Review

Parathyroid carcinoma

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Background: **Parathyroid carcinoma is a rare malignancy affecting 0·5–5 per cent of all patients with primary hyperparathyroidism. This article reviews the literature on the pathogenesis, pathology, clinical features, diagnosis and management of parathyroid carcinoma.**
Methods: **A Medline search was performed and all relevant English language articles published between 1970 and 2005 were retrieved. The search words included 'parathyroid carcinoma', 'pathology', 'genetics', 'management' and 'radiotherapy'. Secondary references were obtained from key articles.**
Results and conclusion: **The exact aetiology of parathyroid carcinoma remains obscure. Recently, the *HRPT2* gene has been implicated in its pathogenesis and may prove to be a genetic target in future. Surgical resection is the accepted 'gold standard'. There is now a growing consensus on the use of adjuvant radiotherapy as it has been shown to provide a survival benefit.**

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Introduction

In 1904 de Quervain was the first to report a patient with a non-functioning parathyroid carcinoma[1], and in 1933 Sainton and Millot were first to report a patient with a functioning parathyroid carcinoma[2]. The rarity of this tumour has precluded any prospective study and knowledge gained so far is the result of individual case reports and retrospective studies. Patients with parathyroid carcinoma are usually 10 years younger than those with benign lesions and usually present with profound symptoms of hyperparathyroidism. They often have grossly raised serum parathyroid hormone (PTH) and calcium levels. However, small subgroups with non-functioning carcinoma have normal serum PTH and calcium levels.

Incidence and demographics

Approximately 700 patients with parathyroid carcinoma have been described in the world literature[3,4]. The National Cancer Registry Database in the USA reported an incidence of 0·005 per cent of all registered cases[5]. Parathyroid carcinoma accounts for 0·5–5 per cent of all patients with primary hyperparathyroidism. The reported incidence is less than 1 per cent in Europe and the US and 5 per cent in Japan[6,7]. This wide variation may be due to genetic or environmental influences, local referral practice or may represent underdiagnosis or overdiagnosis of the disease[3]. The carcinomas do not have the gender predilection observed with benign tumours, which show a definite female preponderance (3 : 1). Most cancers present in individuals aged between 40 and 60 years, but a patient as young as 8 years has been reported[8].

Aetiology

The exact aetiology of parathyroid carcinoma remains unclear. Multiple risk factors, including radiation, familial hyperparathyroidism and hereditary hyperparathyroid–jaw tumour syndrome (HPT-JT) have been suggested but none has been confirmed. No predisposing dietary factors have been identified[9]. Inadequate sunlight exposure has been observed to be a risk factor for benign hyperparathyroidism but not for carcinomas[9,10]. Radiation has been implicated as a risk factor for parathyroid carcinoma but the association is weak. Only five (1·4 per cent) of 358 patients reviewed by Koea and Shaw[7] had a previous history of neck irradiation. There is an increased risk in patients with the rare autosomal dominant disorder familial hyperparathyroidism[7,11,12]. In a series of 43 patients from the Mayo clinic, two had this condition[13]. Finally, HPT-JT is an autosomal dominant disease characterized by the

occurrence of parathyroid and fibro-osseous tumours of the jaw bones. There is a greatly increased risk of parathyroid carcinoma with this syndrome[11,12,14]. In a series of six patients with HPT-JT one had a parathyroid carcinoma[15].

Molecular oncogenesis

Parathyroid malignancy has been noted in association with multiple endocrine neoplasia (MEN) type 1 and 2A syndromes[16,17]. Chromosomal aberrations leading to activation of some oncogenes and tumour suppressor genes have also been implicated in the pathogenesis of the disease. Kytola *et al.*[18] reported that losses of 1p, 4q and 13q, and gains of 1q, 9q, 16p, 19p and Xq, were more commonly observed in parathyroid carcinoma than in adenomas. Loss of the 11q13 region, the commonest chromosomal aberration observed in parathyroid adenoma, is absent in carcinoma. Mutations in genes that are involved in the regulation of cell cycle activity (*parathyroid adenoma 1* gene (*PRAD1*), *p53* and *retinoblastoma tumour suppressor* gene) may contribute towards malignant transformation, but their exact role is unclear. Loss of a region on chromosome 13 which contains codes for the retinoblastoma and hereditary breast carcinoma susceptibility gene (*BRAC2*) has been observed in parathyroid carcinoma[19–21].

More recently, it has been suggested that mutations in the *HRPT2* gene, which is associated with HPT-JT, can lead to malignant transformation of parathyroid cells[22–24]. Shattuck *et al.*[25] noted mutation in this gene in ten of 15 patients with sporadic parathyroid carcinoma. Haven *et al.*[26] demonstrated that combined loss of heterozygosity at 1q (*HRPT2*) and 11q (*MEN1*) in parathyroid tumours is suggestive of malignant behaviour. It has been proposed that individuals with *HRPT2* mutation should be monitored on a regular basis with serum calcium estimation to facilitate early detection and potential cure of this cancer[22]. Further clarification of molecular oncogenetic changes in parathyroid carcinoma should provide better tools for early diagnosis and define biological targets for new and more effective therapy.

Pathology

Parathyroid carcinoma is usually a single-gland tumour, but multiglandular involvement does occur[27]. Koea and Shaw[7] observed a higher incidence of malignant transformation in the left inferior gland, whereas other series have described a right inferior gland preponderance[28,29]. Primary parathyroid carcinomas in ectopic locations, mainly mediastinal, have been described, but the ectopic position of the gland *per se* does not predispose it to malignant transformation. Parathyroid carcinoma may occasionally coexist with a pre-existing benign lesion[16,30].

Macroscopic features

Carcinomas are mostly irregular, firm to hard tumours, with a greyish or white colour. Adenomas are soft, oval and reddish brown to tan in appearance. Carcinomas are large, usually over 3 cm in diameter, and may be palpable at presentation[31]. Most of these tumours weigh between 2 and 10 g[13]. Fibrosis and local tissue infiltration are frequently observed with carcinomas but can also be encountered with benign adenomas, especially if large and haemorrhagic, and as a complication of previous surgery. During surgery carcinomas may be seen invading the ipsilateral thyroid gland, strap muscles, recurrent laryngeal nerve, oesophagus and trachea. A local recurrence must be interpreted with caution, as intraoperative rupture of an adenomatous lesion is known to seed the operative field with viable cells leading to recurrent benign disease[7].

Microscopic features

The parathyroid carcinoma is generally surrounded by a capsule from which fibrous septa extend into the tumour, creating a typical lobular appearance. The tumour cells may be arranged in trabecular, solid or acinar architectural patterns (*Figs 1* and *2*); chief cells are almost always the predominant cell type. Sparse oxyphil and transitional oxyphil cells may be found and, very rarely, they may predominate. The tumour cells tend to be large, although nuclear pleomorphism is variable, as are the presence and size of nucleoli[32]. Tumour cell mitoses are commonly observed, and focal calcification, cystic changes and areas of coagulative necrosis may also be apparent.

Schantz and Castleman[33] were the first to define histopathological criteria by which to differentiate a parathyroid adenoma from a carcinoma. According to these authors, fibrous trabeculae, mitotic figures, and capsular and blood vessel invasion were more often observed in carcinomas and, of these, the presence of mitoses within parenchymal cells was the single most valuable criterion for differentiation. However, other authors have pointed out that mitotic activity can occasionally be seen in adenomas and hyperplastic glands[34–36]. McKeown *et al.*[37] have noted that the presence of cellular pleomorphism and atypia *per se* are not reliable indicators of malignancy, and mitotic activity in parenchymal cells must be distinguished from mitotic activity in endothelial cells. The mitotic activity in carcinoma is generally low, but higher mitotic activity has been observed in poorly differentiated tumours and

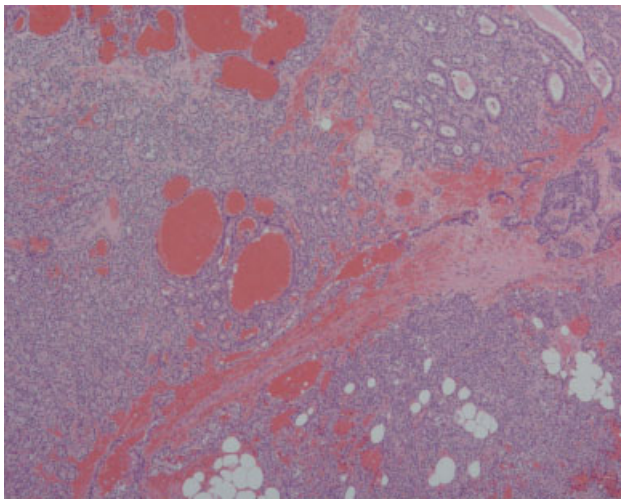

Fig. 1 Parathyroid carcinoma visualized by low-power microscopy. Lobules of neoplastic parathyroid tissue are separated by fibrous bands. (Haematoxylin and eosin stain; original magnification ×4)

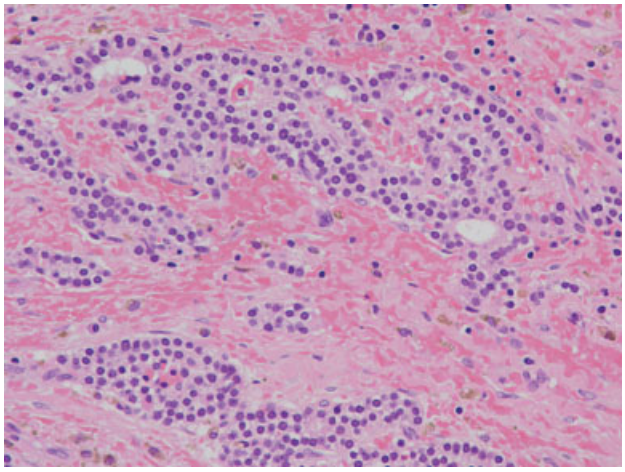

Fig. 2 Parathyroid carcinoma visualized by high-power microscopy. Trabeculae and acini of monomorphic neoplastic parathyroid cells occur within dense fibrous tissue. (Haematoxylin and eosin stain; original magnification ×40)

is associated with a poor prognosis[34]. Bondeson *et al.*[32] have noted that as many as one-fifth of carcinomas do not show the typical fibrosis and trabecular growth pattern; these features can also be seen in parathyroid hyperplasia and adenomas. According to these authors, the triad of macronucleoli, more than five mitoses per high-power field and necrosis was associated with aggressive behaviour in terms of recurrent disease. In a recent analysis of 27 patients with parathyroid cancer, fibrous bands, mitoses and vascular invasion were observed individually in 37 per cent of patients. Capsular invasion was observed in 26 per cent, and trabeculae and lymphovascular invasion was seen in only 11 per cent[21,38].

Flow cytometry has shown that tumour cell aneuploidy occurs frequently in carcinomas, but this has also been demonstrated in 25 per cent of adenomas[32]. Immunocytochemical staining for retinoblastoma protein and the cell cycle-associated antigen Ki67 have been proposed to differentiate benign from malignant parathyroid lesions, but both are observed to a variable extent in benign lesions[14,39,40]. Immunochemistry for PTH should be carried out to confirm the parathyroid origin of a carcinoma, especially if non-functioning[41].

So, in the absence of pathognomonic diagnostic criteria, a definitive pathological diagnosis of parathyroid carcinoma may not be possible, especially in its less aggressive forms[37]. However, diagnostic accuracy should be improved by the recognition of the constellation of macroscopic and microscopic features in combination with multidisciplinary correlation. In future, this may be supplemented by molecular investigations. An unequivocal diagnosis of parathyroid carcinoma can only be made on demonstration of distant or locoregional metastasis. For recurrent tumours, it is important to review the operation notes and original histology slides as the histological criteria used initially to label a tumour as benign may in fact represent the malignant nature of the lesion.

Clinical features

Most parathyroid carcinomas are functional, producing raised levels of serum PTH and calcium, but a few are non-functional with normal serum PTH and calcium levels. Symptoms and signs are mostly secondary to hypercalcaemia rather than expansion of the tumour itself. Patients may present with general symptoms of anorexia, weight loss, fatigue, weakness, nausea, vomiting, polyuria and polydipsia. Specific symptoms of bone pain, pathological fracture, recurrent renal colic, recurrent severe pancreatitis, peptic ulcer disease and anaemia are much commoner in parathyroid carcinoma than benign hyperparathyroidism.

Classical target organs of PTH, namely kidney and bones, are affected with greater frequency and severity in parathyroid carcinoma[3,13,14,42,43]. The prevalence of renal involvement in benign primary hyperparathyroidism is less than 20 per cent[14,44,45]. In contrast, Wynne *et al.*[13] reported a 56 per cent prevalence of nephrolithiasis and an 84 per cent prevalence of renal insufficiency in parathyroid carcinoma. Radiological hyperparathyroid skeletal features, such as osteitis fibrosa cystica, subperiosteal

erosion and 'salt and pepper' skull, are more commonly observed in parathyroid carcinoma (44–91 per cent)[13,14]; less than 5 per cent of patients with benign disease have these features[14,44].

Benign parathyroid tumours are rarely palpable on clinical examination whereas 30–76 per cent of parathyroid carcinomas can be palpated[14]. Occasionally, there may be an associated recurrent laryngeal nerve palsy. At the time of presentation 15–20 per cent of patients with cancer have lymph node metastasis and up to one-third have distant metastasis, usually to lung or bone[6,9,10]. Hypercalcaemic crisis, although rare, is more commonly associated with parathyroid carcinoma than benign tumours[10]. Approximately 75 per cent of patients presenting with hypercalcaemic crisis have renal and bone disease, and 40–50 per cent have a palpable tumour[10,46].

Diagnosis

The preoperative diagnosis of parathyroid carcinoma is extremely difficult and primarily rests on a triad of clinical, biochemical and radiological examination. The presence of a palpable neck mass along with primary hyperparathyroidism is suspicious of parathyroid carcinoma, although most neck lumps turn out to be thyroid masses[14,47]. Similarly, an associated recurrent laryngeal nerve palsy in a patient with primary hyperparathyroidism is also very suggestive.

The biochemical abnormalities observed in benign primary hyperparathyroidism are usually overexpressed in parathyroid carcinoma. Patients with benign disease usually have raised serum PTH and calcium levels. They may have very few symptoms and are often discovered while being investigated for an unrelated problem. In contrast, patients with parathyroid carcinoma have PTH levels 3–10 times above normal, but values as high as 75 fold may occur[14,28]. They present with severe hypercalcaemic symptoms and have calcium levels above 14 g/dl (more than 3·5 mmol/l) or 3–4 mg/dl above the upper limit of normal. The serum levels of alkaline phosphatase and α and β subunits of human chorionic gonadotropin are also raised[14,45].

Fine-needle aspiration cytology of a suspected parathyroid carcinoma is not recommended as the histological diagnosis is extremely difficult and sampling errors may create false negatives[40,48]. There is also a potential risk of track seeding; Spinelli *et al.*[49] have described a patient with cutaneous spread of parathyroid carcinoma following aspiration cytology. During surgery the presence of a firm to hard, greyish-white, lobulated mass surrounded by a dense fibrous capsule should raise the suspicion that the lesion is malignant. In addition, the presence of enlarged lymph nodes and infiltration into contiguous structures is highly suggestive of parathyroid carcinoma. Frozen-section analysis is of little value, as the distinction between adenoma and well differentiated carcinoma is very difficult[14,40].

Various imaging modalities such as ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI) and isotope scintigraphy (sestamibi) can be used to investigate parathyroid carcinoma. These investigations are not diagnostic but are effective in determining the size and location of the abnormal parathyroid gland, which is of value in planning curative resection. The choice of imaging should be guided by the clinical presentation.

Ultrasonography and ^{99m}Tc-sestamibi scanning are the primary means of assessing parathyroid lesions. Sestamibi is effective in localizing abnormal parathyroid tissue, with a sensitivity and specificity of 84·4 and 95·5 per cent respectively[48,50]. Ectopic lesions in the neck can be assessed using sestamibi, ultrasonography and contrast CT, whereas MRI with gadolinium and fat suppression is the method of choice for localizing an ectopic gland in the mediastinum[51]. Although ultrasonography, sestamibi and contrast CT are useful for cervical parathyroid recurrences, MRI with gadolinium and fat suppression is superior[51]. During any assessment of recurrence, MRI also avoids the artifacts produced by surgical clips that make interpretation of CT scans difficult[52]. Selective venous catheterization with PTH measurement can be used if non-invasive imaging fails to identify the lesion or results are equivocal[52]. Both ^{99m}Tc-sestamibi scan and contrast CT are useful in assessing distant metastases.

Management

Initial surgery

The treatment of parathyroid carcinoma is essentially surgical. The single most effective therapy is *en bloc* resection of the primary lesion at the time of the initial operation, as extensive local invasion and distant metastases are uncommon. Most patients initially undergo operation for presumed benign primary hyperparathyroidism and so a high index of suspicion and intraoperative recognition of macroscopic tumour characteristics is of great importance. Parathyroid carcinoma is not recognized by the surgeon in about 25 per cent of patients at the time of initial parathyroidectomy[6].

Patients with suspected parathyroid carcinoma should undergo exploration of all four parathyroid glands, as it can coexist with adenomas and hyperplasia[16]. The standard *en bloc* resection of the tumour involves removal of the parathyroid gland along with the ipsilateral thyroid lobe[9]. Holmes *et al.*[43] suggested a more

aggressive approach including ipsilateral thyroidectomy, isthmusectomy, skeletonization of the trachea, excision of the neighbouring strap muscles and removal of the recurrent laryngeal nerve, if involved. However, this has not gained popularity in major endocrine centres. Resection of the recurrent laryngeal nerve can almost always be avoided[53] but, when the recurrent laryngeal nerve is obviously involved, its sacrifice is necessary[52]. Therapeutic modified radical neck dissection is indicated if cervical nodes are involved at the time of initial neck exploration[9]. Prophylactic or radical neck dissection does not improve survival and is associated with an increased risk of operative complications[54]. The goal of thyroid lobectomy is to obtain a clear resection margin, rather than to eliminate a process arising in the thyroid gland itself[55,56]. Great care must be taken to avoid capsular rupture, as cell spillage is associated with multifocal recurrence and persistent hypercalcaemia. Patients who have an *en bloc* resection have a longer disease-free and overall survival than those who have a lesser procedure[7,54].

The major issue of controversy is the management of carcinoma diagnosed after operation by histology. Fujimoto *et al.*[57] suggested follow-up at intervals of 3 months, as tumours with biologically low malignant potential and minimal invasion are not always followed by local recurrence and the true extent of dissemination cannot always be determined for more invasive tumours. According to Shane[14], if the gross characteristics were suggestive and the subsequent pathology is aggressive, with extensive vascular or capsular invasion, or if the patient remains hypercalcaemic, re-exploration of the neck is indicated. In the absence of these criteria patients can be followed up with serial measurement of serum calcium and PTH.

After operation all patients require careful long-term monitoring. In the early postoperative period symptomatic hypocalcaemia may occur secondary to redeposition of calcium into the bones (hungry bone syndrome); this requires treatment with intravenous calcium. Supplemental calcium and calcitriol must be prescribed to maintain calcium at the lower limit of the normal range[14]. Once the suppressed parathyroid glands recover and adequate bone deposition has taken place, the requirement for supplemental calcium and calcitriol will drop and eventually these agents can be stopped. Thereafter, serum calcium and PTH levels should be monitored every 3 months.

Management of recurrence

In spite of a potentially curative resection, parathyroid carcinoma has a recurrence rate of more than 50 per cent[9]. Most recurrences occur 2–3 years after the initial operation, but this period is variable and a prolonged disease-free interval of as long as 23 years has been reported in the literature[9,14]. This emphasizes the importance of long-term follow-up of patients who have had a parathyroidectomy for malignant disease. A short disease-free interval is associated with poor prognosis. Recurrent disease presents with rising levels of serum calcium and PTH. Rarely, a patient may present with a severe hypercalcaemic crisis. Parathyroid carcinoma metastasizes through both lymphatic and haematogenous routes. The regional lymph nodes are common sites of metastatic disease (30 per cent) and distant metastases most frequently involve the lungs and bones, followed by the liver and other visceral organs. Cervical recurrences are palpable in 45 per cent of patients[58].

An accurate localization of the disease and exclusion of widespread metastatic deposits is essential (*Fig. 3*). Initially, non-invasive imaging should be used to detect locoregional or distant metastases. Ultrasonography is fast, inexpensive and can detect cervical recurrences. Sestamibi can detect local recurrence and distant metastases. MRI and CT are particularly useful for mediastinal and thoracic recurrences. If these are negative or equivocal, selective venous catheterization and PTH measurement is recommended[52].

Surgery is the most effective treatment for recurrent parathyroid carcinoma[9,14,48,52,59]. The aim of surgery is to reduce the tumour load and normalize the serum calcium level. For localized locoregional tumour, cervical and mediastinal exploration with wide resection, including thymectomy, is recommended[9]. In the presence of localized metastatic disease, surgical resection is advisable. To provide effective palliation, multiple operations for further recurrences are justified[9,14,52,59]. In a study by Kebebew *et al.*[52], patients with recurrent parathyroid carcinoma had an average of three recurrences and reoperations, and this was associated with a complication rate of 6·2 per cent, when intentional sacrifice of the recurrent laryngeal nerve was excluded.

Chemotherapy and radiotherapy

The rarity of this tumour precludes any prospective study to examine the effects of chemoradiation and most knowledge so far is from case reports. Until recently, radiation therapy on its own or in combination with surgery was considered to be ineffective[7,13]. However, three recent reports have stimulated an interest in adjuvant radiation therapy[21,60,61]. The Mayo Clinic has reported a disease-free survival at a median follow-up period of 60 months in four patients who received postoperative

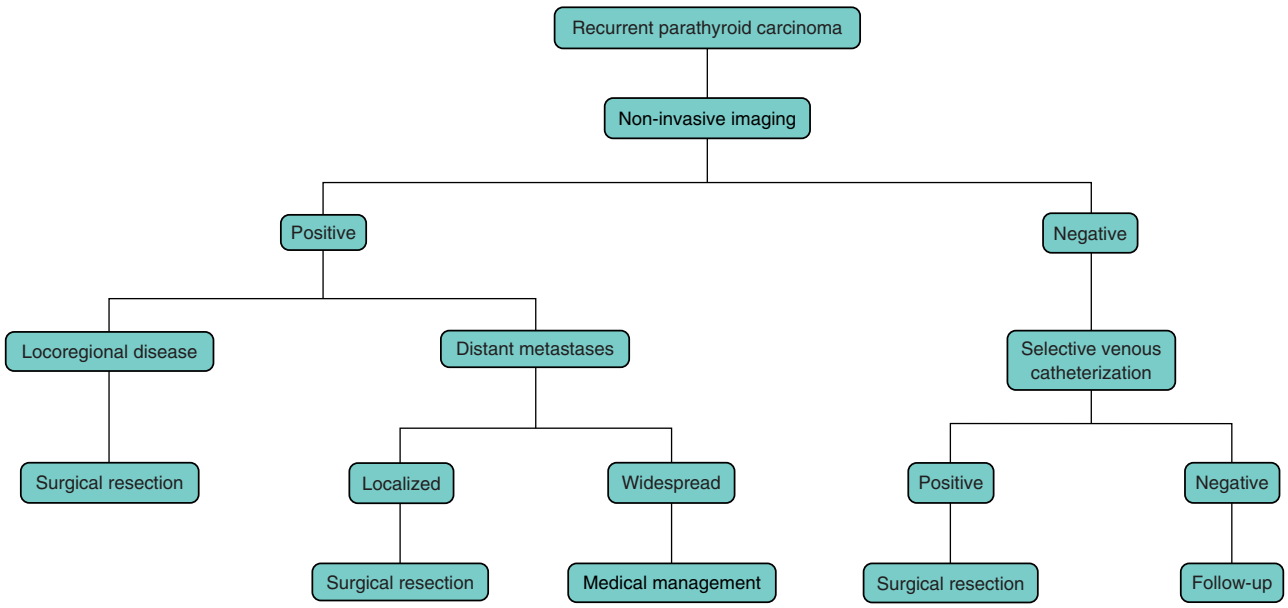

Fig. 3 Management of recurrent parathyroid carcinoma

radiotherapy[60]. The MD Anderson experience suggests a lower local recurrence rate if adjuvant radiation is given after surgery, independent of the type of operation and the disease stage[21]. These studies provide some evidence that parathyroid carcinoma may be a radiosensitive tumour and adjuvant radiotherapy may have a role in the control of locoregional disease progression. There is a growing consensus in support of adjuvant radiation and it may have direct survival benefits.

Chemotherapeutic agents in various combinations have been used to control the tumour burden of widespread or unresectable disease and, in general, these attempts have been disappointing[3,13]. Bukowski *et al.*[62] reported successful treatment of a patient with unresectable pulmonary metastases using a combination of cyclophosphamide, 5-fluorouracil and dacarbazine. Eurelings *et al.*[63] reported a good response to a combination of chemotherapy and radiotherapy in a patient with metastatic non-functioning parathyroid carcinoma.

Medical management

Medical management may be indicated for patients with hypercalcaemia secondary to parathyroid carcinoma who are awaiting investigation and surgery, or in those with unresectable or widely metastatic disease. Patients with parathyroid carcinoma almost always die from uncontrollable hypercalcaemia rather than from the tumour burden itself[13,48,57,59]. They usually have widespread metastatic or unresectable locoregional disease. The therapeutic aim in these individuals is effective control of hypercalcaemia.

In an acute hypercalcaemic crisis, urgent restoration of fluid volume is needed along with the administration of loop diuretics to promote rapid excretion of calcium. Effective long-term control of serum calcium levels requires the addition of drugs that interfere with osteoclast-mediated bone resorption; bisphosphonates (clodronate, etidronate and pamidronate) are the most widely prescribed. Mithramycin, although not very effective and more toxic, is indicated as a reserve drug for life-threatening hypercalcaemia, unresponsive to intravenous bisphosphonates[14]. Gallium nitrate is an effective hypocalcaemic agent but its use is limited by nephrotoxicity[64]. Calcitonin also reduces serum calcium levels but its effect is short lived. WR-2721 (amifostine) is a chemoprotective agent that acts by inhibiting PTH secretion. It is effective in controlling hypercalcaemia but severe toxicity limits its use[14,65].

Newer approaches to the management of hypercalcaemia include the use of calcimimetic agents and immunotherapy. Calcimimetic agents are allosteric modulators of calcium receptors and they reduce the serum levels of PTH and calcium[66]. Dendritic cell immunotherapy and immunization with human and bovine PTH peptides are new techniques that may have a promising future[67,68].

Non-functioning parathyroid carcinoma

Non-functioning parathyroid carcinoma is extremely rare with only 14 reports in the literature[61]. Patients do not present with raised levels of serum PTH and calcium, and so the disease remains asymptomatic, typically being detected late and often at an advanced stage. Patients with these tumours usually present with a palpable neck mass, dysphagia and hoarseness due to involvement of the recurrent laryngeal nerve[69]. Meticulous *en bloc* resection remains the treatment of choice as the long-term prognosis depends on a complete resection of all tumour tissue. Lack of a specific blood marker makes the early detection of recurrence difficult and it is hardly surprising that the overall outcome is dismal. Death in patients with non-functioning parathyroid carcinoma is primarily due to the volume of regional disease and metastases[70]. Few patients survive longer than 2 years[69,71].

Outlook

Parathyroid carcinoma is a slow growing tumour of low malignant potential. It has a tendency to infiltrate into the surrounding muscles, thyroid, recurrent laryngeal nerve, trachea and oesophagus. It spreads into the contiguous nodes via the lymphatics, and distant metastasis takes the haematogenous route. Cervical nodes (30 per cent) and lung (10–40 per cent) are most commonly involved, followed by liver (10 per cent)[14,33,59]. Occasional involvement of the bone, pleura, brain, pericardium and pancreas occurs[14,63]. Death is usually due to hypercalcaemia and its related metabolic consequences (renal disease, cardiac arrhythmia and pancreatitis) rather than the tumour load itself.

In spite of the best surgical effort, the recurrence rate ranges from 33 to 78 per cent[13,52,54]. The mean time to recurrence is usually between 3 and 5 years (range 1–20 years)[52,54]. Hundahl *et al.*[5], in their study of 286 patients, reported survival rates of 85·5 and 49·1 per cent at 5 and 10 years respectively. Clayman *et al.*[21] from the MD Anderson Cancer Center reported survival rates of 85 and 77 per cent at 5 and 10 years respectively. The higher survival rate at 10 years in the latter group may be attributed to an improvement in supportive care and, more specifically, in the control of hypercalcaemia[21].

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