

## Review Article

# Challenges in Parathyroid Cancers: A Review

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### Abstract

Parathyroid carcinomas are rare neoplasms, with a reported incidence of less than 1% of cases of primary hyperparathyroidism. Diagnosis and treatment of parathyroid carcinoma remains a challenge, as many of the pathologic features are neither sensitive nor specific in differentiating from benign parathyroid lesions. The rule of 3's (serum calcium of more than 3mmol/L and size of the adenoma being more than 3cm) is helpful in risk identifying a cancer. Ultrasound of the neck and Tc-99m pertechnetate/Tc-99m sestamibi (MIBI) scan remains the two main modalities of investigation of parathyroid disease. Although en-bloc treatment is recommended for parathyroid cancer, it is only performed in up to 12% of cases. This review illustrates the challenges in diagnosis and treatment of parathyroid carcinoma.

**Keywords:** cancer, genetic, hypercalcaemia, hyperparathyroidism, parathyroid

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### Introduction

Parathyroid carcinomas are rare malignancies, and account for less than 1% of cases of primary hyperparathyroidism (PHPT). There appears to be no gender predilection unlike in cases of sporadic adenomas where the incidence is more common in women. The etiology is unclear but certain conditions have been shown to be associated with the disease. Parathyroid carcinoma occurs in 15% of hyperparathyroidism-jaw tumor (HPT-JT) syndrome, which is an autosomal dominant condition characterized by the parathyroid tumours and fibro-ossifying tumours of the jaw bones (1). Other inherited conditions that predispose to parathyroid cancers include familial hyperparathyroidism (2), and multiple endocrine neoplasia (MEN) type-1 (1,2). Factors predisposing to parathyroid cancer are summarized in Table 1.

Diagnosis of parathyroid cancers remains a challenge because of the indolent nature of the disease.

Variations of serum calcium levels, size of the parathyroid lesion and the parathyroid hormone (PTH) levels may help to suspect parathyroid cancers in patients with parathyroid disease. Surgery remains the only hope for cure and other adjuvant treatment options are available for recurrent and metastatic disease. The objective of this review article is to highlight

**Table 1:** Factors predisposing to parathyroid cancer

Factors predisposing to parathyroid cancer
Hereditary hyperparathyroid-jaw tumor syndrome (HPT-JT)
Multiple endocrine neoplasia syndromes (MEN-1 and MEN-2A)
History of irradiation of the head and neck
Familial isolated primary hyperparathyroidism (PHPT)
Parathyroid adenoma or hyperplastic parathyroid gland
Prolonged secondary hyperparathyroidism
End-stage renal disease

the challenges in diagnosis and management of parathyroid cancers and to summarize the treatment modalities available in the current surgical practice.

### Challenges in studying the genetics of parathyroid cancer

The problem with studying the genetic patterns of parathyroid cancer is the rarity of the condition. The prevalence of the condition is about 0.005% of all cancers (3) and only accounts for about 1 % of all causes of primary hyperparathyroidism (4,5). The origins of parathyroid cancer has been a subject of debate but recent evidence suggests that these cancers originate *de novo* (6) rather than progression from a benign adenoma or hyperplastic glands, which is extremely rare (7).

Parathyroid tumours can be both monoclonal and polyclonal in origin (8). A significant monoclonal component has been shown in MEN-1 related familial parathyroid tumours (9), non-familial parathyroid hyperplasia (10), renal parathyroid disease (10,11) and also parathyroid carcinoma (12,13). Oncogenes play a role in the development of parathyroid tumours include the CCND1/PRAD1 oncogene (14,15) and MEN1 tumour suppressor gene (16-18). Whilst these mutations have been shown in a third of parathyroid adenomas, rarely have they been seen in parathyroid cancer. Interestingly, somatic p53 somatic mutations have not been shown in parathyroid cancers (19). Using comparative genomic hybridization (CGH) Kytola et al. showed loss of 1p, 4q, and 13q as well as gains of 1q, 9q, 16p, 19p and Xq imbalances occurring significantly more in carcinomas than adenomas. In this series a sequential progression from benign tumours to the malignant state were shown in affected members of 1q-linked families (6).

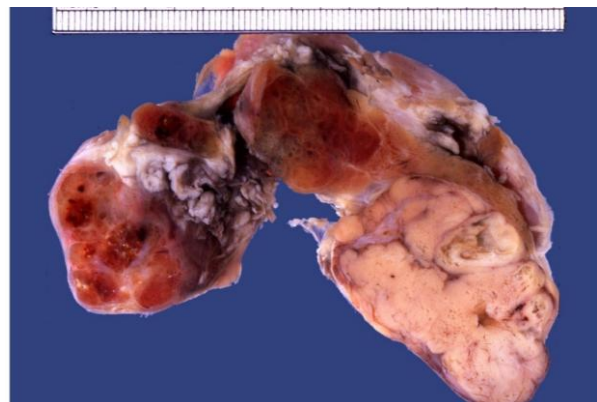
It is important for clinicians to consider underlying genetic cause. Patients with germ-line HRPT2 mutations develop parathyroid carcinomas especially in about 15 % of patients with Hyperparathyroidism Jaw-Tumor syndrome (HPT-JT) and a small subset of families with familial isolated hyperparathyroidism (20,21). The HRPT2 gene encodes the protein parafibromin. HPRT2 mutations are commonly seen in parathyroid carcinoma but uncommon in adenomas (21-23). Another gene that that have been postulated to play a role in malignant transformation of the parathyroid gland include loss of function of retinoblastoma (RB1) tumour suppressor gene (24), in a secondary fashion (13).

### Challenges in pathologic evaluation

Parathyroid cancers are generally large, lobulated, irregular, greyish-white, firm to hard tumours (typically larger than 3cm) and often tethered to the adjacent tissues (25,26) (Fig. 1). Local invasion commonly occurs into the ipsilateral strap muscles and thyroid lobe, recurrent laryngeal nerve, oesophagus and trachea (27). Up to 20% of patients may present with lymph node metastasis (28) and metastases may be 7.5 times more likely in patients with tumors  $\geq 3$  cm than those with tumors  $< 3$  cm (29). Distant metastasis occurs in about 3-4% of patients (30,31).

The histological diagnosis can be difficult and challenging as some of the features exhibited by carcinomas may also be seen in benign adenomas as well as hyperplastic parathyroid lesions (32). Schantz and Castleman in 1973, established a set of criteria for the pathological diagnosis of this malignancy based on their analysis of 70 parathyroid cancers. Table 2 highlights the histological features that are associated with a higher risk of malignant behavior.

Essentially, a histologic diagnosis of malignancy can only be made if there is histologic evidence of invasion into capsular or extracapsular vessels, adjacent extracapsular structures in the neck (without prior instrumentation) or metastases. Other features such as coarse nodularity with fibrous bands are seen more frequently in malignancy but may occasionally occur in benign lesions which have undergone fibrous scarring due to degenerative changes. Cytologic atypia (enlarged nuclei with macronucleoli) is described more frequently in carcinoma, however, these features alone are insufficient for a histologic diagnosis of



**Figure 1:** Gross appearance of a case of parathyroid carcinoma (top right) with adjacent thyroid gland. Fleishy pale tan appearance with slightly irregular borders.

**Table 2:** Histological features of parathyroid carcinoma.

<b>Most definitive features</b>
<ul style="list-style-type: none"><li>• Capsular invasion with growth into adjacent tissues</li><li>• Vascular invasion (vessels in capsule or surrounding tissue)</li><li>• Perineural invasion</li></ul>
<b>Non-definitive features that may be seen in malignancy</b>
<ul style="list-style-type: none"><li>• Band-forming fibrosis</li><li>• Solid growth pattern</li><li>• Coagulative necrosis*</li><li>• Mitotic activity &gt;5 figures per 50 high power fields*</li><li>• Macronucleoli*</li></ul>

\*When seen together, this triad of features is associated with malignant behavior (88).

malignancy (Fig. 2 and 3). Even mitotic counts show significant overlap between benign and malignant lesions and are an unreliable indicator of malignancy. Frozen section is generally not helpful in distinguishing benign from malignant disease (33).

Where the distinction between cancer and atypical adenoma is difficult, immunostaining with parafibromin appears to be helpful in cases with complete absence of nuclear staining (34,35). Ki-67, cell proliferative marker has been used as a marker to identify parathyroid cancers (36) but as a single modality marker is unreliable in differentiating these from benign adenomas due to significant overlap between the two entities. Combination with other markers like parafibromin (37) and APC (38) may have some predictive role in diagnosis, but these are more useful as marker of prognosis in cancer recurrence (39).

### Challenges in clinical presentation

Parathyroid cancer may be difficult to distinguish from benign primary hyperparathyroidism especially when non-functional. Most cases of parathyroid cancer are usually symptomatic and present with severe hypercalcaemia. Symptoms may be profound weakness, dehydration, nausea and vomiting, acute pancreatitis and hypercalcaemic crisis (26). Nearly two-thirds of the patients present with serum calcium values of more than 3mmol/L and have a tumour size of more than 3 cm (the <3 + <3 rule) (40). Patients may also present with severe bony and renal disease

unlike primary hyperparathyroidism from benign causes (Table 3).

Besides those highlighted in Table 3, patients may also present with local pressure symptoms of dysphagia, dysphonia, dyspnea and ear pain, a result of local invasion. Invasion can also be into the carotids, strap muscles and mediastinum (26,31,41). Regional lymph node metastasis occurs in up to 8% of patients, and distant metastasis in 4-5% of cases with the most common site being the lung, bones and liver (30,42).

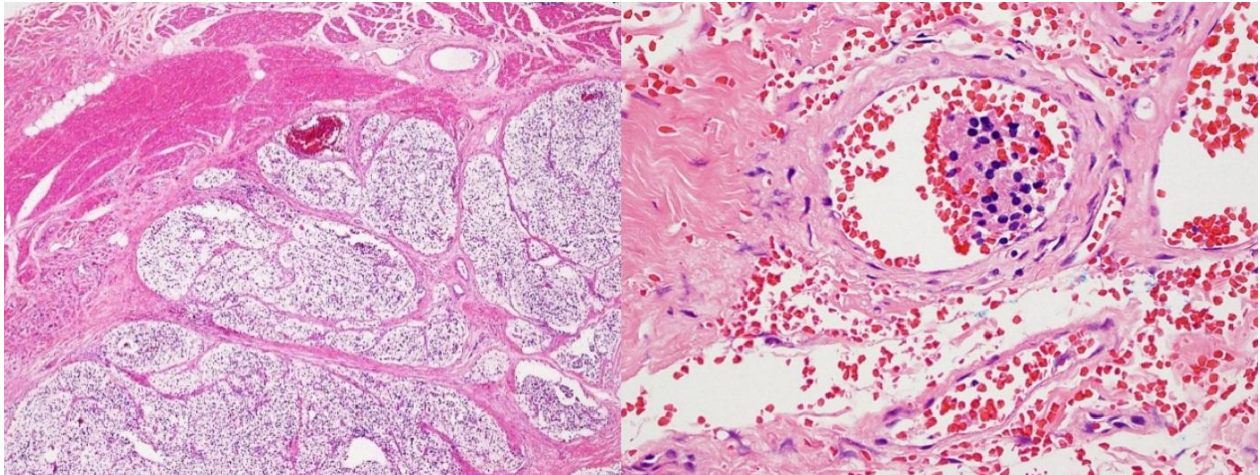
Physical examination may show the presence of constitutional symptoms of malignancy, namely weight loss, fatigue, anorexia and wasting of muscles, which is unlike in patients with benign primary hyperparathyroidism. Hoarseness of voice in the absence of previous neck surgery and hyperparathyroidism should raise suspicion of parathyroid malignancy. Up to 50% of patients may present with a palpable neck mass unlike in those with primary hyperparathyroidism (27).

### Challenges in diagnosis

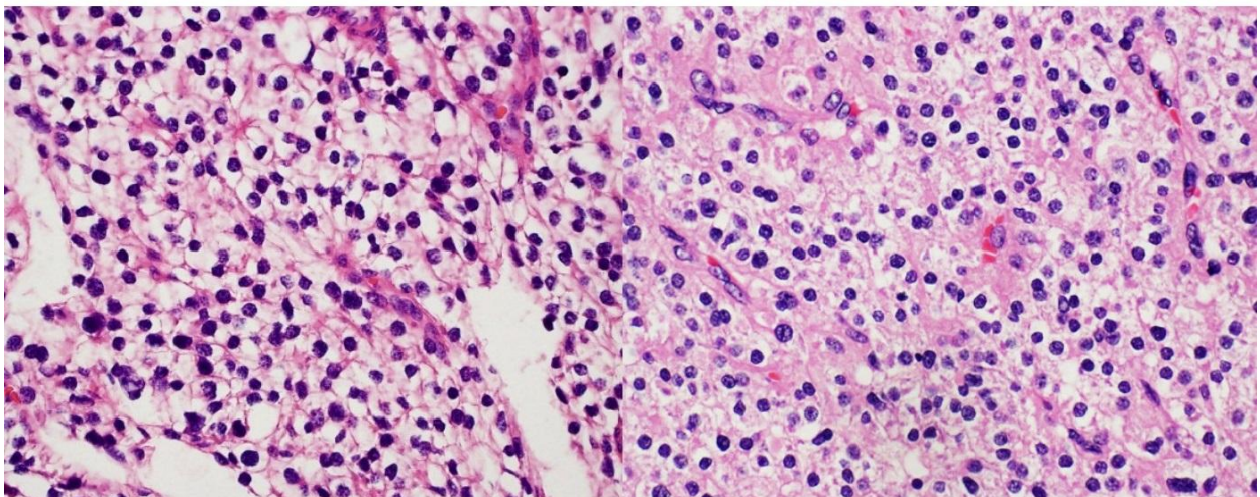
There is no single diagnostic test for parathyroid cancer, but the diagnosis should be entertained in patients with very elevated serum calcium and parathyroid hormone. The rule of 3's (serum calcium of more than 3mmol/L and size of the adenoma being more than 3cm) is helpful in risk identifying a cancer. Schultz and Talat (40) showed that the positive predictive value (PPV) of the <3 + <3 rule for exclusion of parathyroid cancer is 99.8%. The PTH levels are usually 5 to 10 times that of the normal value (43,44) in cancer, but the levels might be elevated even in large benign adenomas. Patients usually have elevated alkaline phosphatase and low serum phosphorus levels, a result of significant bony involvement. A small proportion might have normal calcium despite high PTH levels. Other markers like human chorionic gonadotropin (serum and urine) (45, 46) and N-terminal parathyroid hormone (47) have been evaluated to differentiate it from benign tumours but have a low sensitivity for its use in routine clinical practice.

### Preoperative investigations

The two modalities of investigation of parathyroid disease include ultrasound of the neck and Tc-99m pertechnetate/Tc-99m sestamibi (MIBI) scan. High-resolution ultrasound scan facilitates anatomic localization of parathyroid glands especially large glands and indicate the presence of malignancy based



**Figure 2:** Left: Low power photomicrograph of a case of parathyroid carcinoma, showing the coarse nodularity. The tumour directly abuts the surrounding skeletal muscle tissue (top left corner). Original magnification x 20. Right: Parathyroid carcinoma showing vascular invasion (tumour embolus within a vessel, associated with some fibrin). The vessel is outside the confines of the tumour. Original magnification x 200.



**Figure 3:** Left: Parathyroid carcinoma - high power photomicrograph showing sheets of cells with slightly raised nuclear:cytoplasmic ratios. Marked nuclear pleomorphism is not apparent. Original magnification x 400. Right: Parathyroid adenoma - high power photomicrograph showing nests of cells with mild variation in nuclear size. Compare with parathyroid carcinoma. Original magnification x 400.

**Table 3:** Difference in clinical features between benign parathyroid adenoma and parathyroid carcinoma.

<i>Clinical Feature</i>	<i>Benign</i>	<i>Carcinoma</i>
<i>Female male ratio</i>	3-4:1	1:1
<i>Average age in years</i>	55	48
<i>Asymptomatic</i>	Less than 5%	More than 80%
<i>Serum calcium (mmol/L)</i>	Usually less than 3	More than 3
<i>Serum PTH</i>	Mild elevation	Marked elevation
<i>Neck mass</i>	Rare	Common
<i>Renal involvement</i>	4-20%	30-80%
<i>Skeletal involvement</i>	Less than 5%	34-90%
<i>Hypercalcaemic crisis</i>	Rare	Common

on morphological findings (48) (Fig. 1). In one series parathyroid carcinomas accounted for 12% of atypical features on ultrasound (49). Table 4 highlights the sonological features of parathyroid malignancy.

Technetium-99m-sestamibi was first discovered during myocardial perfusion studies and showed to have persistent uptake in parathyroid tissue (50). The sensitivity of MIBI in localizing adenomas is about 80% (range 50-90%) (51,52). In imaging for parathyroid carcinoma, they help in localizing the location in both functioning and non-functioning tumours, show the presence of metastatic disease (53,54) and help differentiate Brown's tumours from metastatic disease.

Other imaging modalities that may be used include computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) scan. CT can provide information in relation to invasion of the tumour to surrounding structures and is the modality of choice for detecting metastatic lesions. MRI and PET may have a role in the detection of recurrent and metastatic PC (55). PET/CT is superior to conventional CT to identify bone marrow disease early in the initial phases and demonstrate the absence of relapse or hyperfunction of the contralateral parathyroid (or secondary hyperparathyroidism) in patients with a history of parathyroid cancer (56).

Fine needle cytology of the primary lesion may be associated with risk of seeding along the needle track, however, it can be useful in assessing suspected metastatic parathyroid carcinoma, particularly with the use of immunocytochemical staining for parathyroid hormone on cell block material. In the primary lesion, cytologic evaluation is unable to reliably distinguish between benign lesions and carcinoma due to the lack of reproducible cytomorphologic features of malignancy, and the inability to assess capsular or vascular invasion (57). However, cell block material has the potential for immunostaining with parafibromin to assess for loss of nuclear staining in evaluating suspicious parathyroid masses preoperatively.

### Challenges in treatment

Parathyroid cancer is an indolent and rare malignancy but with significant aggressive potential. Patients may present with symptomatic disease or severe life threatening hypercalcaemia (31). The aim of treatment should be remove the tumour completely at the first operation because of tendency to recur locally, besides managing the debilitating hypercalcaemia. The role of

**Table 4:** Sonographic features of parathyroid cancer

Sonographic features of parathyroid cancer
Gross invasion
Marked tumor irregularity with rounded appearance
Ratio of length to maximal width is usually below 0.5
Lack of deformability
Suspicious vascularity
Calcification
Heterogeneous in appearance
Evidence of metastatic nodal disease

routine adjuvant chemotherapy and radiotherapy is limited.

Surgery is the most effective modality in the management of parathyroid cancer. Complete oncological clearance with microscopic negative margins (R0) offers best cure and minimizes risk of local recurrence (31,58). To enable a successful and complete resection, the surgeon should have an index of suspicion and recognize parathyroid malignancy. Although en-bloc treatment is recommended, it is only performed in up to 12% of cases (30). In one series, adequate resection at the first operation was only seen in 14% of cases (42). Koea and Shaw in their review of 372 patients treated between the periods 1933 to 1999 showed that local recurrence was significantly lower in patients who underwent en-bloc resection compared to simple parathyroidectomy (27). Asare et al. in their cohort of 733 patients treated showed 'complete' and 'incomplete' tumor resection was associated with improved survival (59) but there was no data on tumour recurrence. The general consensus though appears to be that of performing en-bloc resection, where a parathyroid malignancy is encountered (5).

One of the challenging scenarios encountered may be when histologic examination of an adenoma suggests the possibility of parathyroid cancer following a simple parathyroidectomy. If the features are suggestive of an aggressive disease with vascular and capsular invasion, early reoperation with excision of adjacent structures may be considered (60). However, in the absence of any invasive features, monitoring of serum calcium and PTH is sufficient. The role of intraoperative PTH (ioPTH) in the management of parathyroid cancer is less evident in the literature unlike its use in the management of benign parathyroid disease. In a cohort of 8 patients treated with en-bloc

resections, Solorzano et al. achieved an iPTH drop >50% from baseline (61). Adam et al showed similar results in their small cohort of four patients (62).

Parathyroid cancer is a radioresistant cancer and EBRT has no effect on the treatment of local recurrence or metastatic disease. However, some case studies have shown a reduction of local recurrence with the use of 50 to 70 Gy after surgical resection (63-65) in a mean follow up time of about 60 months. Selvan et al. seem to suggest that the timing of EBRT was important in that the recurrence was lower if given in the immediate postoperative period (64). The difficulty with advocating EBRT as a mandatory adjuvant treatment for parathyroid cancer is that it is rare with a variable clinical course and the diagnosis.

The role of chemotherapy in the management of parathyroid carcinoma is limited. Generally, chemotherapy is not effective and the results published from case series has been disappointing (66,67). One study has demonstrated partial response to dacarbazine and combination regimes with fluorouracil and cyclophosphamide (68,69). There is no survival benefit with chemotherapy in patients with parathyroid cancer.

### Managing hypercalcaemia

An important cause of morbidity and mortality is hypercalcaemia in patients with parathyroid cancer. Whilst surgery is the most effective mode of treatment, but in cases with refractory disease or metastatic disease, managing hypercalcaemia can be challenging. There are not many effective therapies to manage this debilitating problem, but some of the modalities are cinacalcet therapy, bisphosphonates, denosumab therapy. Patients may present with severe dehydration that requires aggressive fluid management besides the hypercalcaemia.

Cinacalcet is an allosteric modulator of the calcium-sensing receptor and directly reduces parathyroid cell hormone secretion. In one study, two thirds of inoperable parathyroid cancer had reduction of their serum calcium, mostly in patients with severe hypercalcaemia (70). The reduction in serum calcium and PTH with cinacalcet appears sustained over a long period (70,71). Bisphosphonates have been used to treat hypercalcaemia in the acute setting and usually lowers calcium to the normal level in a couple of days, however, they are not without their side effects when used over a long period of time (72).

Denosumab is a human monoclonal antibody that binds the cytokine RANKL and is an essential factor

initiating bone turnover (73). Studies have shown a significant reduction of serum calcium with denosumab treatment in comparison to treatment with bisphosphonates (74,75) and has been shown to be efficacious where other modalities of treatments have failed (76). Immunotherapy (77,78), ablative treatments with ethanol, radiofrequency (RFA) or transcatheter arterial embolization (TAE) (79) are other modalities that have tried in inoperable metastatic disease.

### Recurrence after surgery

The recurrence rate after surgery ranges between 33 to 82% (44,80,81) and usually appears in the first years of treatment (31). The most significant factor associated with recurrence is tumour spillage or incomplete resection. In cases of recurrence, reoperations may be needed for local control, especially in cases where there are symptoms from significant hypercalcaemia and high PTH and this is seen in up to 50% of patients (31,82). There are instances where the recurrence occurs many years after initial treatment (44,82). In cases where patients present with repeated recurrences especially in extracervical regions, metastatectomies may be needed for palliation of symptoms (67). Repeated surgical intervention is associated with high rate of complications to the tune of 17-60% in this group of patients (31,44,82).

### Metastasis

Lymph node metastasis are uncommon and involves the central compartment with a reported incidence 3-32% (42,82) and involvement of nodes appears to more in recurrent parathyroid cancer (82). Patients with nodal involvement had 3.5 times higher risk for cancer recurrence and 4.9 times higher risk of overall death on univariate analysis (40). However, Hsu et al. showed that lymph nodal involvement had no predictive value on overall mortality though patients had 5 times higher risk of disease-specific death on univariate analysis (29). Distant metastasis occurs usually via the blood stream to the liver and lungs, with an incidence of about 10 to 40% (60,83,84). The estimated 10-year survival ranges between 35 to 70% (42,60). Presence of distant metastasis has an impact of survival with a mean survival of 4.5 years (42,60, 85).

### Prognosis

The chance for the best outcome is early identification and complete resection of the cancer at the first operation. Survival is variable in parathyroid cancer and most cases of mortality are from uncontrolled

hypercalcaemia. About 30 to 80% of patients will develop recurrence and the mean time to recurrence is approximately 3 years (60). Survival data from various National Registries showed an overall survival of 85% and 49–77% at 5 and 10 years follow-up (30,42,80, 82). Prognosis is also worse in patients with non-functioning parathyroid cancers as patients have higher incidence of local invasion and metastatic disease (86,87). In patients with recurrent disease, 5-year survival is less than 15%.

### Conclusion

Parathyroid cancer is an indolent and rare malignancy with significant aggressive potential. Diagnosis and treatment of parathyroid cancers still remains a challenge to the endocrine surgeons. Surgery still remains the only hope for cure for parathyroid cancers. The aim of treatment should be remove the tumour completely at the first operation because of tendency to recur locally. Other modalities of treatment include chemotherapy, ablative therapy, radiotherapy and use of calcimimetics to control hypercalcaemia, especially in metastatic disease.

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