Parathyroid Cancer: Etiology, Clinical Presentation and Treatment

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Abstract. Parathyroid carcinoma (PC) is an uncommon finding, accounting for only 1-2% of patients with primary hyperparathyroidism (HPT), but a relatively higher incidence has been reported in Italy and Japan. The etiology of the tumour remains unclear, but molecular analysis studies have hypothesised the involvement of mutations of several genes in the pathogenesis of PC, including the oncogene cyclin D1 or PRAD1 located at the chromosome 13, the retinoblastoma and the p53 tumour suppressor gene. The clinical presentation of patients with PC is mainly related to the increased secretion of PTH rather than to the tumour burden. The pre-operative diagnosis of malignancy is very difficult to obtain, and, thus, intra-operative recognition of PC is mandatory. However, reliable signs of malignancy are rarely detectable. Probably, only vascular invasion, that correlates with tumour recurrence and metastases, should be considered useful in confirming malignancy, although both Ki-67 and Cyclin D1 have been recently used to aid in the definitive diagnosis. The en bloc resection of the tumour, together with ipsilateral thyroid lobe and adjacent structures, only if involved, avoiding any capsular rupture of the mass, represents the gold standard of surgical treatment of patients. Although the PC has traditionally been considered as a radioresistant tumour, there are some retrospective data holding a possible benefit from post-operative irradiation. No cytotoxic regimen with proven efficacy is currently available for patients with PC, but since hypercalcemia is ultimately the most frequent cause of death, several studies have suggested the usefulness of bisphosphonates (i.e., clodronate, pamidronate and zoledronate), calcitonin, and calcimimetic agents (i.e., cinacalcet) in patients with PC and severe hypercalcemia. In conclusion, PC is a rare malignancy and the NCDB survey reports an overall five- and ten-year survival rate of 85% and 49%, respectively. However, it is very difficult to predict the clinical behaviour of patients with PC and probably the ultimate prognosis depends on successful resection of the tumour at the initial surgery.

Parathyroid carcinoma (PC) is an uncommon finding, accounting for only 1-2% of patients with primary hyperparathyroidism (HPT); a relatively higher incidence has been reported in Italy and Japan (1-3). In contrast to benign HPT, the gender distribution is roughly equal in patients with PC and their age of presentation is approximately a decade earlier than the mean age of patients with parathyroid (PT) adenomas (4, 5). The etiology of PC remains unclear. Multiple risk factors, including neck irradiation, end-stage renal disease, multiple endocrine neoplasia (MEN) syndromes, and familial hyperparathyroid-jaw tumour syndrome (HPT-JT) have been suggested, but none have been confirmed (6). Recent molecular analysis studies have hypothesised the involvement of mutations of several genes in the pathogenesis of PC, enclosed the oncogene cyclin D1 or PRAD1 (parathyroid adenoma 1) located at the chromosome 13, the retinoblastoma tumour suppressor gene (RB gene), and the p53 tumour suppressor gene (4). Interestingly, in 20-40% of the patients with PT adenomas and in up to 91% of those with PC, an overexpression of the oncogene cyclin D1 was found (7). Inactivating mutations of the HRPT2 gene, which is probably a tumour suppressor gene, have been described both in patients with familial PC, predominantly in the HPT-JT syndrome and in those with sporadic PC (8). The allelic loss of p53 (a nuclear phosphoprotein that restricts cell proliferation by inducing growth arrest and/or apoptosis) was...
also typically found in patients with PC (9, 10). Szende et al. reported that apoptosis and mitosis are rarely seen both in PT adenomas and in PT gland hyperplasia, whereas nuclear p53 positivity was found in all the examined PC (11). The clinical presentation of patients with PC is mainly related to the increased secretion of parathyroid hormone (PTH) rather than to the tumour burden. Fifty percent of the patients present signs and symptoms such as fatigue, weakness, depression, arthromyalgias, polyuria and polydipsia. Typically, they show both renal involvement (nephrolithiasis, nephrocalcinosis, impaired renal function) in up to 80% of the cases, and bone disease (diffuse osteopoenia, subperiosteal resorption) in up to 90% (4, 12). Concomitant kidney and bone disease at presentation is considered a strong predictor of malignancy and, moreover, from 20% to 50% present with a palpable neck mass, which is an extremely uncommon finding in patients with PT adenomas (4, 13, 14). Patients with PC have very high levels of both serum calcium (>14 mg/dl) and serum PTH (>5 times normal), in contrast to that usually found in those with benign HPT, while normocalcemic PC is extremely unusual (7, 12, 15, 16).

Pathological Findings and Surgical Treatment

The pre-operative diagnosis of malignancy is very difficult to obtain and, thus, intra-operative recognition of PC is mandatory (16). The tumour usually appears as a grey, firm, poorly circumscribed mass that is densely adherent to the surrounding soft tissues of the neck or the thyroid gland (17). However, no reliable signs of malignancy are often detectable, even on final pathology, and none of the historic criteria suggested by Shantz and Castelman are pathognomonic of PC, since several of such features may also be found in PT adenomas (1). Probably, only vascular invasion, that correlates with tumour recurrence and metastases, should be considered useful in confirming malignancy, although both Ki-67 and Cyclin D1 have been recently used to aid in the definitive diagnosis (2, 14, 18). Immunohistochemical markers (i.e., PCNA, Ki-67, p53, AgNOR counts) and nuclear DNA content are not useful in predicting the clinical outcome of patients with PC, while the presence of spindle cells and coagulation necrosis together in standard specimens should be considered a negative prognostic factor (18). PC is usually easy to localise due to its relatively large size. However, imaging studies including neck ultrasonography (US), 99mTc-sestamibi scintigraphy and computed tomography scanning (TC) do not represent a reliable way to confirm malignancy, except in the presence of invasive tumours (19-21).

Surgery is the only effective treatment for PC and, thus, an appropriately aggressive surgical procedure in patients with a high risk of suspicion should be emphasised (16). As mentioned previously, an experienced surgeon should suspect malignancy when (a) the size of the PT gland is greater than 3-4 cm, (b) the mass is firm or hard, (c) there is a local invasion of the adjacent structures, and (d) lymph node involvement (15% of patients) is found (22). The en bloc resection of the tumour, together with ipsilateral thyroid lobe and adjacent structures, only if involved, avoiding any capsular rupture of the mass, represents the gold standard of surgical treatment of PC (2, 7, 13, 23). Incomplete resection of the primary lesion results in fatal recurrences (7). Patients with suspected PC should undergo exploration of all the PT glands, since the cancer can coexist with both PT adenomas and hyperplasia (6). Intra-operative assay of quick-PTH may be of value to confirm the complete resection of the hyperfunctioning PT tissue (7). Accurate monitoring of serum calcium levels should be performed post-operatively, to avoid severe hypocalcemia, that may require calcium and calcitriol administration (4). Most of the authors emphasise the importance of an aggressive initial approach in reducing the local and distant recurrences (24). An interdisciplinary management of patients with PC has also been suggested (25). Although PC may have an indolent course, relapse occurs in about 50% of cases, usually from 1 to 5 years after initial surgery and, approximately, 25% of the patients develop lung and bone metastases during follow-up (4, 5, 12, 26). Repeated surgery for recurrence is considered a good palliation (2, 27).

Adjuvant Therapies and Management of Hypercalcemia

Although PC has traditionally been considered as a radioresistant tumour, there are some retrospective data holding a possible benefit from post-operative irradiation (4, 12). Chow et al. treated 6 patients after radical resection of PC with 40 Gy/15 fractions, delivered to the tumour bed and a surrounding field delimited by the hyoid bone, the clavicular heads and comprising the paratracheal lymph nodes, with no evidence of recurrence after a follow-up ranging from 1 to more than 10 years (28). More recently, two other small experiences with adjuvant radiotherapy have been reported. Four patients were treated at the Mayo Clinic with 70 Gy, 35 daily fractions and none of them showed any signs of recurrence after more than two-year follow-up (29). Only one out of the six patients treated post-operatively with 60 Gy at the MD Anderson Cancer Center developed a local relapse (30). With the limitation of the very low number of patients, the short period of follow-up and the inevitable bias of selection, these encouraging data may justify the proposal of adjuvant irradiation for patients at higher risk of local relapse, i.e., when (a) there is histological evidence of residual disease at, or within 2 mm
of the resection margin, (b) the tumour is cleaved from surrounding structures or its pseudocapsule breaks during the intervention, or (c) the drainage lymph nodes are involved (28, 30). The follow-up of patients radically operated is based on periodical physical examinations with accurate palpation of neck, and locoregional lymph nodes along with radiological exams of the neck, such as US, CT scan or magnetic resonance imaging. Since even very small amounts of re-growing PC may produce high levels of PTH with relevant hypercalcemia, serum assessments of calcium and PTH every four to six months usually allow for the recognition of relapse at a clinically-asymptomatic level. If such is the case, imaging with metabolic radiotracers (i.e., \(^{99m}\)Tc-sestamibi scintigraphy or 18-FDG PET) might help to locate the single or multiple sites of relapse (31-35). Recurring patients usually experience one or more local relapses before developing systemic metastases to the lungs, liver or bone; therefore, a periodical imaging of the thorax with plain X-rays or with CT scan may be reasonably performed at longer intervals, but is of minimal advantage in terms of cost-effectiveness.

The management of local or systemic relapse is always radical re-resection, whenever allowed by tumour location and involved organs, not only in the lung and in the liver, but even in the bone in case of localised disease (33, 36-39). Although the chances for ultimate cure in recurring patients are very low, the benefits of surgery in terms of control of hypercalcemia may last even for years and justify repeated interventions as long as the patient is able to tolerate them (27). Palliative radiotherapy may be employed for inoperable cervical or mediastinal masses and bone metastases, with only sporadic reports of prolonged disease control beyond two years (29, 40). No cytotoxic regimen with proven efficacy is currently available for patients with PC. A regression of mediastinal mass and pleural effusion have been reported in a patient with non-functioning tumour, receiving a combination of methotrexate, doxorubicin, cyclophosphamide and lomustine (41). A transient biochemical response of PTH and calcium levels was obtained in a patient treated with dacarbazine alone, while another patient was reported to achieve complete response of lung metastases with normalisation of serum calcium level after treatment with 5-fluorouracil (500 mg/m\(^2\) daily, 24-h continuous infusion, for 4 days), cyclophosphamide (500 mg/m\(^2\) daily for 4 days) and dacarbazine (200 mg/m\(^2\) daily for 4 days) (42, 43).

More recently, other authors have tested the same drugs as well as carboplatin, bleomycin and paclitaxel on more than 10 patients with recurrent diseases and reported only one transient response (30, 40, 44). Biochemical responses to experimental alternative approaches have been anecdotally reported. The long-acting somatostatin analogue octreotide induced a reduction in levels of PTH in a patient with a metastasis to the iliac bone, which was subsequently operated (39). Immunisation against PTH was elicited in vivo by repeated injections of human and bovine PTH-derived peptides in a woman with severe hypercalcemia from metastatic PC. Antibodies against PTH were detected within 4 weeks of initial injections and titres increased with repeated doses of immunogens, with a concomitant and clinically relevant fall of serum calcium levels. After more than 24 months, calcium levels were still normal and radiological response of pulmonary metastases was noted, possibly as a result of immune-dependent tumour destruction (45). Attempts to enhance specific antitumour immunity by means of subcutaneous vaccinations with autologous dendritic cells pulsed in vitro with patient’s tumour extracts were also performed in a patient with PC. Evidence of specific immune response to tumour lysate was obtained both in vitro by T-cell proliferation assays and in vivo by positive delayed-type hypersensitivity in the skin toward tumour lysate, but PTH and calcium levels did not decrease and tumour progression was unfortunately registered after 12 cycles of immunisations (46).

Since almost all PCs are functionally active, patients with inoperable recurrences suffer invariably from severe hypercalcemia with known signs and symptoms involving the kidney, the bone and the central nervous system. Hypercalcemia is ultimately the most frequent cause of death, even in patients with relatively low tumour burden (4). The medical management of PTH-induced hypercalcemia is superimposable to that caused by all malignant diseases, requiring vigorous intravenous hydration along with loop diuretics (i.e., furosemide), which enhance renal excretion of calcium, sometimes in association with corticosteroids in order to decrease also intestinal calcium absorption. Old agents, such as mithramycin, ethylphosphorothoric acid and gallium nitrate have practically been abandoned due to their limited activity and huge side-effects, especially for the kidney. Several bisphosphonates have been shown to decrease serum calcium levels by inhibiting PTH-dependent osteoclast activation. Both clodronate and etidronate proved to be of some efficacy in patients with parathyroid cancer when given intravenously, while the oral formulation is inactive (47-49). Subsequently, more potent agents (i.e., pamidronate and zoledronate) have become available, and currently they represent the drugs of choice. Doses of 90 mg of pamidronate are administered monthly by slow infusion over at least 2 hours; they have been demonstrated to induce prolonged remission of hypercalcemia in patients with PC (38-50). Zoledronate is the most potent drug of this class, at a standard dose of 4 mg infused over 15 minutes, although periodical monitoring of renal function is strongly recommended for some cases of acute renal insufficiency (51, 52). Calcitonin is the physiological hormone that

Lumachi et al: Parathyroid Cancer (Review)

4805
counteracts PTH by enhancing renal excretion of calcium and inhibiting bone resorption. A derivative of salmon calcitonin is available for subcutaneous or intra-muscular injection, and should be given at the dose of 100 to 400 UI, three times a day according to the severity of hypercalcemia, which usually starts to recede within 12-24 hours but then tends to rise again after a few days. Calcitonin has been demonstrated to produce an appreciable but not long-lasting calcium decrease in some patients with malignant parathyroid tumours (38-39).

Since the production of PTH is negatively controlled by ionised calcium, which binds to the calcium-sensing receptor (caSR) on the surface of the PT cells and generates a signal of down-regulation, agents able to potentiate this homeostatic control might be effective in suppressing PTH levels and, in turn, reducing serum calcium itself. The prototype of these "calcimimetic" agents is Cinacalcet, a new drug which interacts with the membrane-spanning segments of the CaSR and enhances signal transduction, presumably by inducing conformational changes in the caSR receptor which reduce the threshold for activation by ionised calcium and suppress PTH secretion in the absence of a change in the level of extracellular calcium (53). Cinacalcet is given orally, 30 to 60 mg daily and has been shown to provide a durable reduction of serum calcium levels in patients with both benign and malignant parathyroid diseases (54, 55). A new experimental approach to treating malignant hypercalcemia involves the blockade of receptor activator of nuclear factor-kappa B ligand, usually abbreviated as RANKL. RANKL is a key element in the differentiation, function, and survival of osteoclasts, which play an essential role in removing Ca++ from the bone in response to PTH stimulation. Denosumab (AMG 162) is a new, fully human monoclonal antibody against RANKL, which has been developed to antagonise osteolysis and PTH-related hypercalcemia. A recent randomised trial conducted in patients with multiple myeloma or bone metastases from breast cancer demonstrated that just a single subcutaneous dose of denosumab was able to induce a reduction in the level of bone resorption markers comparable to that obtained by pamidronate, but more prolonged in time because its effects were still persistent after 84 days (56).

In conclusion, PC is a rare cause of malignancy, and data from the National Cancer Data Base (NCDB) survey include an overall five- and ten-year survival rate of 85% and 49%, respectively (5). However, the clinical behaviour of patients with PC is very difficult to predict, and probably the ultimate prognosis depends on successful resection of the tumour at the initial surgery (22).

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