Management and Surgical Treatment of Parathyroid Carcinoma: a 6-years’ experience of single centre of Endocrine Surgery Unit

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Abstract

Parathyroid carcinoma (PC) affects 0.1–0.3% of the general population and represents the rarest malignant neoplasms among endocrinological disease, representing less than 1%. Differential diagnostic from malignant to benign disease is challenging and the best therapeutic treatment and management are still debated in literature. The aim of this study is the evaluation of management and surgical treatment of Parathyroid Carcinoma after 6 years enrollment from the Endocrine Surgery Unit of the University Hospital of Bari. A retrospective observational study was carried out using a prospectively maintained database of patients affected by primary hyperparathyroidism underwent surgery in the Endocrine Surgery Unit between January 2017 and September 2022. Nine patients were included with histological diagnosis of PC and the evidence of pre operative high levels of serum PTH and calcium. No mortality was recorded while the incidence of recurrence was 22.2% with a disease-free survival of 8 and 10 months respectively. PC represents a great challenge in terms of pre-operative diagnostic, management and treatment. Surgical approach represents the first best option for PC in referral endocrine surgery units. The early identification of risky patients should be dominant to plan an appropriate therapy and to perform an adequate en bloc surgery.

Introduction

Parathyroid carcinoma (PC) affects 0.1–0.3% of the general population and represents the rarest malignant neoplasms among endocrinological disease, representing less than 1%. The histological examination detects PC in the majority of cases, because a preoperative diagnosis is difficult due to the absence of specific criteria and the impossibility of fine-needle aspiration because the violation of parathyroid capsule could determine subsequent tumour seeding.

Etiology of PC is still unknown. PC may occur in sporadic cases, most common and especially single-gland disease, or may be associated to hereditary endocrinopathies as Multiple Endocrine Neoplasia type 1 (MEN1) or type 2A (MEN 2A), HPT-jaw tumor syndrome (HPT-JT) or in familial isolated hyperparathyroidism (FIHP). The increasing of parathyroid hormone (PTH) and serum calcium represent clear signs of hyperparathyroidism with subsequent signs and symptoms. Patients (pts) can be affected by gastrointestinal, neurological, cardiological, bone and kidney diseases and in some cases palpable neck mass. Unfortunately, metastatic disease could affect 10–30% of pts at the time of the diagnosis, presenting lung, liver and bone invasion.

The differential diagnostic from parathyroid hyperplasia and adenomas could be complex, but the suspicion of cancer increases in cases of certain findings, as higher levels of serum PTH and calcium, parathyrotoxicosis, palpable neck mass. PTH reaches high levels, from 3 to 10 times higher than the normal serum value in cases of PC. 98% of cancers are functioning tumors with more frequent bone and kidney disease, while only 2% are characterized normal serum levels of PTH and calcium with the evidence of palpable and invasive mass.

Prognosis is poor for PC because of mortality due to uncontrollable levels of hypercalcemia and subsequent diseases. The overall survival rate at 5 years is 78–85% and at 10 years is 49–70%.

Differential diagnostic from malignant to benign disease is challenging and the best therapeutic treatment and management are still debated in literature. Several studies revealed the inefficacy of Chemo and Radiotherapy and further options such as immunotherapy and targeted therapies have been proposed in several studies.

The aim of this study is the evaluation of management and surgical treatment of Parathyroid Carcinoma after 6 years enrollment from the Endocrine Surgery Unit of the University Hospital of Bari. Secondary aim is to compare the results from existing studies. PC remains a difficult disease to detect in pre-operative and to prevent. The early identification of risky patients should be dominant to plan an appropriate therapy and to perform an adequate en bloc surgery.

Material And Methods

A retrospective observational study was carried out using a prospectively maintained database of patients affected by primary hyperparathyroidism with suspected parathyroid carcinoma who, according to guidelines for management of primary hyperparathyroidism from the American Association of Endocrine Surgeons, underwent surgery in the Endocrine Surgery Unit between January 2017 and September 2022. Consecutive patients over 18 years old, with final histopathological finding of parathyroid carcinoma were included in the study. Patients with secondary or tertiary hyperparathyroidism, parathyroid hyperplasia and parathyroid adenoma were excluded.

All patients underwent physical examination, cervical ultrasound, computer tomography and 99m Tc sestamibi scintigraphy as part of their diagnostic work-up to locate the lesion; F-fluorodeoxyglucose pet/ct was performed only in selected cases.

Gender, age, clinical symptom at admission, family history, serum PTH, calcium, phosphate, creatinine and 24-hour urinary calcium and phosphate level were recorded preoperative. Calcium was recorded 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), creatinine in mg/dL (range 0.84–1.21), 24-hour calciumia in mg/kg/24 h (normal value < 4 mg/kg/24 h) and 24-hour phosphaturia in g/L/24h (normal value < 1.35 g/L/24h). Postoperative parameters registered included serum PTH, calcium, and possible surgical complications. All patients underwent follow-up every 6 months, for the first 2 years, and annually thereafter. 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 considered transient if lasting less than six months and definitive if lasting longer. The informed consent was obtained from all patients before enrolment. All investigations complied with the principles of the Declaration of Helsinki.

Statistical Analysis
Continuous parameters were reported as medians and IQRs. The categorical variables were recorded as numbers and percentages. Statistical analysis was carried out using RStudio (R version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria).

Results

Nine out of 40 patients affected by hyperparathyroidism, 6 (66.6%) female and 3 (33.3%) male patients, with a median age of 59 years (IQR 46–62), were included in the study. At admission 2 (22.2%) patients had nephrolithiasis, 4 (44.4%) bone disease, 4 (44.4%) chronic kidney failure (2 of them waiting for kidney transplantation), one Berger's disease and 3 patients (33%) were asymptomatic. None had family history of parathyroid carcinoma.

In the pre-operative work-up all of patients had high level of PTH (median 432 pg/mL, IQR 296.5–877) and hypercalcemia (median value 11.20 mg/dL, IQR 11-14.30) except one female patient, with 8.8 mg/dL, that discovered parathyroid carcinoma during a total thyroidectomy for thyroid goitre. Calciuria and phosphaturia were recorded in only 2 patients. Parathyroidectomy was performed in 5 patients, while 4 patients underwent parathyroidectomy with concurrent thyroidectomy for thyroid goitre. No intraoperative complications were recorded. Open parathyroidectomy was performed with mini-cervicotomy in 7 patients, while 2 pts underwent robotic surgery. All patients were discharged on the second postoperative day. Five patients (55.5%) had transient postoperative hypocalcemia treated with oral calcium supplementation and three (33.3%) patients developed definitive postoperative hypoparathyroidism, any other postoperative complication was observed. Two patients recorded high postoperative PTH, 180 and 249 pg/mL respectively, while in 7 patients was in normal range. Histopathological examination revealed parathyroid carcinoma in all of patients with Ki67 always ≥ 4% (median value 4%, IQR 4–7) and with chromogranin positive in 3 (33%) patients, synaptophysin was positive in 2 (22.2%) patients.

After a median follow-up of 36 months (IQR 12–48), no mortality was recorded while the incidence of recurrence was 22.2% (2 patients) with a disease-free survival of 8 and 10 months respectively. Follow up included endocrinological, surgical and dental evaluation, renal US scan, biochemical blood test. Two patients had the highest postoperative PTH of all the series and both underwent parathyroidectomy with uneventful recovery and discharged on the second postoperative day.

The clinical data of patients with parathyroid carcinoma have been summarized in Table 1.
Table 1  
Clinicopathologic features of parathyroid carcinoma patients

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age</th>
<th>Clinical Symptoms</th>
<th>Calcium (mg/dL)</th>
<th>PTH (pg/mL)</th>
<th>Phosphate (mg/dL)</th>
<th>Creatinine (mg/dL)</th>
<th>Phosphaturia (mg/dL)</th>
<th>Calcium (mg/dL)</th>
<th>Surgery</th>
<th>Calcium Post (mg/dL)</th>
<th>PTH Post (pg/mL)</th>
<th>Defi hyp/pare</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>46</td>
<td>nephrolithiasis, osteopenia, osteoporosis</td>
<td>11.2</td>
<td>1800</td>
<td>1.9</td>
<td>0.96</td>
<td>38.1</td>
<td>7.3</td>
<td>TT + PrT</td>
<td>10.1</td>
<td>28</td>
<td>Yes</td>
</tr>
<tr>
<td>M</td>
<td>65</td>
<td>nephrolithiasis, osteopenia, osteoporosis</td>
<td>9.7</td>
<td>180</td>
<td>45</td>
<td>1.65</td>
<td>0</td>
<td>0</td>
<td>Inferior right PrT</td>
<td>10.2</td>
<td>180</td>
<td>No</td>
</tr>
<tr>
<td>F</td>
<td>43</td>
<td>CKF</td>
<td>8.8</td>
<td>/</td>
<td>/</td>
<td>14.3</td>
<td>0</td>
<td>0</td>
<td>TT + PrT</td>
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<td>&lt; 6</td>
<td>Yes</td>
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<tr>
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<td>14.3</td>
<td>/</td>
<td>/</td>
<td>1.06</td>
<td>0</td>
<td>0</td>
<td>TT + PrT</td>
<td>6.5</td>
<td>&lt; 6</td>
<td>Yes</td>
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<td>61</td>
<td>CKF, Berger's disease osteopenia, osteoporosis, fatigue, dyspeisa</td>
<td>11.1</td>
<td>238</td>
<td>3</td>
<td>0.63</td>
<td>546</td>
<td>323</td>
<td>inferior right PrT</td>
<td>7.4</td>
<td>37</td>
<td>No</td>
</tr>
<tr>
<td>M</td>
<td>37</td>
<td>CKF, Berger's disease osteopenia, osteoporosis, fatigue, dyspeisa</td>
<td>17.6</td>
<td>355</td>
<td>/</td>
<td>1.51</td>
<td>0</td>
<td>0</td>
<td>inferior right PrT</td>
<td>8.5</td>
<td>249</td>
<td>No</td>
</tr>
<tr>
<td>F</td>
<td>62</td>
<td>CKF, Berger's disease</td>
<td>14.3</td>
<td>1156</td>
<td>7</td>
<td>12.3</td>
<td>0</td>
<td>0</td>
<td>superior, inferior right and inferior left PrT + TT</td>
<td>5.5</td>
<td>8</td>
<td>Yes</td>
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<tr>
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<td>57</td>
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<td>14.1</td>
<td>598</td>
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<td>0.9</td>
<td>0</td>
<td>0</td>
<td>inferior right PrT</td>
<td>9.3</td>
<td>13</td>
<td>Yes</td>
</tr>
<tr>
<td>M</td>
<td>63</td>
<td>CKF</td>
<td>11</td>
<td>432</td>
<td>7.5</td>
<td>9.46</td>
<td>0</td>
<td>0</td>
<td>inferior left PrT</td>
<td>6.7</td>
<td>78</td>
<td>No</td>
</tr>
</tbody>
</table>

TT = total thyroidectomy PrT = parathyroidectomy PTH = parathyroid hormone CKF = chronic kidney failure

Discussion

The best therapeutic option to cure pts affected by PC is a pre or intra operative diagnostic and the complete resection of the tumour at the first initial surgical approach.

In this study, 9 cases of PC have been detected in 6 years, according to the evident percentage in literature. The prevalence of female sex is relevant (66,6%) and this result can be important in case of suspicion of PC, considering the same prevalence in primary hyperparathyroidism. The median age is 59 years (IQR 46–62), while Machado et al reported a tendency of younger age, about 50 years at the time of the diagnosis. The certain diagnostic of PC was evident after the histological examination in all cases. All patients presented high serum levels of PTH and calcium.

The first surgical approach was parathyroidectomy in 5 patients with subsequent secondary surgical step according to multidisciplinary evaluation; in 4 cases thyroidectomy was performed because of compressive goitre. The same experienced endocrine surgeon performed all procedures, respecting all principles of en bloc surgery: complete exploration, bloodless field, minimal manipulation of the tumour, evaluation of nodal involvement and exploration of ipsilateral laryngeal nerve. In all cases, no nodal or nerve involvement was evident. The suspicion of PC could be also intraoperative, because the tumour presents hard consistency, fibrous capsule and a white or grey hue and adherent to nearby structures (Figs. 1 and 2). Adenomas can appear softer and reddish coloured with well-defined limits.

Two cases of recurrence (22,2%) are not still treated because of clinical condition not suitable for surgery. According to Certani et al, 3 years represent the mean time to diagnose recurrence, although some studies reported recurrences after 20 years. In case of recurrences, surgery still represents the best therapeutic option with the main aim at relieve symptoms and to eradicate residual disease.
Several studies contributed to understand the natural history, diagnostic, genetics and treatment of PC. Unfortunately, the rarity of this disease, the existing results from report of few cases and a lack of complete clinical data represent the main cause of the absence of adequate guidelines. Moreover, follow-up information are not usually available.

The prevention of PC is difficult and the best expectation is to develop specific genetic analysis and pre-operative diagnostic. In 2017, Silva-Figueroa et al\textsuperscript{18} proposed a prognostic scoring system to detect PC. The score was based on 3 risk groups (low, moderate and high) according to 3 main variables and the recurrence free survival rate. Actually, this score is not still validated but it could be associated to clinical, genetic and histological markers in order to realise a pre-operative PC diagnosis. In 2021, Shulte et al\textsuperscript{19} distinguished the main histological and clinical features between parathyromatosis, atypical parathyroid adenomas and PC. This study included a strict number of cases and revealed a higher level of cellular necrosis in PC and in adenomas without a clear distinction.

According to the existing results in literature, the suspicion of PC should be based on severe PTH high levels, hypercalcemia, bone and kidney diseases and evident neck mass. The best therapeutic option still remains surgery according to en bloc surgery concepts in referral endocrine surgery units\textsuperscript{17,20,21,22}. The role of immunotherapy could be useful to decrease tumour size in isolated cases, as demonstrated by Betea et al\textsuperscript{23}. According to Wei and Hariri, two cases of inoperable metastatic PC underwent experimental immunotherapy with satisfying results\textsuperscript{8}.

Genetic and epigenetic investigations are in progress, in order to identify specific factors and characterize biological molecules and genetic network of PC's cells and subsequently, targeted therapies\textsuperscript{12}.

**Conclusions**

PC represents a great challenge in terms of pre-operative diagnostic, management and treatment. Its rarity is not helpful to acquire clear genetic, clinical and histological features. Surgical approach represents the first best option for PC in referral endocrine surgery units. In this context, in order to offer the best treatment, to optimize clinical management and surveillance, multidisciplinary team should play a key-role. Further multicentric trials are necessary to improve pre-operative diagnostic and outcomes, to prevent recurrences and to recognize risky patients.

**Declarations**

- **Ethics approval and consent to participate**
  - All experiments were performed in accordance with relevant guidelines and regulations (such as the Declaration of Helsinki).
  - The need for approval was waived by Ethics committee of Hospital University of Bari due to retrospective nature of the study.
  - Informed consent was obtained from all subjects

- **Consent for publication**
  - Not applicable

- **Availability of data and materials**
  - The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

- **Competing interests**
  - The authors declare that they have no competing interests

- **Funding**
  - This research received no external funding

**Authors' contributions**

- Conceptualization: A.P., A.P. and R.L.
- Methodology: G.T. and F.C.
- Software: M.S., A.S.
- Validation: A.P., A.P.
- Formal analysis: G.T., F.C.
- Investigation: R.L., F.C. and M.S.
- Resources: A.S., G.T. and F.C.
- Data curation: F.C., M.S. and A.S.
- Writing—original draft preparation: F.C., G.T. and R.L.
- Writing—review and editing: A.P, A.P., M.S.
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Not applicable

References


Figures
Figure 1

Intraoperative visualization of parathyroid gland

Figure 2

Suspected PC after parathyroidectomy