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Parathyroid Carcinoma – A Tertiary Centre's Experience Over 15 Years

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Abstract

Objectives:

To determine the rate of recurrence, metastasis and survival outcomes of patients diagnosed and treated for parathyroid carcinoma.

Methods:

Retrospective chart review for patients diagnosed with parathyroid carcinomas between 01/01/2007 – 31/12/2022 in a UK tertiary centre.

Results:

14 patients were identified, all of whom received surgery following their diagnosis. On presentation, all patients (100%) were hypercalcaemic, with 2 patients (14%) having metastatic lesions. There was a single case (7%) of loco-regional recurrence following surgery. 6 patients passed away after a median follow-up of 2.5 years, 4 due to causes related to parathyroid carcinoma.

Conclusions:

Surgical excision remains the mainstay of treatment, but this can only be undertaken after the patient has been medically stabilised. Mortality in this group of patients generally arose from the effects of hypercalcaemia. Metastasis and recurrence from our cohort were rare, but long-term follow-up with monitoring of calcium and PTH levels remains key.

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Introduction

Parathyroid Carcinoma is a rare malignancy [1], estimated to consist of 0.005% of all cancers [2,3] and to be the cause of <1% of primary hyperparathyroidism [1,2]. Due to its rarity, parathyroid carcinomas are incompletely understood, with some reviewers reporting less than 1000 documented cases [3] and a recent systematic review finding only 79 cases between 1898 and 2018 [4]. As a result, the creation of guidelines for the management of parathyroid carcinoma has been difficult.

Worldwide, parathyroid carcinoma is the rarest endocrine cancer [1]. Unlike parathyroid adenomas, parathyroid carcinomas appear to affect both genders equally and are common in patients aged between 40-60 years [2,4]. For sporadic cases of parathyroid carcinoma, the main risk factors include previous head and neck irradiation and long-standing secondary/tertiary hyperparathyroidism in rare cases [5,6]. Several genetic syndromes have been linked to Parathyroid Carcinoma, including Hyperparathyroidism-Jaw Tumour Syndrome (HPT-JT), Multiple Endocrine Neoplasia Type 1, Type 2A and Familial Isolated Hyperparathyroidism [5–7].

Most cases of parathyroid carcinoma present with severe hypercalcaemia and primary hyperparathyroidism [1,3,8–11]. Outside of these cases, diagnosing parathyroid carcinoma can be difficult [1,9]. An ultrasound scan is currently regarded as the best initial imaging modality [1,2,9], with findings such as cystic structures, irregular borders, and calcification being signs suspicious of malignancy [1,2]. If these are present, further axial imaging such as CT, MRI or PET-CT scans can be used for evaluation and surgical planning [1,2,9]. Microscopically, no specific histological hallmark features for parathyroid carcinomas have been found [1,11]. Current guidelines recommend looking for angioinvasion, lymphatic invasion, perineural invasion,

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invasion into adjacent anatomic structures or histologically/cytologically documented metastatic disease to help guide diagnosis [8]. Genetic markers for parathyroid carcinoma are thought to include CDC73, CCND1 and PI3K/AKT/mTOR; CDC73 is the most common and mutated gene in HPT-JT [1,4,11].

Surgical resection is described as the gold standard treatment for parathyroid carcinoma in the literature, with no current role for chemotherapy or radiotherapy in its management [1,4,12]. Despite this, recurrence rates have been reported to be 50-60% at 2-5 years following treatment [4]. For patients in whom surgical management is unsuccessful, the most common cause of fatalities is uncontrolled hypercalcaemia which often proves to be resistant to medical treatment [4,9].

As a tertiary centre, we wanted to determine the most frequently used treatment methods and patient outcomes for cases of Parathyroid Carcinoma. To this end, we reviewed all the cases of parathyroid carcinoma treated by our unit in the past 15 years.

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Methods

A retrospective review was conducted to identify patients diagnosed and treated for parathyroid carcinoma between 01/01/2007 and 31/12/2022 at our tertiary centre.

Patients were identified by searching our local histological database for specimens diagnosed with parathyroid carcinoma using coding. Following this, a general search of all the parathyroid sample reports from the period was analysed to find any specimens that had been incorrectly coded.

Once identified, the patient's clinical record was analysed to obtain demographic information, investigation/radiology results and the overall outcomes of their management. The primary outcome of our review was to determine the survival rate and the rate of recurrence and metastasis following treatment. The patients included in the study were not subject to any harm and all patients had their privacy protected by ensuring the anonymity of the data collected.

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Results

A total of 14 patients were identified in the period between 01/01/2007 and 31/12/2022 who had been diagnosed and treated for parathyroid carcinoma in our centre. The median age of diagnosis was 67 years old, with the youngest patient being 31 years old and the oldest being 86 years old. The gender ratio for the cohort was 43%:57% (6:8 patients) for males and females respectively.

On initial presentation, 11 (79%) patients had signs and symptoms suggestive of hypercalcaemia. Of these, 5 patients (45%) required hospital admission to control their hypercalcaemia. All patients were hypercalcaemic on blood tests, with the median adjusted calcium level being 3.02 mmol/L and the highest adjusted calcium value being 6.00 mmol/L (figure 1). PTH levels were similarly raised; the median PTH value was 44.65 pmol/L and the maximum value was 582 pmol/L (figure 2).

Ultrasound imaging was performed in 4 patients, with the most common axial imaging before treatment being PET scans, performed in 7 patients. Based on these blood results and imaging findings, parathyroid carcinoma was suspected in these patients, who were offered surgery. 2 patients were found to have metastatic disease, with one patient having lesions in the liver, lung, and bone whilst the other patient had mediastinal disease.

Following assessment, all patients in the cohort received surgery as their primary treatment. The mean time from the patient's initial assessment to surgery was 55 days and the primary procedure performed for all patients was a parathyroidectomy. An ipsilateral thyroidectomy was performed during the initial procedure in 3 patients and was delayed in 1 patient. A

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further patient required mediastinal exploration during the initial procedure due to the extent of the disease on imaging. Follow-up procedures were needed for 3 patients, 2 to achieve better resection margins and 1 for recurrence. Only 1 patient received palliative radiotherapy following surgery and no patients received chemotherapy.

Immediately after surgery, the median adjusted calcium levels were 2.65 mmol/L and the median PTH value was 5.2 pmol/L. The most updated findings for the patient's biochemistry results are presented in Table 1. There was one case of a loco-regional and metastatic recurrence, with positive lymph node disease with extra-nodal spread in levels 2-6 and metastasis in the trachea and oesophagus. At the time of writing, there were no other recorded episodes of recurrence in the cohort.

After a median follow-up period of 2.52 years, 6 patients had passed away – 4 of the causes related to parathyroid carcinoma. The causes of death included uncontrolled hypercalcaemia (2/4, 50%), end-stage liver failure secondary to hungry bone syndrome (1/4, 25%) and metastatic spread of disease (1/4, 25%). Unrelated causes of death included one case of advanced gastric cancer and a case of metastatic sarcoma. The disease-specific mortality was 33% (4/12) whilst the all-cause mortality was 43% (6/14), with a 5-year and 10-year disease survival rate was 67% (figure 3).

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Discussion

The management of parathyroid carcinoma is challenging due to the lack of specific pre-operative clinical features distinguishing it from parathyroid adenomas [9]. Within the literature, severe hypercalcaemia and hyperparathyroidism are the primary features for a majority of parathyroid carcinoma cases [3,8–11], with studies citing that serum calcium levels above > 3 mmol/L and serum PTH levels > 3 times the upper limit of normal are highly suspicious for parathyroid carcinoma [8]. These findings were seen in most of our cohort, with 8 patients having adjusted calcium levels above 3 and most PTH levels being > 3 times the upper limit of normal. Other than biochemistry results, palpable neck lumps and cervical lymphadenopathy have been reported in 40-70% and 15-30% of parathyroid carcinoma cases respectively (3), with a neck lump greater than 3 cm in diameter being highly suspicious of parathyroid carcinoma [9,13]. Skeletal and renal symptoms have also been reported, with some case series suggesting renal and skeletal disease being present in up to 50% of all parathyroid carcinoma patients [14]. Whilst signs and symptoms of bony and renal disease were seen in most of our patient cohort, palpable neck lumps and cervical lymphadenopathy were not commonly seen. Overall, the clinical presentation findings from our cohort are supportive of severe hypercalcaemia and hyperparathyroidism being the primary presenting symptoms of parathyroid carcinoma.

Surgical resection with good margins is widely considered the gold standard treatment for parathyroid carcinoma [1,4,9], with a recent systematic analysis demonstrating that surgery was associated with better survival outcomes [4]. The extent of the surgical resection required for the management of parathyroid carcinoma remains controversial. Some authors advocate for an en-bloc resection, in which the ipsilateral thyroid lobe and isthmus are removed, the

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trachea is skeletonised, and any skeletal muscle immediately related to the tumour is removed [1,4,9,11]. Following resection, debate exists within the literature on whether to perform concomitant neck dissection due to limited data [9]. Overall, it is thought that lymph node involvement in parathyroid carcinoma is predominantly in the central neck compartment and rarely in the lateral neck [15]. As such, the prevailing opinion is to perform neck dissections when positive lymph node disease has been identified [16]. Otherwise, most authors do not recommend the need for an ipsilateral neck dissection by default (1,11). Without an en-bloc resection, authors have reported recurrence rates approaching 50% [1].

In contrast, other authors have reported that the extent of surgery does not appear to influence patient outcomes and mortality [3,17,18]. Youngs et al. conducted a retrospective cohort study of patients treated for parathyroid carcinoma involving 136 patients and found that the addition of an ipsilateral thyroidectomy did not improve survival [18]. Similarly, a retrospective review conducted between 1966-2009 involving 37 patients reported that the extent of the initial procedure did not significantly affect mortality [17]. In our institution, most patients underwent a parathyroidectomy as the primary procedure. Only three patients received an ipsilateral thyroidectomy during the initial procedure due to findings during the operation suggestive of thyroid involvement, with a further patient receiving a delayed thyroidectomy following a multi-disciplinary team (MDT) discussion. Despite this, we only recorded one case of recurrence following the initial treatment in our cohort. This finding may reflect that an en-bloc resection in the initial procedure may not always be required in cases of parathyroid carcinoma. However, the number of patients is too small to make a meaningful statistical analysis. Operation findings with MDT input should guide the decision of whether to proceed.

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Outside of surgery, there is no evidence that other treatments are effective. Parathyroid carcinomas are considered radio-resistant (11) and the use of adjuvant radiotherapy is debated. Whilst some case studies have reported that adjuvant radiotherapy can reduce the risk of loco-regional recurrence [10,11], a large retrospective analysis in the USA did not demonstrate any survival benefit of radiotherapy [19]. Considering these conflicting data, further multi-centre studies will be required to see if any subgroups of patients may benefit from radiotherapy. Similarly, little evidence exists to support the use of chemotherapy in the management of parathyroid carcinomas, with the lack of effective biological models increasing the difficulty in identifying effective chemotherapy agents (1). Several chemotherapeutic regimes have been reported in the literature, including agents such as Dacarbazine or Cyclophosphamide; unfortunately, these only achieve short-term remission and are from studies with small numbers of patients [9,11,20].

Survival rates for parathyroid carcinoma within the literature have been cited to be 85% at 5 years and between 49-77% at 10 years [10]. In our institution the 5- and 10-year survival rates for parathyroid carcinoma were lower at 67%, with most of the mortalities occurring within a year of diagnosis. This finding may reflect the older age of our population, with the median age of diagnosis being 67 years old and two of the patients passing away due to causes unrelated to parathyroid carcinoma. Within the literature, poorer prognoses have been linked to the presence of distal metastatic lesions (4) and disease recurrence within 36 months of the original diagnosis (22). This was seen in the disease-specific deaths within our cohort with the patient who suffered recurrence within a year of diagnosis passing away soon after.

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Management of recurrence disease consists of surgical resection of recurrent and metastatic lesions [9]; locoregional recurrence is common, with the lungs being the most common location for distal metastasis [10]. A common problem in late-stage parathyroid carcinoma is medically resistant hypercalcaemia [4,21]. Current management options include bisphosphonates, denosumab and cinacalcet, but unfortunately, it has been reported that these lose effectiveness with time [4]. In our cohort, patients with advanced disease deteriorated within a year of diagnosis so we were unable to make any conclusions regarding the use of these medical agents.

To summarise, our retrospective single-centre case series provides useful insights into managing parathyroid carcinoma. It demonstrates that key presenting symptoms in parathyroid carcinoma include severe hypercalcaemia and significantly elevated PTH levels in keeping with literature findings. This case series also proves the effectiveness of prompt surgical management and may indicate that a parathyroidectomy is all that is required to achieve good outcomes.

Limitations of this case series include low numbers due to the condition's rarity and that it represents the experience and outcomes of a single centre. Further research into this condition may require multi-centre prospective studies due to its low incidence and the development of good biological models to investigate alternatives to surgical management.

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Summary:

- Parathyroid Carcinoma is an endocrine malignancy characterised by severe hypercalcaemia and primary hyperparathyroidism that is poorly understood due to its rarity.

- Surgical treatment remains the gold standard of management for Parathyroid Carcinoma, though the extent of surgical resection required remains under discussion within the literature.

- The data from this case series suggests that an en-bloc resection and/or ipsilateral thyroidectomy may not always be needed for all cases of parathyroid carcinoma to achieve low recurrence rates and good outcomes.

- An MDT approach should be adopted due to the complexity of managing this condition to increase the chance of favourable patient outcomes.

- As a rare condition, further multi-centre data is needed to confirm this finding and to identify the optimal management of this condition.

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