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Clinical Research Article

Time to Recurrence as a Prognostic Factor in Parathyroid Carcinoma

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Abstract

Background: Parathyroid carcinoma (PC) is a rare and challenging disease without clearly understood prognostic factors. Adequate management can improve outcomes. Characteristics of patients treated for PC over time and factors affecting prognosis were analyzed.

Methods: Retrospective cohort study including surgically treated patients for PC between 2000 and 2021. If malignancy was suspected, free-margin resection was performed. Demographic, clinical, laboratory, surgical, pathological, and follow-up characteristics were assessed.

Results: Seventeen patients were included. Mean tumor size was 32.5 mm, with 64.7% staged as pT1/pT2. None had lymph node involvement at admission, and 2 had distant metastases. Parathyroidectomy with ipsilateral thyroidectomy was performed in 82.2%. Mean postoperative calcium levels were different between patients who developed recurrence vs those who did not ($P = .03$). Six patients (40%) had no recurrence during follow-up, 2 (13.3%) only regional, 3 (20%) only distant, and 4 (26.6%) both regional and distant. At 5 and 10 years, 79% and 56% of patients were alive, respectively. Median disease-free survival was 70 months. Neither Tumor, Nodule, Metastasis system nor largest tumor dimension ($P = .29$ and $P = .74$, respectively) were predictive of death. En bloc resection was not superior to other surgical modalities ($P = .97$). Time between initial treatment and development of recurrence negatively impacted overall survival rate at 36 months ($P = .01$).

Conclusion: Patients with PC can survive for decades and have indolent disease course. Free margins seem to be the most important factor in initial surgery. Recurrence was common (60%), but patients with disease recurrence within 36 months of initial surgery had a lower survival rate.

Key Words: parathyroid carcinoma, management, outcomes, prognosis, survival

Abbreviations: CaT, serum total calcium; PC, parathyroid carcinoma; TNM, Tumor, node and metastasis system.

Parathyroid carcinoma (PC) is a rare malignant neoplasm with an incidence of 0.02 to 0.05 cases per 100 000 inhabitants (1-4). However, recent studies have shown an increase in its occurrence (2, 3, 5). The North American Surveillance, Epidemiology, and End Results database registered in the past 16 years that the incidence of PC has increased by 60% (6).

The diagnosis of PC is challenging and can be questionable because of controversial pathological criteria. Diagnosis is only possible years after initial treatment with the development of metastatic disease (7). Preoperative diagnosis is virtually impossible, except when there is recurrence of previously treated disease or in unequivocal pathological demonstration of lymph node or distant metastasis (3, 5). Preoperative suspicion of malignancy is based on clinical characteristics, markedly high hypercalcemia, and/or presence of a palpable neck mass (2, 3, 5, 8).

The importance of adequate treatment justifies the need for a preoperative suspicion of malignancy. If suspected early, future additional procedures may be avoided, with an increased risk of morbidity and may also improve survival results (2, 5). In parallel, by reducing the expectation of malignant disease, unnecessary radical interventions may be avoided (2).

Experience with PC management and treatment results is still limited. Prognostic factors are not clearly understood; some patients present with a rapid and fatal disease, whereas others have an indolent course, even with metastatic disease (9).

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This study aimed to analyze the characteristics of these patients over time and the impact of clinical and laboratory characteristics before and after treatment on the prognosis of a large cohort treated at a single academic institution. Here, we show that time to recurrence may be an important prognostic factor in PC.

Patients and Methods

All patients diagnosed with PC between 2000 and 2021 in the Division of Head and Neck Surgery at Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, a university public hospital and a reference center for parathyroid disease, were included (10).

This was a retrospective cohort study with the following inclusion criteria: patients who had clinical follow-up and/or underwent surgical procedures at the institution, either as the first treatment or for salvage purposes. Only patients whose main treatment was surgery (in the neck or chest) were included, even after undergoing adjuvant therapy or complementary treatments (ie, chemotherapy, radiotherapy, ablation by interventional radiology techniques, or immunotherapy), regardless of clinical and/or pathological staging.

In patients without a previous pathological diagnosis, preoperative suspicion of malignancy was based on clinical characteristics such as exuberant symptoms (neurological impairment, pancreatitis, or brown tumor), markedly high hypercalcemia (serum total calcium level >14 mg/dL), and/or presence of a palpable neck mass. Intraoperatively, suspicion was raised when fibrosis surrounding the involved parathyroid gland, invasion, or adherence of the tumor to adjacent structures.

If malignancy was suspected preoperatively, en bloc surgery (including parathyroid, ipsilateral thyroid lobe, and central compartment lymph node dissection) was the standard treatment at the institution until 2014. However, since then, tumor resection with clear margins has been considered adequate treatment. Thus, a patient with postoperative diagnosis of PC who had less than en bloc resection was not candidate to neck reexploration if the margins were clear—for instance, a complete intrathyroidal PC was treated with ipsilateral thyroid lobectomy without elective neck dissection (11).

The final diagnosis of PC was based on 1 or more histopathological findings of complete capsular invasion, unequivocal vascular invasion, metastasis, or previous diagnosis of parathyroid carcinoma and recurrence. Patients diagnosed with atypical adenomas or inconclusive diagnoses were excluded.

For the cases initially operated in other institutions, whenever possible, a review and new analysis of the paraffin blocks was carried out by the same pathology service to standardize the reports as much as possible. For those whose analysis was not possible because of unavailable material, specimens from subsequent surgeries at the institution were analyzed by the same pathology service, confirming the diagnosis of PC.

All pathological reports were reviewed to standardize the description to the current staging classification of the eighth edition of the Tumor, Nodule, Metastasis (TNM) system of the American Joint Committee on Cancer and Union for International Cancer Control (12).

Demographic and clinical parameters (sex, age, ethnicity, comorbidities, clinical findings, presence of regional and/or distant metastases, staging), germinative *HRPT2/CDC73* gene mutation, surgical aspects (parathyroid location, invasion or adherence to adjacent structures, and size in the largest dimension), histology, and outcomes (including, but not restricted to, radiotherapy, chemotherapy, or immunobiologicals) were analyzed.

Laboratory tests and medications were reviewed at the following time intervals: preoperative, immediate postoperative (within the first month), 6 months, 1 year, and annually thereafter, or until death.

Laboratory tests recorded (reference ranges) included: serum total calcium (CaT) (8.6-10.2 mg/dL), serum ionic calcium (4.6-5.3 mg/dL), serum phosphorus (2.7-4.5 mg/dL), serum alkaline phosphatase (male, 40-129/female, 35-104 U/L), serum PTH (15-65 pg/mL). The following medications were also collected: calcimimetics, bisphosphonates, calcium carbonate, calcitriol, or vitamin D.

Hospitalization after initial treatment, including its cause, was also assessed. Disease-free and overall survival rates were also analyzed.

The presence of persistent or recurrent disease was considered for both biochemical and structural evidence, whichever occurred first. Persistent disease was conceptualized when there was evidence of disease before the 6-month follow-up. Recurrent disease, in turn, when it occurred from 6 months onwards.

During follow-up, further investigation was conducted in patients with biochemical recurrence to localize structural reminiscence and/or metastatic disease (ie, local, cervical lymph nodes, and lung). When identified, cytoreduction or tumor resection was performed, if feasible, such as reoperation, neck dissection, and radiofrequency ablation. When unsuccessful or infeasible, especially in patients with distant metastasis, palliation was performed using chemotherapy, radiotherapy, and/or immunotherapy.

The study was approved by the Committee on Research Ethics and data were collected and managed using Research Electronic Data Capture (13, 14).

Categorical variables are presented as frequencies and compared using either the χ^2 test or Fisher exact test, when appropriate. The distribution of continuous numerical variables was tested using the Kolmogorov-Smirnov test. Variables with normal distribution are presented as mean and SD and were compared using Student *t* test or ANOVA. Nonparametric distribution data are presented as medians and first (Q1) and third quartiles (Q3). Survival was analyzed using the Kaplan-Meier survival curve and compared using the log-rank (Mantel-Cox) test.

Results

Seventeen patients aged 17 to 64 years (mean, 46.6 ± 13.8 years) were enrolled. Almost one-third of the patients were of African descent. The time from symptom onset to diagnosis varied from 1 to 36 months (mean, 12.7 ± 11.9 months). Most patients presented with severe symptomatic disease and 7 of the 16 patients (43.8%) presented with brown tumors and pathologic fractures. Few patients were admitted with preoperative suspicion and palpable neck masses (Table 1).

Eleven patients (64.7%) had previously undergone surgery at other institutions. Of these, 5 (45.4%) underwent review of paraffin blocks in the institution. There was no information on the site of the involved parathyroid glands in 6 cases. In the remaining 11 cases, 7 were in the superior parathyroid gland (63.6%) and 4 in the inferior gland (36.4%). The initial

Table 1. Demographics and symptomatology of parathyroid carcinoma

	Number of cases	%
Sex		
Female	9	52.9
Male	8	47.1
Ethnicity		
White	11	64.7
Afro descendent	5	29.4
Not declared	1	5.9
Comorbidities		
Systemic hypertension	12	70.6
Type 2 diabetes	3	17.6
Chronic obstructive pulmonary disease	2	11.8
Dyslipidemia	1	5.9
Glaucoma	1	5.9
Hepatitis B	1	5.9
Hypothyroidism	1	5.9
Migraine	1	5.9
Obesity	1	5.9
Otosclerosis	1	5.9
Polycystic ovary syndrome	1	5.9
Symptoms at diagnosis		
Weakness/osteomuscular pain	8	50.0
Osteoporosis/osteopenia	8	50.0
Pathological fracture	7	43.8
Nephrolithiasis	7	43.8
Brown tumor	7	43.8
Gastrointestinal	4	25.0
Acute renal disease	3	18.8
Neurologic	2	12.5
Paresthesia/cramps	2	12.5
Pancreatitis	1	6.3
Other	7	43.8
Palpable neck mass		
No	4	23.5
Yes	1	5.9
No information available	12	70.6
Pretreatment carcinoma suspicion		
No	10	58.8
Yes	7	41.2

tumor size was reported in 14 patients. It varied from 15 to 53 mm (mean, 32.5 ± 12.2 mm). The initial pT stage was also evaluated in 14 cases as follows: 6 (35.3%), pT1; 5 (29.4%), pT2; and 3 (17.6%), pT3. Thus, the initial pT stage was pTx in 3 patients (17.6%). None of the patients had lymph node metastasis on admission. Two patients had distant metastasis at the time of diagnosis. One patient had only lung metastases and the other had lung and bone metastases. The preoperative CaT ranged from 11.0 to 19.0 mg/dL (mean, 14.7 ± 2.6 mg/dL).

Table 2 lists the operative strategies used in this study. Parathyroidectomy with ipsilateral thyroidectomy was the most common procedure performed (82.2%). In addition, one-half of these cases (7 of 14) had central neck dissection.

Table 2. Operative strategies

	Number of cases	%
Initial procedure		
PTx + thyroidectomy + ND level VI	7	41.1
PTx + thyroidectomy	7	41.1
PTx only	2	11.7
Other operation	1	5.8
Number of surgeries for each patient		
1	8	47.1
2	4	23.5
3	0	0.0
4	2	11.8
5	1	5.9
6	2	11.8

Abbreviations: ND, neck dissection; PTx; parathyroidectomy.

Postoperatively, hungry bone syndrome occurred in 5 patients. In 4 cases the information was unavailable, and the remaining 8 had no severe hypocalcemia after the procedure. No other major complications were noted.

Although most patients benefited from surgery, 60% had persistent or recurrent disease with marked hypercalcemia (mean follow-up time, 6.4 years).

There was a marked difference in the values of postoperative calcium when patients were stratified as controlled or recurrent cases. The median CaT values were significantly different between the 2 groups at 6 months (ANOVA, $P = .02$; adjusted $P = .03$; Dunn multiple comparison test) and 24 months (Mann-Whitney, $P = .007$). The controlled group showed lower calcium values compared with the recurrent group (Fig. 1A). Nevertheless, the analysis over time is difficult because many patients with recurrence undergo reinterventions, leading to reduction in serum CaT. In contrast, PTH was not as discriminative as calcium in marking early recurrent disease. Although the median values were significantly higher in the recurrent/persistent group, the difference was not statistically significant (ANOVA, $P = .08$) (Fig. 1B).

No further treatment was performed in 10 patients (58.8%). Six patients (35.2%) had 1 or more treatments after surgery. Five patients underwent radioablation and 2 patients underwent external beam radiotherapy and cytotoxic chemotherapy (dacarbazine and cyclophosphamide). In 1 case, ultrasound-guided ethanol injection of local recurrent disease, with temporary response, was used, as previously reported (15). Sorafenib and erdafitinib were used in 1 case each, both for patients presenting with distant recurrence during follow-up; sorafenib was used in 1 patient for approximately 12 months, with progressive disease, culminating in death with the disease 7 years after the initial treatment. Erdafitinib was administered to another patient presenting with an *FGFR1* fusion 3 years after the recurrence diagnosis, with disease stabilization as the best response and an initial drop (4 months) of PTH serum level, in a follow-up of 4 years. No information was available after surgery for 1 patient.

In terms of serum calcium level control, 11 patients received bisphosphonates, either alone or in association with calcimimetics (nine cases). In 3 of 7 cases with available information, denosumab was used with satisfactory results in terms of symptomatic control when hypercalcemia was refractory to bisphosphonates.

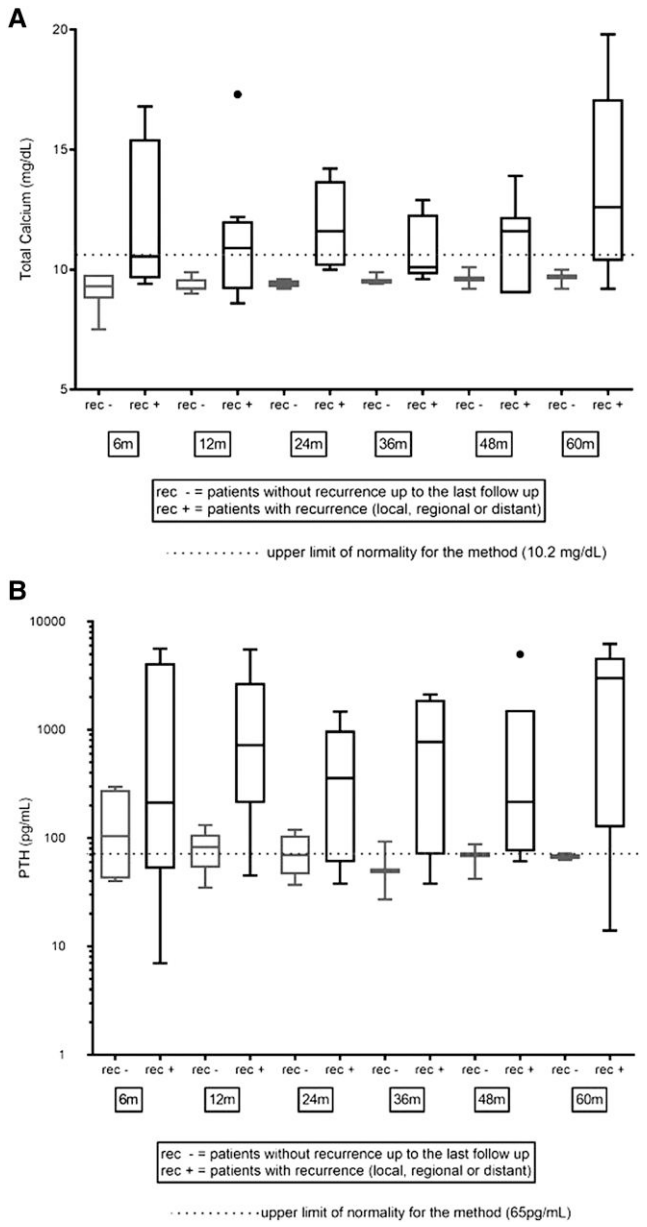

Figure 1. Tukey box plot of total calcium (A) and PTH (B) pattern after initial treatment according to recurrent disease or not.

Considering only 15 patients without distant metastatic disease at diagnosis, 6 (40%) had no evidence of recurrent/persistent disease up to their last follow-up (mean follow-up time, 7.1 years). Two (13.3%) patients had only regional recurrence, 3 (20%) had only distant, and 4 (26.6%) had both regional and distant recurrence/persistence (Table 3). Of those, persistence was seen in only 1 patient who underwent en bloc surgery.

Figure 2 shows the Kaplan-Meier curves for disease-free and overall survival. At 5 and 10 years, 79% and 56% of the patients were alive, respectively. Some patients survived for more than 20 years after PC diagnosis. However, they were not necessarily cured. The median disease-free survival was 70 months.

The TNM staging system was not predictive of mortality in the present study. The log-rank (Mantel-Cox) test yielded $P = .29$, when comparing survival according with TNM. Curiously, patients with T3 tumors had better outcomes,

Table 3. Results and follow-up data after initial treatment

	Number of cases	%
Recurrence/persistence during follow-up		
No recurrence	6	40.0
Locoregional and distant recurrence/ persistence	4	26.6
Distant metastasis only	3	20.0
Locoregional recurrence only	2	13.3
Site of locoregional recurrences		
Local (esophagus, striated muscle, fat tissue)	4	50.0
Level I-V ipsilateral lymph nodes	3	37.0
Level VI ipsilateral lymph nodes	2	25.0
Level VI contralateral lymph nodes	2	25.0
Level I-V contralateral lymph nodes	0	0.0
Site of distant metastasis		
Lung and pleura	3	42.8
Lung	1	14.2
Lung, bone, and pleura	1	14.2
Lung, bone, pleura, mediastinum, strap muscle (dorsum)	1	14.2
Not accessed (biochemical)	1	14.2
Hospitalization during follow-up		
Yes	10	58.8
No	6	35.2
Not available	1	5.8
Hospitalization cause		
Hypercalcemia control	7	70.0
Other (nephrolithiasis, bone fracture)	4	40.0

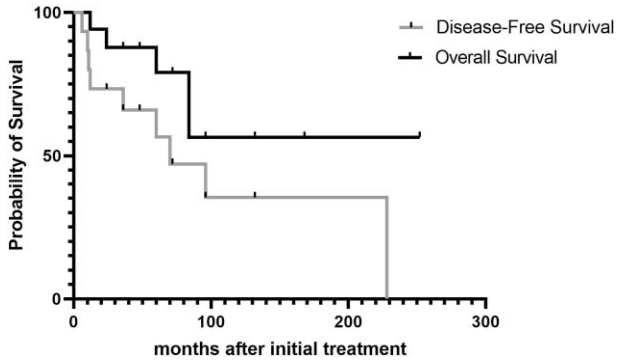

Figure 2. Kaplan-Meier curves for overall vs disease-free survival.

although the difference was not statistically significant (Fig. 3A). This observation was related to the absence of a significant difference in survival when patients were stratified by the median of the largest dimension of the tumor, that is, 33 mm ($P = .74$, log-rank [Mantel-Cox] test) (Fig. 3B). Furthermore, the TNM staging system was also not predictive of recurrence in these patients. The log-rank (Mantel-Cox) test yielded a $P = .07$.

Larger tumors were not associated with a higher risk of distant metastasis. Mean parathyroid size in 7 cases with distant metastases was 28.3 ± 10.1 mm (minimum, 17 mm; maximum, 40 mm)—not different of the mean size of the 7 cases

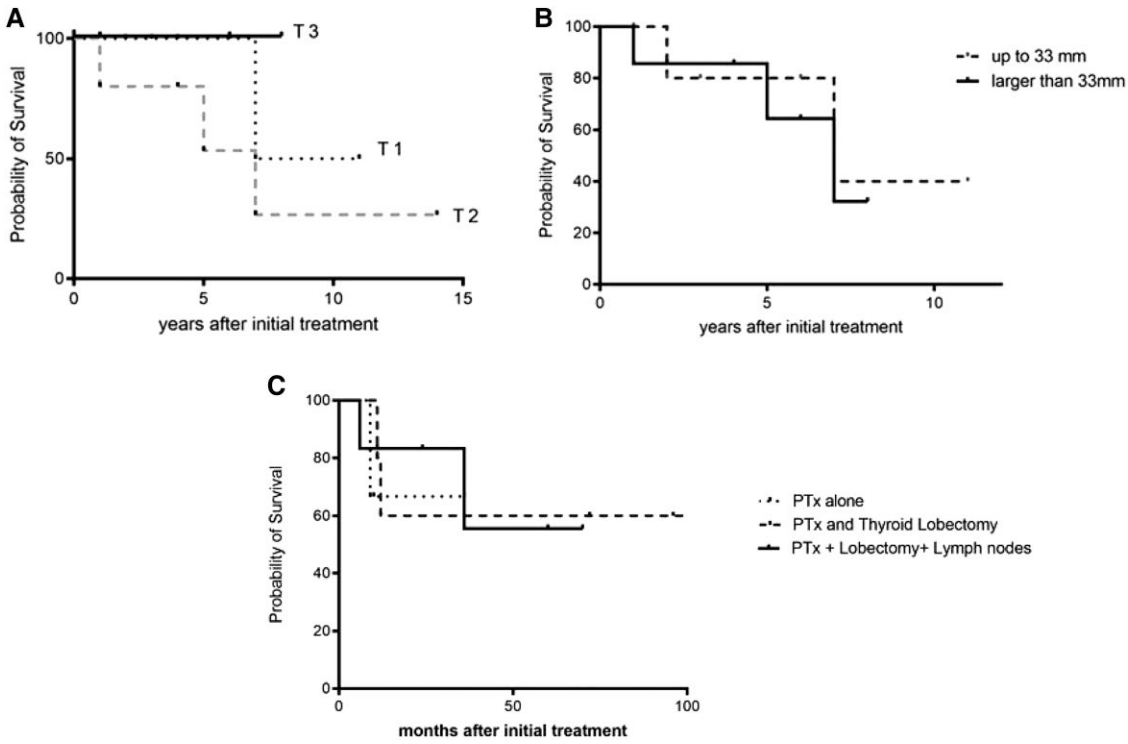

Figure 3. Comparison of Kaplan-Meier survival curves according to initial pT stage, based on the 8th edition of the TNM (A), tumor size (B), and the type of surgery initially performed (C).

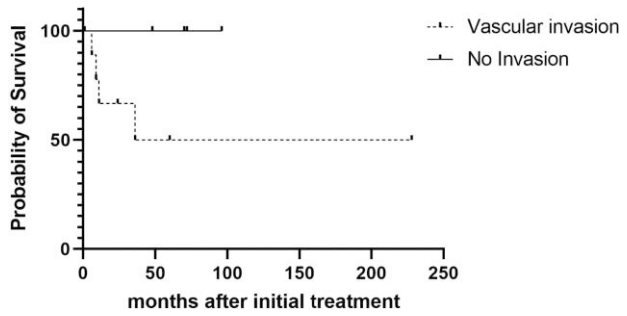

Figure 4. Comparison of Kaplan-Meier curves for survival between patients who had vascular invasion in the pathology report vs patients who did not.

without distant metastasis, 36.9 ± 13.4 mm (minimum, 15 mm; maximum, 53 mm) ($P = .20$, Student t test).

According to the type of surgery performed in terms of mortality, en bloc resection was not superior to resection of the parathyroid tumor without thyroid lobectomy and ipsilateral level VI lymph node resection ($P = .97$, log-rank [Cox-Mantel] test) (Fig. 3C). This was also observed in terms of recurrence ($P = .35$, log-rank [Mantel-Cox] test).

Vascular invasion, despite the graphic appearance, was not statistically significant for mortality ($P = .11$, log-rank [Mantel-Cox] test) (Fig. 4). In addition, vascular invasion was also not predictive of recurrence ($P = .37$, log-rank [Mantel-Cox] test).

Only 2 patients had positive surgical margins in the pathology report. One underwent en bloc surgery, with recurrence and death. Another underwent parathyroidectomy and partial thyroidectomy, evolving with loss of follow-up after suspected recurrence.

The time between the initial treatment and the development of recurrent disease (locoregional or metastatic) negatively affected overall survival rates. Figure 4 shows the survival curves when the patients were stratified according to recurrence before and after 24 and 36 months. The difference was marginal and not significant at 24 months ($P = .06$, log-rank test) (Fig. 5A). However, it was clearly significant when the disease recurred before 36 months, resulting in poor survival (median of 5 years) ($P = .01$, log-rank [Cox-Mantel] test) (Fig. 5B).

Mortality data and patient current status are shown in Table 4.

List of the enrolled patients, as well as their main clinical, surgical, pathological, follow-up, and laboratorial characteristics, can be seen in Supplementary File 1 (16).

Discussion

In the present study, we observed that patients with PC recurrence before 36 months had the worst outcome compared with those who presented with recurrence later. This may reflect different biological behaviors of the tumor, despite the pathological appearance or the largest dimension of the tumor. This finding is in contrast with the result observed in series of a single center with 37 patients that addressed time to recurrence (11). In our cohort, this clinical stratification of time to recurrence was more discriminative than TNM staging and initial tumor size. Both of these contrasting expectations deserve some reflection.

The TNM staging system for PC is relatively recent. In 1999, Shaha and Shah published the first proposal, called the Shaha system (17). More recently, Talat and Schulte (called the Schulte system) published a stratification in 2010

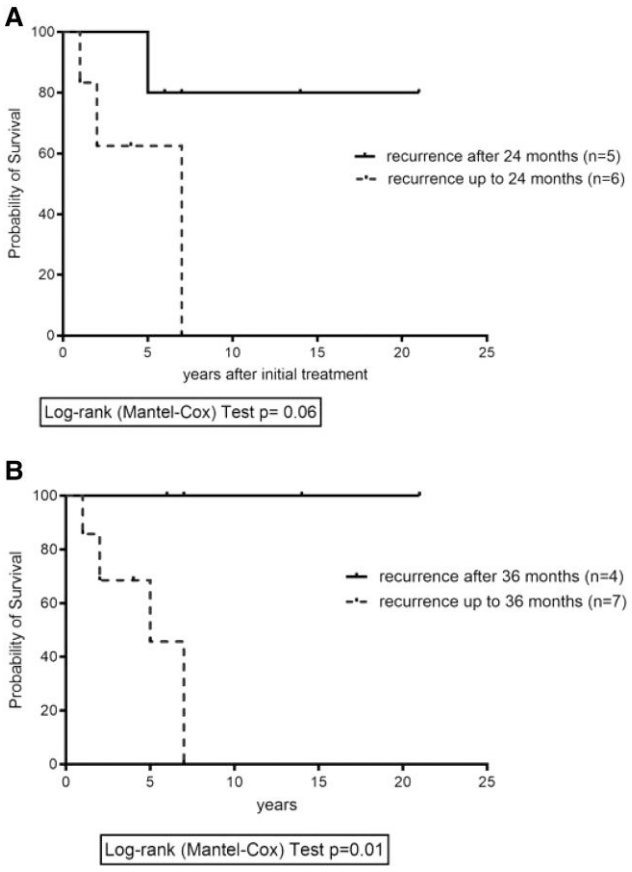

Figure 5. Comparison of Kaplan-Meier curves for survival between patients who developed recurrent disease up to (A) 24 months and (B) 36 months of follow-up vs patients who did not develop recurrence at follow-up.

Table 4. Mortality data and patient current status

	Number of cases	%
Death		
No	10	58.8
Yes	5	29.4
Not available	2	11.7
Cause of death		
Progression of disease	2	40.0
Nonrelated causes	0	0.0
Unknown	3	60.0
Current situation		
Alive without disease	7	41.1
Alive with disease	5	29.4
Death of disease	5	29.4

(18) and validated it in 2012 (19). The main differences between them are that the extension to the soft tissues is T3 in the Shaha system and T2 in the Schulte system. Schulte stratified patients with low- and high-risk tumors.

In 2017, PC was included in the eighth edition of the American Joint Committee on Cancer/Union for International Cancer Control TNM Cancer Manual. Nevertheless, it is recognized that the available data on tumor characteristics and prognosis are limited and that it is premature to propose a staging system (12). Contrary to other observations, the present study was not able to support the ability of the current TNM to predict the risk of death. Asare et al supported the use of TNM as meaningful in PC, with distant metastases reflecting the highest risk factor impacting survival (20). In the present series, the long-term survival of patients with pT3 stage was apparently superior to that of pT1 patients, without statistical difference. A criticism to be made in the current system is the lack of discrimination of macro- or microscopic invasion. In the present series, in patients with microscopic involvement of adjacent structures, an outcome similar to those without the same involvement was observed when the lesion was removed with free margins. Another problem with this classification is that the location of the primary cancer may be a confounding factor; for example, the superior parathyroid gland is closer to the esophagus than the inferior parathyroid, and more prone to microscopic invasion, even at an early stage. In the TNM system, any microscopic extension to the esophagus is classified as T3 rather than T1. In future revisions of the system, the primary tumor location (and parathyroid glands are notably variable in their positions) should be addressed.

When analyzing the survival curves correlating the occurrence of locoregional or distant metastases, a causal link was found. This observation had already been explored by Schantz and Castelman in 1973 (21). Corroborating this finding, our patients who had a diagnosis of metastasis before the third year of follow-up showed a lower survival rate than those presented after this period. Interestingly, all patients in the present cohort who showed evidence of metastasis after 36 months remained alive, with a mean follow-up time of 13.6 years (range, 6-21 years). In line with our finding, a meta-analysis by Tsai et al observed that relapse time before 12 months was associated with higher mortality rates (9). Despite having been suggested in the 1970s, this relation between time to recurrence and mortality was not sufficiently investigated in later years. And yet, it seems to be of great interest in terms of understanding the biological behavior of PC, which is still limited. Of note, the present cohort showed 1 patient who presented with distant recurrence after 12 months of initial treatment and remained alive after 4 years of follow-up, despite the early recurrence. The patient received erdafitinib in a study protocol with disease stabilization.

The risk of recurrence in patients with PC is relatively common and usually occurs later, with indolent course (3, 5, 22, 23). In most cases, there is a gradual increase in PTH levels, with a hypercalcemic crisis marking the advanced recurrent disease (5). In this study, a 60% rate of both locoregional (mean time, 28 months) and/or distant recurrence (mean time, 41.6 months) were seen. Hypercalcemia resulting from recurrence may require treatment; 62.5% of patients required hospitalization during follow-up, and of these, 70% were due to hypercalcemic crisis.

Hypercalcemia is a more specific marker than PTH for the detection of early recurrences. When the curves of CaT and serum PTH were observed over time in patients who did not present with metastasis at diagnosis, despite fluctuations resulting from hypocalcemic agents and tumor cytoreductive interventions, both patients who presented with metastasis at follow-up and those who did not have elevated levels of both parameters. However, these levels remain markedly higher in patients with metastasis. Analyzing CaT and PTH separately, the median of CaT was significantly lower for the group that did not present recurrence or relapse than for the group

in which the event occurred. In contrast, the initial postoperative PTH levels remained high in both groups, with no statistical significance. The median above the threshold value for normality until 24 months for the group that did not have recurrence may represent the response of normal parathyroid glands to the bone remineralization process ("hungry bone disease"). This observation is relevant because physicians and patients may be concerned about the risk of recurrence with an "abnormal" PTH result that only reflects bone remineralization. Thus, PTH as a postoperative tumor marker cannot be used alone and must always be compared with calcium levels before recurrence is suspected.

The incidence of locoregional recurrence varies from 30% to 75% and 15% to 30% for distant metastases (mainly to the lung, bone, liver, mediastinum, and brain) (3, 5, 20, 23). The mean time for the appearance of distant metastasis was approximately 23 months (20). Observing only the first 2 to 4 years after initial therapy, this number can reach up to 50%, even with a disease-free survival time of up to 23 years (5). Thus, suspected or diagnosed cases of PC should be followed up for a long period, with periodic measurement of calcium and PTH. There are reports of distant metastasis appearing 10 years after diagnosis of PC, emphasizing the importance of long-term follow-up for these patients (20). In a series from the MD Anderson Cancer Center in the United States, Christakis et al demonstrated a 5-year disease-free survival rate between 62% and 66%, in the periods between 1980 and 2001 and 2002 and 2015, respectively, demonstrating that, despite a 35-year difference, the results remain similar (24).

Regarding factors proven to be relevant in the increase in recurrence rates, tumor size >3 cm was found in the literature, with a cumulative increase in its incidence at 5 and 10 years (20). Three other studies showed that tumor size was a better predictor of prognosis than lymph node status (18, 25, 26). However, in the present sample and in other reports (11), this was not significant. This may indicate that measuring only the largest tumor does not reflect its burden. Perhaps 3-dimensional measurement precisely aided by preoperative computed tomography, for example, may provide helpful information in future studies.

In a retrospective review of 733 patients with PC from the National Cancer Database, age at diagnosis, male sex, and tumor size had a modest effect on survival. Lymph node involvement or neck dissection did not have a statistically significant effect on prognosis, contrary to complete tumor resection, which had a hazard ratio of 0.42 (0.22-0.81) (25). However, another large retrospective study (1022 patients) with the same database concluded that the presence of positive lymph nodes and advanced age predicted lower overall survival and increased risk of death, although the chance of recurrence could not be assessed (27). The presence of metastatic disease and tumors larger than 3 cm were associated with worse overall survival rates in another study in the same database (28). However, such an association could not be observed in the present study.

In addition to size, radical resection at the initial operation, compared with focused parathyroidectomy alone, was associated with significantly lower recurrence rates (1, 4, 5, 22), with an odds ratio of 13 in 1 study (4). Another study compared survival with surgical technique in the first operation with an overall survival rate of 59.6% in patients undergoing en bloc resection compared to 16.7% in those undergoing less radical resections, with a mean survival time of 90 months in the first and 13 months in the second (29). Again, the present cohort presented a different result, with no statistically significant difference between the groups. This indicates that resection of the lesion with free margins is more important than the type of surgery performed and, in a certain way, reinforces the problem of parathyroid tumor location in relation to neighboring structures (11).

After the diagnosis of recurrence, reoperation proved to be effective in disease-free and overall survival, as well as in controlling hypercalcemia (1, 5). It may prolong survival by approximately 7 years (1). This may explain why, despite the relatively high incidence of recurrence, PC has favorable long-term survival rates (70%-90% at 5 years and 50%-80% at 10 years) (1, 3, 6, 22, 24, 27). In the present series, survival rates were in accordance with these rates.

The present study had a relevant number of subjects and data considering the relatively fewer cases among the series already published, mainly because of the rare nature of the disease, especially in the context of a single institution. However, there are some limitations: difficulty in conducting multivariate or conditional analyses with statistical inference; it is based on a single center, and some patients had an initial operation outside the institution. As a rare disease, there is no clear protocol, and some different treatments and drugs were used at the discretion of the teams at different times over a large span of time; difficulty in reviewing pathology slides from the first operation of all patients operated outside the institution, preferably by a single pathologist. Nevertheless, the data and findings suggest that the biological behavior of parathyroid carcinoma is not homogeneous, which encourages further research on prognosis and markers, aiming for multicentric analysis.

Conclusion

In most cases, patients with PC survive for decades and have an indolent disease course. The possibility of late metastasis requires a lifetime follow-up. Resection of the lesion with free margins appears to be the most important factor in initial surgery, despite the type of surgery. Patients with disease recurrence for up to 36 months had a higher risk of death and shorter survival.

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Disclosures

The authors have no related conflicts of interest to declare.

Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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