH levels and tumor weights to predict PC was considerably greater than that of hypercalcemia (Figs. 2 and 3 and Table 4), even though serum calcium levels were also higher in the PC subgroup (Table 2). For the four patients whose cancers were undiagnosed during surgery, both PTH levels and tumor weights exceeded respective cutoff values.

To evaluate the probability of diagnosing PC, a logistic regression method was used that was based on serum calcium and PTH levels and the weight of the tumor removed (Table 5). Crude OR showed that patients with higher levels of serum calcium and PTH and heavier tumor weights were more likely to have PC. After adjusting for tumor weight and serum calcium, the OR associated with PTH did not change, whereas the discriminating effect of tumor weight and calcium both disappeared (this means that all discriminative information can be derived from PTH levels alone). The R^2 value was .26, and this means that approximately one fourth of the variance was explained by these three factors.

DISCUSSION

Several factors account for the difficulty in establishing a correct diagnosis of PC. First, PC mimics benign PHP clinically, and given the rarity of PC (it never exceeds 5% of cases of benign PHP in series of respectable sizes: 2.9% in ours but 1% in most series[9,11,12,20]), the diagnosis is seldom suspected. Second, although parathyroid infiltration into adjacent neck structures is obviously synonymous with PC,[3,4,15,21] such extreme conditions are not the rule: only 38 cases (28%) in a 1991 Japanese survey of 138 cases[20] (however, some degree of adherence to the thyroid gland is quite regularly observed[22]—four times in the present series).

Thus, the scarcity in PC of macroscopic signs customarily suggestive of neoplasia (as in this series) may account for changes in the histological criteria of the disease, because most authors[18] have now adopted Schantz and Castleman's[16] definition, by which more discrete histological features suffice in establishing a diagnosis of PC.[1,3] These features (which have been used in this study) include possible combinations of the following: a trabecular pattern, mitotic figures, thick fibrous bands, or capsular and blood vessel invasion. For obvious reasons, diagnosis is even more difficult in the frozen-section setting[8] (incorrect in four of our nine cases) and may lead to parsimonious tumor resections in conditions when more generous ones (if not necessarily more curative) would seem safer.

Curiously enough, PC frequently displays other features that may facilitate its diagnosis before surgery. Female prevalence is not as striking as in PHP,[10,14,16,20,23,24] and patients tend to be younger, even though neither sex nor age reached statistical significance in this report.[9] All but one of our nine patients were clearly symptomatic; the most discriminative finding in our series was a combination of urinary and skeletal symptoms[10,14,22] (it is indeed a classic feature of PC to be more frequently and more severely symptomatic compared with benign PHP[1,18]). A palpable neck mass,[6,8,10] described in nearly 1 in 3 cases of PC in a series of 61,[16] was noted only once in this study.

The severity of hypercalcemia may prove more useful than symptoms for suggesting PC before surgery: whereas the 302 patients with benign PHP had calcemias averaging 2.89 ± .33 mmol/L, for the 9 patients with PC, levels increased to 3.45 ± 1.05 mmol/L (a significant difference; $P < .04$). Such differences have already been reported[9]; several series have shown 65%[20] to 75%[4] of PC patients with calcemias >3.5 mmol/L. Despite such differences, the sensitivity and, particularly, the positive predictive value of serum calcium for PC are disappointing (56% and 14%, respectively), as reflected by a considerable overlapping of patients with PC and benign PHP (Fig. 2). Increments are more striking for mean PTH determinations[18,20]: 2.6 times the upper level of normal value in cases of benign PHP, versus 10.3 in PC ($P < 10^{-5}$). This was confirmed in a series of 43 cases from the Mayo Clinic (mean increase, 10.2 times the upper limit of normal)[14] but was not the case in a smaller California report, which failed to disclose significant differences in PTH levels between adenomas and PC.[22] To a slightly lesser degree, the same holds true for tumor weight, a finding clearly demonstrated in an American series in which 10 PC patients had parathyroid glands exceeding 2.5 g (mean, 7.2 g).[6] Although more promising than serum calcium, PTH increments and tumor weight are unable to predict PC reliably in all instances (indeed, when the prevalence of a disease is low, false-positive results can be expected to outnumber true-positive ones: even when the sensitivity and specificity of a given test are high, the positive predictive value is still low). However, the probability of PC was nil in our series when the PTH was increased <4 times the upper limit of normal, the tumor weight was <1.9 g, or both.

The most effective treatment in PC is surgical and should consist of an en-bloc resection, avoiding rupture and spillage of the tumor.[20] In the event of a correct diagnosis of PC being available during surgery (and, obviously, also before), attention should be given to the possible invasion of the resection margins. Doubt on the thyroid side (or the presence of nodular thyroid disease) should entail en-bloc ipsilateral thyroidectomy[13] (even though histology may fail to find residual cancer in the thyroid specimen resected, as occurred four times in this series). By the same token, jugular lymph node dissection should be performed only in cases of grossly enlarged lymph nodes, a situation reported 9 times in 18 patients with metastatic disease in a series of 59[16]: we performed it once in a patient with normal-appearing nodes, but histology failed to disclose lymphatic metastases. This rather aggressive attitude seems justified by the futility of repeat surgery[22,25] or of other more conservative treatments in case of recurrent PC.[2,6,11–14]

In conclusion, there are intraoperative indications clearly suggestive of PC, such as gland firmness or infiltration into adjacent structures, usually the thyroid. These findings, however, may be absent, as in

this series. Consequently, one should seriously contemplate the diagnosis of PC in the presence of an abnormally large parathyroid gland and/or of unusually high levels of serum calcium or—better still—of PTH, even if this study failed to pinpoint irrefutable and pathognomonic cutoff values for these three parameters to assess PC. However, the diagnosis of PC can be reliably ruled out for the many patients in whom PTH increments are inferior to 4 times the upper limit of normal range, tumor weights are < 1.9 g, or both, and this should help to reassure the surgeon who renounces extensive resections, because the probability of PC is nil below these values.

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