

Parathyroid cancer

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Abstract: Parathyroid carcinoma is an exceedingly rare endocrine malignancy first described in 1933. It accounts for between 0.5% and 5% of all cases of primary hyperparathyroidism. Parathyroid carcinoma is unusual among endocrine malignancies, being more hormonally active than its benign counterpart. Parathyroid carcinoma poses a diagnostic challenge both clinically and histologically due to the lack of features which can definitively distinguish malignant from benign disease early in its clinical course. Here, we describe the clinical features of the disease, and present the current opinion on optimal management. Further, we analyse the most recent histological advances made to aid in the diagnosis and management of this rare, but potentially devastating, disease.

Keywords: Parathyroid gland; parathyroid cancer; endocrine malignancy; primary hyperparathyroidism

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Introduction

Parathyroid carcinoma is an exceedingly rare endocrine malignancy first described by Sainton and Millot in 1933 (1,2). It accounts for between 0.5% and 5% of all cases of primary hyperparathyroidism (3-9). Further, it is the least commonly seen endocrine cancer worldwide (4). Parathyroid carcinoma is unusual among endocrine malignancies, being more hormonally active than its benign counterpart (10). Parathyroid carcinoma poses a diagnostic challenge both clinically and histologically due to the lack of features which can definitively distinguish malignant from benign disease early in its clinical course.

A high index of clinical suspicion in cases of severe primary hyperparathyroidism is therefore required to correctly diagnose parathyroid malignancy and thus offer patients complete primary excision of the parathyroid tumour and surrounding structures—the only known curative treatment. The diagnosis of parathyroid carcinoma is difficult to ascertain on initial histology with many cases being incorrectly labelled as benign. Metastases, occurring later in the disease process, are the only unequivocal criterion of malignancy. The course of parathyroid carcinoma is indolent but progressive with patients

succumbing to the effects of uncontrolled hypercalcaemia associated with local recurrence and distant metastases rather than the effect of tumour load, often after a long period of disease-free survival (4).

Clinical presentation

While parathyroid adenomas show a female preponderance parathyroid carcinoma has an equal sex distribution with carcinoma patients being on average one decade younger than those with adenoma, usually in the fourth or fifth decade of life (8,11,12).

Parathyroid carcinoma commonly present with more severe hypercalcaemia than may be associated with primary hyperparathyroidism caused by benign parathyroid adenomas. This is due to the relatively higher levels of parathyroid hormone (PTH). While symptoms such as malaise, nausea, vomiting, mood disturbance and weight loss are largely common to all causes of hypercalcaemia, patients presenting with manifestations of parathyroid bone disease: osteitis fibrosa cystica, subperiosteal bone resorption, 'salt and pepper' skull, absence of lamina dura, diffuse osteopenia, osteoporosis, bone pain and pathological fracture should arouse suspicion of parathyroid carcinoma (3,4,13). In benign

parathyroid disease overt bone disease is unusual in the Western world; however of note is that historically primary hyperparathyroidism presented with large increases in serum calcium and target organ damage due to late presentation with the disease. In countries with poor healthcare infrastructure, therefore, the distinction between benign and malignant disease using the severity of symptoms can be challenging (3).

Concomitant bone and renal disease occurs in 50% of parathyroid carcinomas manifesting as nephrocalcinosis, reduced GFR and renal colic (4). However, completely asymptomatic presentation of parathyroid cancer has been reported in 7-46% of patients in several previous studies, making the symptoms of severe hypercalcaemia with renal involvement highly suggestive, but not a pre-requisite, for the suspicion of parathyroid carcinoma (4,14-16). A palpable neck mass is an additional indicator of the possibility of malignant disease occurring in 15-76% of malignancies and seldom in benign causes (4,5,13,15,17-20).

Laboratory testing

Laboratory testing of PTH and serum calcium aids diagnosis although there is no agreed threshold level for malignancy. Calcium levels in carcinoma are typically above 14 mg/dL *vs.* under 11.2 mg/dL in benign parathyroid disease. In fact PTH levels are typically 5-10 times higher than the upper range of normal while benign disease usually shows a more modest increase (4,14,17,18,20,21). Although severe hyperparathyroidism associated with a benign disease process is uncommon it is not unreported and elevated PTH therefore has not been shown to be statistically significant in the differentiation between benign and malignant disease. In addition to calcium levels, alkaline phosphatase (ALP) levels have been shown to be significantly higher in parathyroid carcinoma than in benign disease—with levels under 300 IU/L making carcinoma unlikely (16). Raised ALP reflects that action of PTH on the bone and it has been mooted by Bae *et al.* that as PTH causes loss of cortical bone before cancellous bone, a raise in ALP may be a useful diagnostic marker before skeletal manifestations such as fractures (16).

The measurement of human chorionic gonadotrophin (hCG) levels in parathyroid cancer is currently being researched. After the incidental finding of raised baseline serum hCG levels in patients with parathyroid cancer Rubin *et al.* found that persistently raised or increasing urinary hCG levels in parathyroid cancer correlate with a more

aggressive stage of disease related to pathological fracture and death. This has led to the hypothesis that urinary hCG levels may have the potential to discriminate between benign and malignant parathyroid disease (22). This hypothesis is supported by Stock *et al.* who found elevations in alpha and beta sub-units of hCG which fell after surgical cure (23). Further investigation is required to delineate the role of hCG testing in the diagnosis and prognosis of parathyroid malignancy.

Non-functional parathyroid carcinoma

Non-functioning parathyroid carcinoma represents between 10% and 25% of parathyroid carcinomas (24). Although first reported by De Quervain in 1904 (25), non-functional parathyroid carcinoma remains an exceedingly rare malignancy with fewer than 30 cases reported in the literature worldwide (26,27). Symptoms are caused by local growth and invasion of surrounding tissues and patients succumb to systemic tumour burden rather than the effects of uncontrolled hypercalcaemia (8,26). Wilkins and Lewis have reported an older age range for non-functional parathyroid carcinomas with most patients presenting in their sixth or seventh decade (26). Neck mass at presentation is more common than with functional parathyroid carcinoma, with half of patients presenting with a neck mass between 5 and 11 cm in size (26).

Diagnosis in this case is based almost entirely on histological findings, metastases or local recurrence as patients are normocalcaemic at diagnosis with PTH and ALP in the normal range. A high proportion—up to 80%—present with a neck mass often associated with dysphagia, hoarseness or vocal cord paralysis and dyspnoea (4,20,26). They are often misdiagnosed as thyroid or thymic carcinoma due to the symptoms of locally advanced disease. Immunohistochemistry for PTH, thyroglobulin, thyroid transcription factor 1 and calcitonin can help to ascertain the correct diagnosis (3). Again adequate primary surgical excision is paramount with overall survival directly correlating with the margin status of the initial resection (28).

Predisposition

The aetiology of parathyroid carcinoma is largely unknown. Several authors have reported a potential role of previous neck irradiation and end-stage renal failure however the role is less clear for the development of parathyroid carcinoma than for benign parathyroid adenomas

(3,11,13,18,29-31). Increased risk of parathyroid carcinoma has been reported in association with hereditary syndromes of hyperparathyroidism, particularly hyperparathyroidism-jaw tumour (HPT-JT) syndrome. This is a rare autosomal disorder causing primary hyperparathyroidism and fibro-osseous lesions in the maxilla and mandible. In HPT-JT, approximately 15% of patients develop malignant parathyroid disease (8,32). Recently parathyroid malignancy has also been reported in association with multiple endocrine neoplasia (MEN) type 1 and MEN 2A (33-36).

Imaging

Imaging is useful, as in benign disease, for localisation of a tumour, but cannot reliably distinguish between benign and malignant disease. Ultrasound and 99m Tc-sestamibi scan are the most commonly employed diagnostic imaging studies utilised for parathyroid disease. Ultrasound provides general information on the size and location of the mass with tumours larger than 3 cm significantly more likely to constitute carcinoma than adenoma (37). Features including inhomogeneity, hypoechogenicity and irregularity of borders have been shown to correlate with malignancy, but these features may also be seen in benign parathyroid tumours (38). If carcinoma is a proposed differential diagnosis then a fine needle aspirate for cytology (FNAC) must be avoided due to the risk of seeding the tumour (39,40). Some authors have suggested that parathyroid carcinomas tend to be localised to the inferior glands; however, others have found no association with either the location or number of parathyroid glands involved and malignancy (9,16,27,41).

99m Tc-sestamibi scan enables the identification of abnormal and ectopic parathyroid tissue and is commonly used in the diagnosis of benign lesions (8,37). If malignancy is suspected, then higher resolution studies are of value (42). Contrast computed tomography (CT) can accurately localise the lesion and its relationship with or invasion into surrounding structures. Magnetic resonance imaging (MRI) with gadolinium and fat suppression provides the best imaging of the soft tissues of the neck (37). Both CT and MRI are commonly used when planning en-bloc resection of the lesion and surrounding structures. In the case of recurrent disease, MRI is considered superior as surgical clips in the surgical field can cause artefact when using CT (37).

FDG-PET has been used in cases of parathyroid adenoma, but there is little in the literature on its use in parathyroid cancer (43-45). Evangelista *et al.* in a case study used FDG-

PET/CT as an additional imaging study in five patients with parathyroid cancer. Increased FDG uptake on the basis of suspicious CT changes not corresponding with physiological patterns of uptake were recorded as evidence of recurrence/metastases (37). The benefit of FDG-PET/CT is in its delivery of both anatomical and functional information allowing small tumour deposits to be detected but post-operative inflammation can cause false positive results limiting its use to a minimum of 3 to 6 months post-surgery (37). Due to the small number of studies neither the sensitivity nor specificity can be assessed but it may prove to be a useful tool in the early identification of metastases/recurrence (37,46,47). More recent studies have assessed the use of ¹¹C-choline and Fluorine-18-fluorodeoxyglucose as substrates for PET/CT studies. Early results are promising in identifying the parathyroid glands more accurately than standard FDG-PET/CT studies, although this has not yet been demonstrated specifically for parathyroid carcinoma (43,48).

Selective venous catheterisation and PTH measurement can be utilised if the above measures have failed to localise the lesion, however they are invasive (8).

Intra-operative diagnosis

As clinical features can be inconclusive in the differentiation between benign and malignant disease the intra-operative appearance of the tumour is a useful diagnostic tool. Intra-operative features which arouse suspicion of parathyroid carcinoma are a large (>3 cm), irregular firm mass, occasionally lobulated and usually surrounded by a dense fibrous capsule that gives it a white or grey-brown hue. Conversely adenomas are smaller, soft, round and red-brown in colour. Malignancies infiltrate and adhere to surrounding structures—commonly the ipsilateral thyroid and strap muscles, the ipsilateral recurrent laryngeal nerve, oesophagus and trachea (2,5). Lymph node metastases are present at operation in 3-19% of cases and distant metastases in 3-4% of patients (6,7,14,18-20). Surgeons do not recognise parathyroid cancer in up to 25% of cases—not surprising due to the rarity of the condition and often lack of pre-operative suspicion (49).

Frozen sections are not helpful in distinguishing benign from malignant disease. Excisional biopsy is not recommended due to the risk of intraoperative seeding of malignant tissue. Exploration of all four glands may be required as carcinoma of multiple glands has been documented in the literature, although there is no agreed consensus on this (50,51).

Histological diagnosis

Metastasis remains the only definitive marker of malignancy. No TNM staging system is available for parathyroid carcinoma firstly because the disease does not uniformly metastasise to the lymph nodes and secondly because the size of the tumour does not appear to play a role in prognosis (1,18). The histological criteria for parathyroid carcinoma most commonly used is that established by Schantz and Castleman in 1973 based on the evaluation of 70 parathyroid carcinomas: presence of parenchymal mitoses, trabeculated parenchyma including thick fibrous band and capsular or vascular invasion (52). However, many of these features can also be observed in atypical parathyroid adenomas. Capsular or lymphovascular invasion remains the most specific marker of parathyroid carcinoma (4).

Neoplastic cells, generally chief cells, are arranged in a lobular pattern and separated by dense trabeculae, with mitotic figures. Invasion of the capsule is common; with vascular invasion less frequently noted (10-15%) (48). Capsular invasion is characterized by a 'tongue-like' protrusion through the collagenous fibres and should be distinguished from pseudoinvasion because of 'trapping' of tumour within the capsule which can be seen in adenomas (31).

Many of the features described by Schantz and Castleman—adherence to surrounding tissues, fibrous bands, trabecular growth and mitoses—are not pathognomonic of malignancy and can be found in parathyroid adenomas. The diagnostic value of vascular and capsular invasion is still debated (53,54). Interestingly, up to 50% of patients with metastatic parathyroid carcinomas were initially classified as benign on histology in a large study by Sandelin *et al.* (55). Therefore that distinction between benign and malignant parathyroid tumours is very difficult to make on initial histology meaning that histology is often inconclusive leaving a dilemma for the surgeon who has not performed an en-bloc excision whether to return to ensure clear margins or pursue a course of watchful waiting for recurrence and metastases. Some authors have suggested a watchful waiting approach in which reoperation is postponed until tumour recurrence (13,18). However insufficient excision is associated with higher rates of recurrence: one study citing local recurrence in 8% of en bloc resections versus 51% tumour excisions (19).

New tumour markers

Due to the difficulties with accurate differentiation between benign and malignant tumours on histology, recent research

has been focused on identifying immunohistochemical tumour markers. Several oncogenes and tumour suppressor genes have been linked to parathyroid carcinoma (1). Loss of chromosome 13 has been reported by several authors. This deletion codes for the retinoblastoma (Rb) and hereditary breast carcinoma susceptibility (BRCA2) tumour suppressor genes (56-58). Immunohistochemical studies have shown loss of Rb immunostaining in parathyroid cancer (59). Cyclin D1 or parathyroid adenoma 1 (PRAD1) oncogene has been shown to be overexpressed in parathyroid carcinoma and so have also been proposed to play a role in the malignant transformation of parathyroid tumours (1).

HPT-JT syndrome has provided the best evidence for a defined gene in parathyroid malignancy. CDC73 gene mutations (formerly HRPT2)—is the gene responsible for HPT-JT syndrome and parathyroid cancer. Carcinoma occurs in 15% HPT-JT as opposed to under 1% of primary hyperparathyroidism (3). CDC73 mutations were found in 4/4 sporadic parathyroid carcinomas and 0/25 sporadic parathyroid adenomas by Howell *et al.* (33) Shattuck *et al.* found CDC73 mutations in 10/15 patients with parathyroid carcinoma (60). Cetani *et al.* identified the mutation in 9/11 parathyroid carcinomas and 0/4 sporadic atypical adenomas (30,35). Most of the mutations are nonsense and are predicted to result in the lack of or reduced protein expression of parafibromin protein. The prevalence of CDC73 mutations in parathyroid cancer may be as high as 76.6% (3). Germline mutations have been found in 1/3 of subjects suggesting that a subset of parathyroid cancer patients may have a HPT-JT syndrome (35,60,61). CDC73 mutations are found rarely in sporadic benign parathyroid adenomas as demonstrated by Carpten *et al.* finding CDC73 mutation in only 0.8% (1/120) cases of benign parathyroid adenoma (33,35,62,63). It has been proposed that CDC73 mutations may constitute an early event that may lead to parathyroid malignancies and that mutations in CDC73 mutations may be a marker of malignant potential in both familial and sporadic parathyroid carcinomas.

CDC73 encodes the protein parafibromin (parathyroid disease and fibro-osseous lesions). The idea of parafibromin as a tumour suppressor protein has arisen from the observation that parathyroid tumours carrying CDC73 mutations are frequently associated with the loss of parafibromin expression or function. It is hypothesised that after bi-allelic CDC73 inactivation the inhibitor effect of parafibromin on cyclin D1 activity is lost, leading to neoplastic transformation in susceptible tissue such as the

parathyroid glands (64).

CDC73 inactivation has been strongly linked with parathyroid carcinoma with the use of parafibromin as a marker. The loss of nuclear expression of parafibromin has been reported to be 96% specific and 99% sensitive in identifying parathyroid malignancies (65). Further studies have reported successful identification of malignancies using parafibromin however with lower specificity and sensitivities (61,66,67). Absent nuclear staining of parafibromin also characterises HPT-JT associated adenomas.

Without a gold standard test to identify parathyroid carcinoma a high index of suspicion for this rare malignancy is essential.

Treatment

Surgery

Most authors recommend en bloc excision at initial surgery as the only chance of cure (8). En bloc resection refers to the complete excision of the tumour with clear macroscopic margins, generally with ipsilateral thyroid lobe and normal ipsilateral parathyroid gland excision. If there is invasion of surrounding structures, such as the strap muscles, these should be incorporated into the resection. However, the difficulties inherent in the pre-operative and intra-operative diagnosis of parathyroid carcinoma mean that this opportunity for excision at initial surgery is often missed. Adequate surgical excision requires as a minimum the removal of the ipsilateral lobe of the thyroid (49,68,69); however, many authors recommend a more radical excision including the thyroid isthmus, skeletonisation of the trachea, and excision of any skeletal muscle intimately related to the tumour. The normal ipsilateral parathyroid gland should also be excised with the specimen. This extensive resection is not routinely performed (5).

It is imperative to avoid rupturing the tumour capsule due to the risk of seeding the surgical field. The recurrent laryngeal nerve is only resected if found to be involved and non-functioning—several authors recommending pre-operative assessment of vocal cord function to pre-empt the need for resection (8). Parathyroid carcinoma and adenoma may exist concurrently, so it has been suggested that all parathyroid glands be identified, and excised if necessary. However, there is no agreed consensus on four gland exploration: this point remains controversial. Regional lymph node dissection is indicated only if involvement suspected on pre-operative scanning or intra-operatively.

Prophylactic neck dissection has been shown to have no effect on survival, but can increase morbidity (70).

Intra-operative PTH testing (rapid PTH test) has been shown to be useful, especially in surgically naïve patients, as PTH levels can fall significantly after resection of disease, but often not as rapidly as with the resection of benign disease in which PTH levels can normalise within 15 to 30 minutes. However, Givi and Shah have commented on the difficulty posed for the surgeon if levels do not decrease after excision has been completed either due to remaining unidentified tumour in the neck or metastatic disease (8).

Due to the rarity of the disease no prospective data regarding the initial surgical approach exists. Although strongly recommended in the literature, en-bloc resection at primary surgery is only performed in approximately 12–52% of cases (7,11,19). This is important as several studies have found that the recurrence rate in patients who have undergone en-bloc resection is 33% as opposed to 50% in patient who have undergone sub-optimal resection (19,49). Munson *et al.* have suggested that this group of patients may benefit from adjuvant radiotherapy treatment; however this is debated in the literature (28).

Patients are followed-up closely with serial PTH, calcium and ALP blood testing and ultrasound every 3 months. Calcium replacement is organised accordingly—most patients require intravenous calcium replacement soon post-operatively but can then be weaned onto oral calcium replacement and calcitriol (13).

With persistent or recurrent disease it is important to exclude metastases to the lung or bone prior to re-exploration of the neck. It is recommended that at least two non-invasive studies seeking distant metastases should be negative before re-exploration of the neck is planned. However, surgery for recurrent disease is generally palliative, for both relief of local pressure symptoms and for treatment of hypercalcaemia. There is little consensus in the literature as to how or when such surgery should be performed (13,21). Complications of both initial and especially subsequent neck exploration include: recurrent laryngeal nerve injury, transient and permanent hypoparathyroidism, oesophageal or tracheal injury and neck haematoma.

The localisation and treatment of distant disease, although not undertaken with a curative aim, can successfully improve symptoms and lower the serum calcium levels in 68–86% of cases from which the majority of parathyroid cancer patients succumb (14,21). Subsequent re-operations have lower success rates due to the rarity of the disease and its

indolent nature, survival benefit has not been definitively demonstrated with re-operation. Several authors have reported the palliative effect of decreasing tumour burden and improving symptoms by lowering serum calcium levels.

Radiotherapy

Parathyroid carcinoma has been generally believed to be insensitive to radiotherapy for either primary or metastatic disease, but several recent case series have suggested that adjuvant radiotherapy may reduce the incidence of local recurrence and increase disease-free survival (14,15,28). Research from M. D. Anderson has shown that local recurrence appears to be lower if adjuvant radiotherapy is given after initial surgery independent of the type of surgery and the stage of the disease (1). It is difficult to assess the efficacy of adjuvant radiotherapy as many patients have long disease-free intervals after parathyroidectomy alone and the numbers included in these studies are small, however there may be a role of adjuvant radiotherapy in parathyroid cancer (8).

Other treatments

Chemotherapy has not been demonstrated to be beneficial in parathyroid carcinoma. Although short-term responses have been demonstrated with single-agent dacarbazine (70) and combination chemotherapy with flurouracil, cyclophosphamide and dacarbazine in patients with metastatic disease but no survival benefit was shown (71). Reports of response remain limited to case reports (72).

Radiofrequency ablation therapy has been used to treat multiple unresectable metastases in the lung (1,73). A combination of RFA and transcatheter arterial embolization has been used to treat multiple metastatic lesions in the liver (74). Both reports showed improvement in serum calcium and PTH levels. Recurrent disease in the neck has been treated with ultrasound-guided percutaneous alcohol injection and short-term improvements in calcium and PTH levels (75).

Medical treatment

Major morbidity and death in patients with parathyroid carcinoma is due to uncontrolled hypercalcaemia and not tumour burden. Medical management is the mainstay of treatment in patients awaiting surgical intervention and those with unresectable disease. Urgent management with

intravenous rehydration and bisphosphonates although initially often effective in decreasing serum calcium levels become less efficacious with subsequent treatments. Oral bisphosphonates have been found to have no effect in parathyroid cancer. Calcitonin can decrease serum calcium but is only transiently effective. Octreotide (long-acting somatostatin analogue) has also been shown to be effective in limited numbers of patients in decreasing PTH levels (76,77).

Calcimimetics have emerged as a more effective treatment than bisphosphonates in controlling hypercalcaemia. Calcimimetics are allosteric modulators of the parathyroid calcium-sensing receptor and act by binding to these receptors and increasing their sensitivity to extracellular calcium (8,78-81). This causes a decrease in PTH secretion by parathyroid cells. Second generation calcimimetic cinacalcet has been shown to decrease serum calcium by 1 mg/dL in 62% of patients. The greatest decrease in calcium levels was seen in those with the highest starting calcium levels. However despite the decreases in serum calcium levels there was no significant decrease in PTH which remains unexplained (79). Cinacalcet has the added advantage of safe usage in patients with chronic renal sufficiency which effects 84% patients with recurrent disease (82). Most of patients tolerated the drug well with nausea and vomiting being the most common side-effect. If ineffective, dialysis against a low-calcium dialysate is necessary (82).

Immunotherapy targeting PTH has been reported. Immunisation with synthetic human and bovine PTH peptides results in production of anti-PTH antibodies and has been shown to decrease serum calcium by more than 1 mmol/L in a patient with parathyroid cancer and unresectable metastases (83). Tumour shrinkage in addition to an improvement in serum calcium and PTH has been demonstrated in another patient (84). However immunotherapy remains largely experimental and results are limited to case studies.

Denosumab, a monoclonal antibody targeting the receptor activator of nuclear factor kappa-b ligand with potent anti-resorptive actions in bone, will be tested for efficacy in controlling the hypercalcaemia secondary to parathyroid cancer (85).

Recurrence

Recurrence is very common in parathyroid carcinoma with 25-100% of patients cited as developing local recurrence after surgery, most studies citing 50% (49). Recurrence is

detected on average 2-4 years after the initial operation and these patients have a mean survival of 5-6 years after the initial diagnosis (4,14,15,17-19,21,70). Approximately 25% of patients develop distant metastases at some stage of the disease. Distant metastases are rarely present at initial diagnosis. Metastases have been documented as long as 20 years after first diagnosis (13,86). Five-year survival rate from case series and registry are fairly consistent at 76-85% and 10-year survival rates range from 49-77% (7,11,15,21).

Recurrence presents as a slowly increasing PTH and serum calcium level. The most common sites of metastases are to cervical lymph nodes (30%), lungs (40%) and liver (10%) via both haematogenous and lymphatic routes (87). The localisation of metastases is undertaken using the techniques for identifying the initial disease. Ultrasound is effective in localising local metastases to lymph nodes in the neck. Sestamibi scans can localise both local and distant metastases. If further surgical intervention is planned CT and MRI scans are undertaken.

Resectable disease, either local or distant is managed surgically as removal of functioning tumour offers best control of hypercalcaemia (13,21). As a result of this multiple operations to remove maximal amount of tumour are often justified as a palliative measure. Morbidity associated with multiple surgical interventions is cited to be as low as 6.9% (if sacrifice of the recurrent laryngeal nerve is excluded) (21). Patients require on average two to three operations during the course of their disease (8). Decreasing the tumour burden reduces the levels of PTH and calcium therefore lessening the symptoms of hypercalcaemia. Although effective in offering symptomatic relief, the surgical resection of metastases rarely offers the chance of cure (88).

Reports in which the initial treatment was en bloc excision have a longer survival and a longer disease-free period than patients treated with tumour excision alone (70). Reports have shown that 28-50% of patients remain alive with no recurrence at follow-up (14,18,19,48). Although surgery, adjuvant radiotherapy, radio-frequency ablation and calcimimetics have shown responses to clinical parameters there is insufficient information to determine the effect on survival. Prognosis appears to be worse in non-functional parathyroid carcinoma as local invasion and distant metastases are more likely at the time of diagnosis (20,26).

Prognosis

Parathyroid cancer follows a progressive course in which the

tumour invades surrounding structures, local lymph nodes and also haematogenously to the lungs, liver and skeleton. The most important factor in prognosis is the completeness of the initial surgical resection, dependant on pre-operative suspicion of parathyroid cancer. Survival rates for complete excision at initial operation have been cited as up to 90% at 5 years and 67% at 10 years (89). Poor prognostic indicators include lymph node metastases at initial presentation, distant metastases and non-functioning parathyroid carcinoma (19). Clayman *et al.* have suggested males under 45 years old with higher calcium levels (>13 mg/dL) have a more aggressive disease process (1). Recurrence of 25-100% has been cited with a general consensus of 50% of patients developing recurrence after surgical excision (4,49). Once recurrence has occurred then the chances of cure are remote and treatment is generally focused on surgical intervention to decrease tumour burden for symptomatic control and medical control of hypercalcaemia in the case of unresectable disease.

Summary

Designing clinical trials for new treatments is very challenging due to the rarity of parathyroid cancer. Recently increased research into the molecular biology of parathyroid cancer may enable the *CDC73* gene to be targeted for new therapeutic options. However, currently a high index of suspicion for this rare malignancy and adequate en-bloc excision of the tumour at initial surgery offer the best chance of cure and elongated disease-free survival in parathyroid cancer.

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Footnote

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