

# Is extensive surgery really necessary in patients with parathyroid carcinoma?

## Single-centre experience and a brief review of the literature



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### Is extensive surgery really necessary in patients with parathyroid carcinoma? Single-centre experience and a brief review of the literature

**AIM:** Parathyroid carcinoma (PC) represents a rare cause of primary hyperparathyroidism (PHPT).

In this paper, among patients who underwent surgery for PHPT, we compared those with benign parathyroid disease with those affected by PC in terms of demographic and preoperative biochemical features. Moreover, we singularly described all 10 cases of PC treated at our Institution (including a case that occurred in a patient with tertiary hyperparathyroidism) and a brief review of the literature.

**MATERIAL AND METHODS:** Patients undergoing surgery for PHPT in our Unit between 2003 and 2018 were retrospectively analysed. They were divided into two groups: Group A (benign parathyroid disease), Group B (PC).

The case of PC that occurred in the patient with tertiary hyperparathyroidism was not included into the two groups.

**RESULTS:** Three hundred and eight patients were included: 299 in Group A and 9 in Group B. The mean preoperative serum PTH value and mean preoperative serum calcium level were significantly higher in Group B than in Group A ( $P = 0.018$ ,  $P = 0.027$ ; respectively).

Including the case of PC that occurred in the patient with tertiary hyperparathyroidism, 10 patients with PC were treated at our Institution. Among these, 3 underwent a re-exploration. Disease recurrence occurred in 1 (10%) patient, who developed a local recurrence and distant metastases.

**CONCLUSIONS:** In the presence of PHPT characterized by particularly high preoperative levels of serum PTH and calcium this malignancy should be suspected. On the basis of our experience, we believe that extensive surgery is not always necessary.

**KEY WORDS:** Hyperparathyroidism, Parathyroid carcinoma, Parathyroid surgery

## Introduction

Parathyroid carcinoma (PC) represents a rare cause of primary hyperparathyroidism (PHPT). It has been generally estimated that PC accounts for less than 1% of all cases of PHPT, although some authors reported higher rates (up to 5.2%)<sup>1-15</sup>.

Primary hyperparathyroidism (PHPT) is a common endocrine disorder. Prevalence is thought to be 1 to 7 cases per 1000 adults<sup>16</sup>. This condition mainly affects women, with a female/male ratio of approximately 3-4:1<sup>17,18</sup>. As regards the other causes, approximately 80% of patients with PHPT have a single parathyroid adenoma, 10 to 11% have more than one adenoma and less than 10% have a hyperplasia involving all four parathyroid glands<sup>19</sup>.

The absence of specific clinical, biochemical and imaging features makes preoperative differential diagnosis between PC and benign parathyroid disease quite difficult. In some cases PC can be suspected during pre- or intraoperative phases, but definitive diagnosis of this

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malignancy in the vast majority of cases is made after surgery. However, it is important to emphasize that also histopathological diagnosis may be difficult. Many pathological characteristics, such as trabecular architecture and mitotic figures, in fact, are not exclusive of PC, being also present in benign parathyroid diseases, while other histological features, as capsular and vascular invasion or necrosis, are not always present in PC. The main challenge at histopathological examination is to distinguish PC from atypical adenoma. The latter tumor shares some histological characteristics with PC, such as fibrous septa, high mitotic activity and diffuse growth pattern, but lacks unequivocal signs of malignancy, as vascular, capsular and/or perineural invasion. In equivocal cases, diagnosis of PC is confirmed by the occurrence of metastases, which represent the only unequivocal criterion of malignancy<sup>1,3,4,8,9,12-14</sup>.

In the literature, there is a lack of large-scale studies on this tumor, thus its natural course is still unclear and there is no universal consensus on its therapeutic management and follow-up<sup>1-15</sup>.

In this paper, among patients who underwent surgery for PHPT, we compared those with benign parathyroid disease with those affected by PC in terms of demographic and preoperative biochemical features. Moreover, we singularly described all 10 cases of PC treated at our Institution (including a case that occurred in a patient with tertiary hyperparathyroidism) and made a brief review of the literature.

## Material and Methods

In this study patients who underwent surgery for primary hyperparathyroidism in our Unit of General and Endocrine Surgery (University of Cagliari) between January 2003 and December 2018 were retrospectively analysed.

Patients were divided into two groups: those with benign parathyroid disease were included in Group A, those with parathyroid carcinoma in Group B.

The case of PC that occurred in the patient with tertiary hyperparathyroidism was not included into the two groups.

Patients were identified from a prospectively maintained institutional database; those with incomplete data were excluded from the study.

Demographic data (sex and age), preoperative biochemical features (levels of serum PTH and calcium), information on surgical procedure, histopathological findings and follow-up were assessed.

Serum PTH levels were defined normal for values ranging from 10 to 65 pg/mL, while serum calcium levels were defined normal for values ranging from 8.5 to 10.3 mg/dL.

Preoperative localization studies (neck ultrasound and <sup>99m</sup>Tc-sestamibi scintigraphy) were performed routinely.

Intraoperative PTH (ioPTH) determination was routinely used to confirm removal of all pathological glands: the test was defined as positive when the PTH value, 10 minutes after the excision of the suspected pathological gland, dropped by 50% or more from the preoperative value or when it was within reference values. In case of negative test, another measurement was made 20 minutes after the excision and, if the negative result was confirmed, a bilateral exploration was performed.

In case of diagnosis of parathyroid carcinoma at histopathological examination in patients who underwent parathyroidectomy alone, a re-exploration was performed, executing ipsilateral hemithyroidectomy, to make treatment more radical, only in the presence of aggressive histopathological features, such as extensive vascular and capsular invasion, also taking into account the opinion of the endocrinologist. Cervical lymph node dissection was performed only in case of suspicion of lymph node metastases.

All patients were referred to their endocrinologist for postoperative follow-up.

Statistical analyses were performed with MedCalc® 19.1.3. Fisher exact test was used for categorical variables and t-test for continuous variables. *P* values < 0.05 were considered statistically significant.

## Results

A total of 308 patients were included in this study: 299 in Group A and 9 in Group B.

PC accounted for 2.92% of PHPT cases.

In Group A, there were 43 (14.38%) males and 256 (85.62%) females, with a mean age of  $59.4 \pm 13.17$  years old. The mean preoperative serum PTH value was  $319.59 \pm 479.56$  pg/mL, while the mean preoperative serum calcium level was  $11.33 \pm 1.10$  mg/dL.

In Group B, there were 1 (11.11%) male and 8 (88.89%) females, with a mean age of  $63.89 \pm 7.54$

TABLE I - Demographic data and preoperative biochemical features.

	Group A (n = 299)	Group B (n = 9)	P value
Sex			
- Male	43 (14.38%)	1 (11.11%)	1.000
- Female	256 (85.62%)	8 (88.89%)	
Age (years, mean $\pm$ SD)	$59.40 \pm 13.17$	$63.89 \pm 7.54$	0.310
Preoperative PTH (pg/mL, mean $\pm$ SD)	$319.59 \pm 479.56$	$712.22 \pm 725.29$	0.018
Preoperative calcium (mg/dL, mean $\pm$ SD)	$11.33 \pm 1.10$	$12.21 \pm 1.58$	0.027

SD: standard deviation; PTH: parathyroid hormone.

TABLE II - Cases of parathyroid carcinoma treated at our Institution.

Case (Year of diagnosis)	Sex, age	Preoperative PTH (pg/mL)	Preoperative calcium (mg/dL)	Surgical procedure	Re-exploration following histological examination	Recurrence	Follow-up (Years)
1 (2003)	F, 57	122	12.4	Left superior PTX	No	No	16.75
2 (2005)	M, 59	1685	15.7	Mediastinal PTX	No	Local recurrence and lung metastases	14.42
3 (2006)	F, 64	1642	12.2	Right inferior, left inferior and left superior PTX, TT*	No	No**	5.50
4 (2007)	F, 62	187	10.5	Right inferior PTX	Right hemithyroidectomy, CND	No	12.42
5 (2010)	F, 66	185	11.2	Right inferior PTX	No	No	9.67
6 (2013)	F, 52	356	12.1	Right inferior PTX	No	No	6.50
7 (2013)	F, 73	182	10.8	Left superior PTX	Left hemithyroidectomy	No	6.92
8 (2014)	F, 66	1693	13.4	Right inferior PTX	Right hemithyroidectomy, Retrosophageal PTX***	No	5.92
9 (2015)	F, 76	358	11.6	Right inferior PTX	No	No****	1.92
10***** (2018)	M, 51	2582	10.7	Right and left inferior PTX	No	No	1.92

PTH: parathyroid hormone; M: male; F: female, PTX: parathyroidectomy; CND: central neck dissection; TT: total thyroidectomy.

\* Concomitant multinodular goiter.

\*\* Patient died in April 2011 from other disease.

\*\*\* Persistent primary hyperparathyroidism.

\*\*\*\* Patient died in December 2016 from other disease.

\*\*\*\*\* Patient with tertiary hyperparathyroidism.

years old. The mean preoperative serum PTH value was  $712.22 \pm 725.29$  pg/mL, while the mean preoperative serum calcium level was  $12.21 \pm 1.58$  mg/dL.

The comparison between the two groups, in terms of mean preoperative serum PTH value and mean preoperative serum calcium level, resulted in statistically significant results ( $P = 0.018$ ,  $P = 0.027$ ; respectively). These preoperative biochemical features were significantly higher in Group B than in Group A.

On the contrary, no statistically significant difference was found in terms of sex and age. These results are shown in Table I.

The cases of PC treated at our Institution are summarized in Table II.

Including the case of PC that occurred in the patient with tertiary hyperparathyroidism, we reported 10 cases. This malignancy occurred in 8 females and 2 males, at a mean age of 62.6 years old, with a range from 51 to 76 years. As initial surgery all patients but 1 underwent parathyroidectomy alone (in 1 of these cases two parathyroid

glands were removed). The remaining patient underwent removal of three parathyroid glands and total thyroidectomy for a concomitant multinodular goiter.

Following histopathological examination, 3 patients underwent a re-exploration. In 1 case, in addition to ipsilateral hemithyroidectomy, central neck dissection was performed (without evidence of lymph node metastasis at histological examination). In another case, in addition to hemithyroidectomy, removal of a retrosophageal parathyroid gland was done, due to the persistence of PHPT (caused by concomitant benign parathyroid disease).

Disease recurrence occurred in 1 patient, thus the rate was 10%. The patient developed a local recurrence, 6 years after initial surgery, and lung metastases, 8 years after the initial operation.

Currently, among 10 patients, 8 are still alive. About the remaining 2 patients, 1 died in April 2011, 5 years after surgery, and the other died in December 2016, 1 year after the operation, both patients from other diseases. The mean follow-up was 8.19 years.

## Discussion

Parathyroid carcinoma, described for the first time in 1904 by De Quervain<sup>15</sup>, is one of the rarest cancers, accounting for approximately 0.005% of all malignancies in the USA<sup>20</sup>.

Differently from benign PHPT, women and men are usually equally affected. The age at diagnosis is on average between 45 and 50 years old, a decade earlier than benign PHPT<sup>3,4,8,9,12-14</sup>.

PC can be sporadic or occur in the context of genetic endocrine syndromes, as hyperparathyroidism-jaw tumor syndrome (HPT-JT), Multiple Endocrine Neoplasia type 1 (MEN 1), Multiple Endocrine Neoplasia type 2A (MEN 2A) and familial isolated hyperparathyroidism (FIHP)<sup>3,4,7,9,12-14</sup>.

The etiopathogenesis is unknown, however a genetic background has been established. Genomic alterations identified in PC are mostly represented by CDC73 gene mutations, the same gene involved in HPT-JT, codifying for a protein called parafibromin. Moreover, whole exome sequencing identified alterations in other genes, such as PRUNE2 and CCND1, and in well-known oncogenic pathways (PI3K/AKT/mTOR). Alterations of miRNAs and methylation have also been detected<sup>3,4,14</sup>. PC is usually a functioning neoplasm. The variant of non-functioning PC, in which serum calcium and PTH values are normal, is extremely rare (less than 10% of all cases of PC). It is characterized by the tumor mass effect on the surrounding structures and it has been described as a palpable stone neck mass associated with hoarseness (due to palsy of laryngeal recurrent nerve) and dysphagia<sup>3,4,8,9,12-14</sup>.

Clinical manifestations of functioning PC, due to PTH-related hypercalcemia, are similar, but more severe, than those of benign PHPT. At presentation, renal and bone involvement is present in a very high percentage of patients. Other symptoms include malaise, fatigue, weakness, polydipsia, and polyuria. Gastrointestinal symptoms such as abdominal pain, nausea and vomiting, peptic ulcer, severe pancreatitis and constipation can also occur<sup>2-5,8,9,12-14</sup>.

In a patient with PHPT, severe hypercalcemia (> 14 mg/dL), very high serum PTH levels (five times above the normal range), concomitant severe renal and skeletal manifestations and palpable cervical mass should raise suspicion for PC<sup>2-5,8,9,12-14</sup>.

Imaging techniques, as neck ultrasound and <sup>99m</sup>Tc-sestamibi scintigraphy, are useful for tumor localization, but cannot reliably discriminate benign from malignant PHPT<sup>3,4,9,12-14</sup>.

CT and MRI may provide information about lesion extension, eventual invasion into surrounding structures and distant metastases<sup>3,4,9,12-14</sup>.

The role of FDG-PET (fluorodeoxyglucose positron emission tomography) is still controversial. This examination may be useful to detect metastases/recurrence, but

it is important to note that lesions of osteitis fibrosa cystica, that can be present in patients with PC, are hypermetabolic and positive at FDG-PET and, therefore, may be misdiagnosed as bone metastases<sup>3,4,9,12-14</sup>.

Fine needle aspiration cytology is not recommended and should be avoided if PC is suspected because of the risk of tumor cell seeding<sup>3,4,9,12-14</sup>.

Selective venous catheterization with PTH measurement has been used for localizing recurrences when other techniques are negative or equivocal<sup>3,4,9,12-14</sup>.

Surgery is the mainstay of treatment, while usefulness of chemotherapy, radiotherapy and other treatments remains still controversial. The surgical approach mostly suggested consists in an en bloc resection of the pathological parathyroid gland with the ipsilateral thyroid lobe and any adjacent involved structures. Cervical lymph node dissection is mostly recommended only in case of preoperative diagnosis or intraoperative suspicion of lymph node metastases<sup>1-5,8,9,12-14</sup>.

In case of parathyroidectomy alone and diagnosis of PC at histopathological examination, the management of the patient becomes more difficult. In this situation, clinical judgment and prompt decision making to choose further neck exploration or surveillance are required. In the presence of aggressive histopathological features, such as extensive vascular and capsular invasion, a re-exploration to make treatment more radical should be performed<sup>3-5,9,12-14</sup>.

Restoration of normocalcemia after surgery indicates that all hyperfunctioning tissue has been removed. The use of intraoperative PTH determination could be helpful in surgical management<sup>21-27</sup>.

It is important to emphasize that following surgery postoperative hypocalcemia may occur, due to inhibition of remnant parathyroid glands or hungry bone syndrome. This condition must be promptly treated with oral or intravenous calcium supplementation<sup>3,4,8,9,12-14</sup>.

As regards PC recurrence, it is generally reported in > 50% of patients, usually after 2–3 years from surgery, although relapses have been described up to 23 years after initial treatment. For this reason, in patients with this tumor follow-up should be careful and life-long<sup>1,3,4,8,9,12-14</sup>.

The recurrence site is most frequently locoregional, due to incomplete resection at initial surgery and cervical lymph node metastases, however also distant metastases are not infrequent. Lymph node metastases occur in about 15–30% of patients at initial presentation. Distant metastases occur in about 25% of patients during follow-up, usually in lungs, liver and bone<sup>3,4,9,12-14</sup>.

Primary treatment for disease recurrence is surgical removal, both for local recurrences and, if possible, for distant metastases, even through repeated resection<sup>3-5,9,12-14</sup>.

When PC relapses may not be surgically treated, medical treatment is necessary to control hypercalcemia. Saline infusion and loop diuretics are generally used, but

in the majority of cases other drugs are needed. Cinacalcet, an allosteric modulator of the calcium-sensing receptor (CaSR), and agents that block bone resorption, such as bisphosphonates and denosumab, are useful for the control of hypercalcemia and related symptoms<sup>3,4,14</sup>.

Five- and 10-year survival rates between 77-100% and 49-91%, respectively, have been reported. Mortality generally derives from complications of hypercalcemia rather than from tumor burden. As regards non-functioning PC, prognosis remains uncertain due to the exceptional rarity of this malignancy<sup>3,4,9,12-14</sup>.

In this paper, among patients who underwent surgery for PHPT, we compared those with benign parathyroid disease with those affected by PC in terms of demographic and preoperative biochemical features. Moreover, we singularly described all 10 cases of PC treated at our Institution (including a case that occurred in a patient with tertiary hyperparathyroidism).

In accordance with the literature<sup>1-15</sup>, in our experience, the rate of PC in patients with PHPT was 2.92%. In 1 case we found the simultaneous occurrence of benign parathyroid disease and PC.

As regards the comparison between the two groups in terms of mean preoperative serum PTH value and mean preoperative serum calcium level, we found that these preoperative biochemical features were significantly higher in patients affected by PC than in those with benign parathyroid disease. Also this data is consistent with reports of other authors<sup>3,4,9,12-14</sup>.

On the contrary, as regards sex and age of patients with PC, our findings disagree with what is described in the literature<sup>3,4,9,12-14</sup>. In fact, among our patients, PC mainly occurred in woman, with a female/male ratio of 4:1, and diagnosis was made on average at the beginning of the seventh decade of life. However, results obtained from the comparison of two groups in terms of demographic data were not statistically significant.

Another finding which strongly disagrees with what has been reported by other authors concerns the occurrence of relapse<sup>3,4,9,12-14</sup>. In our experience, in fact, the recurrence rate was quite lower, only 10%.

This result is even more singular considering that extensive surgery was not always performed.

This may mean that this surgical approach, consisting in an en bloc resection of the pathological parathyroid gland with the ipsilateral thyroid lobe, is not always necessary but should be adopted only in the most aggressive cases.

At our Institution, also in case of preoperative suspicion of PC, as in some of the cases presented, in the absence at surgical exploration of macroscopic invasion of adjacent tissues by the pathological parathyroid gland we prefer to adopt a less extensive approach, without performing ipsilateral hemithyroidectomy.

About cervical lymph node dissection, we believe that it should be performed only in case of preoperative diag-

nosis or intraoperative suspicion of lymph node metastases. Prophylactic cervical lymph node dissection, in our opinion, is not necessary. In our experience, cervical lymph node dissection was performed only in 1 case, because of intraoperative suspicion of lymph node metastasis. However, no lymph node metastasis was found at histological examination.

In case of diagnosis of parathyroid carcinoma confirmed through histopathological examination in patients who underwent parathyroidectomy alone, we believe that a re-exploration, executing ipsilateral hemithyroidectomy, to make treatment more radical, should be performed only in the presence of aggressive histopathological features, such as extensive vascular and capsular invasion, also taking into account the opinion of the endocrinologist and the patient's preference.

As regards the patient who developed disease recurrence, he underwent parathyroidectomy alone and was not submitted to a re-exploration. In this case, despite the absence of aggressive histopathological features, the tumor recurred. This fact demonstrates that a careful and close follow-up is certainly always mandatory. About the management of disease recurrence, the patient received surgical treatment for the local relapse, while hypercalcemia resulting from lung metastases (which are not surgically treatable) is still managed through medical therapy with Cinacalcet.

Our paper has a considerable limitation. It is a retrospective study based on a prospectively maintained institutional database. For this reason, it is lacking in some important information: preoperative clinical features of patients, aspect of the parathyroid glands at surgical exploration, detailed histopathological findings (including size and weight of the parathyroid glands), and genomic alterations. Unfortunately, in the absence of this data, it is not possible to fully analyze the PC cases presented and, above all, it is not possible to justify their less aggressive behavior.

Thus, further studies are needed to better investigate the possibility to adopt a less extensive surgical approach for the treatment of this rare tumor.

## Conclusions

Parathyroid carcinoma is a rare cause of primary hyperparathyroidism.

Preoperative diagnosis remains still challenging. However, in the presence of PHPT characterized by particularly high preoperative levels of serum PTH and calcium this malignancy should be suspected.

To date, extensive surgery is considered the mainstay of treatment. However, on the basis of our experience, we believe that this surgical approach is not always necessary. Thus, in some cases less extensive surgery could be performed. However, a careful and close follow-up is certainly always mandatory.

## Riassunto

Il carcinoma paratiroideo rappresenta una rara causa di iperparatiroidismo primitivo.

In questo studio, tra i pazienti sottoposti ad intervento chirurgico per iperparatiroidismo primitivo, abbiamo confrontato quelli con malattia paratiroidea benigna con quelli affetti da carcinoma paratiroideo in termini di dati demografici e caratteristiche biochimiche preoperatorie. Inoltre, abbiamo descritto singolarmente tutti i 10 casi di carcinoma paratiroideo trattati presso la nostra Unità Operativa (incluso un caso che si è verificato in un paziente con iperparatiroidismo terziario).

Sono stati analizzati retrospettivamente i pazienti sottoposti a ad intervento chirurgico per iperparatiroidismo primitivo nella nostra Unità Operativa tra il 2003 e il 2018. Gli individui reclutati sono stati divisi in due gruppi: quelli con malattia paratiroidea benigna sono stati inclusi nel Gruppo A, quelli con carcinoma paratiroideo nel Gruppo B. Il caso di carcinoma paratiroideo che si è verificato nel paziente con iperparatiroidismo terziario non è stato incluso nei due gruppi.

Trecentootto pazienti sono stati inclusi nello studio: 299 nel Gruppo A e 9 nel Gruppo B. Il valore preoperatorio medio di PTH ed il livello preoperatorio medio di calcio sono risultati significativamente più alti nel Gruppo B rispetto al Gruppo A ( $P = 0.018$ ,  $P = 0.027$ ; rispettivamente).

Comprendendo il caso del carcinoma paratiroideo che si è verificato nel paziente con iperparatiroidismo terziario, 10 pazienti con questa neoplasia sono stati trattati presso la nostra Unità Operativa: 8 femmine e 2 maschi, a un'età media di 62.6 anni.

In seguito all'esame istologico, in 3 pazienti è stata eseguita una nuova esplorazione cervicale (in 1 caso anche per la persistenza dell'iperparatiroidismo primitivo).

La recidiva della malattia si è verificata in 1 (10%) paziente, che ha sviluppato una recidiva locale e metastasi a distanza.

In conclusione, la diagnosi preoperatoria del carcinoma paratiroideo rimane ancora difficile, tuttavia in presenza di iperparatiroidismo primitivo caratterizzato da livelli preoperatori particolarmente elevati di PTH e calcio questa neoplasia dovrebbe essere sospettata.

Sulla base della nostra esperienza, riteniamo che un intervento chirurgico esteso non sia sempre necessario.

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