CLINICAL REVIEW 122

Parathyroid Carcinoma

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Parathyroid carcinoma is an uncommon cause of PTH-dependent hypercalcemia. The collective published experience with this rare neoplasm has provided a distinctive clinical profile that differs in a number of respects from that of benign primary hyperparathyroidism (1–3). The distinguishing features of parathyroid carcinoma assume even greater prominence when viewed within the current context of primary hyperparathyroidism, which commonly presents today as a mild asymptomatic disease (4–8). In this report, the clinical features, natural history and prognosis of parathyroid cancer are reviewed. Surgical approaches to parathyroid cancer are outlined as well as medical therapies of the hypercalcemia that accompanies recurrent or metastatic disease. As the ultimate prognosis depends to a major extent upon successful resection of the tumor at the time of the initial operation, major emphasis is placed upon those features of parathyroid carcinoma that help to differentiate it from primary hyperparathyroidism due to benign adenomatous or hyperplastic disease.

Incidence

Approximately 290 cases of parathyroid carcinoma were reported in the English literature between 1930 and 1992. Since 1992, more than 100 additional cases have been reported (9–25). Moreover, in 1999 the National Cancer Data Base reported 286 cases of parathyroid carcinoma, the largest series to date (26). In most series, this entity accounts for less than 1% of patients with primary hyperparathyroidism (1–3, 11, 17, 27–31). The disease may be somewhat more common in Japan than in Western countries, accounting for 5% of patients with primary hyperparathyroidism (18, 32–34). In a recent Italian study, 5.2% of patients operated upon for primary hyperparathyroidism were eventually found to have parathyroid carcinoma (15).

Etiology

The etiology of parathyroid cancer is unknown. No clear pattern of predisposing factors has emerged in the cases described to date. However, there are a number of clinical situations that may predispose to the development of para-

thyroid carcinoma. Several cases of parathyroid carcinoma have been reported in patients with a history of neck irradiation (35–37). There have also been a number of reports of carcinoma occurring within an adenoma or a hyperplastic parathyroid gland (38–45), and there is a recent report of parathyroid carcinoma occurring in a patient with prolonged secondary hyperparathyroidism secondary to celiac disease (10). Despite these associations, Shantz and Castleman in an extensive review of 70 cases (28) found no evidence for malignant transformation of previously pathologic tissue.

End-stage renal disease

Parathyroid carcinoma has been described in several patients with end-stage renal disease. A recent case report of such a patient also reviewed 12 patients with parathyroid carcinoma published between 1982 and 1996 who were receiving maintenance hemodialysis (16). All demonstrated hyperplasia of other parathyroid glands (16, 37, 38, 46–50), and one had a history of prior neck irradiation (37). The diagnosis was made an average of 6 yr after the start of hemodialysis. In all cases, parathyroid carcinoma was diagnosed during or after parathyroidectomy on the basis of local invasion (n = 5), tumor pathology (n = 4), or distant metastases (n = 2). The average age of the patients was 49 yr. Only 50% of these patients presented with signs of hypercalcemia; the mean serum calcium level was 10.8 mg/dL, with a range of 8.5–12.6 mg/dL, considerably lower than serum calcium levels generally observed in patients with parathyroid carcinoma (see below). PTH levels were more than twice the upper limit of normal in all patients, not an unusual finding in patients receiving maintenance hemodialysis. Although the tumor recurred in one third of the patients, only one died of hypercalcemia due to recurrent disease. The authors of the review concluded that no preoperative features distinguished hemodialysis patients with parathyroid carcinoma from those with parathyroid hyperplasia and that the clinical course may be more benign because of the tendency for renal insufficiency to lower serum calcium levels.

Familial hyperparathyroidism

Carcinoma has been reported in association with familial hyperparathyroidism (9, 51–56), particularly in the autosomal dominant form with isolated hyperparathyroidism that is not part of the multiple endocrine neoplasia type I (MEN1)

syndrome (57). In one such family, there was no evidence of antecedent hyperplasia in unaffected glands, and chromosomal abnormalities commonly observed in other solid tumors were identified (a reciprocal translocation between chromosomes 3 and 4, trisomy 7, and a pericentric inversion in chromosome 9) (55). Analyses of tumor DNA from one family member with parathyroid carcinoma showed no evidence of *ras* gene mutations, PTH gene arrangement, or allelic loss from chromosome 11q13, the locus of the gene for multiple endocrine neoplasia type 1. In addition, a greatly increased risk of parathryoid carcinoma is associated with the hereditary hyperparathyroidism-jaw tumor syndrome (52, 56, 57), recently localized to chromosome 1q21-q31 (58). Arnold and colleagues have also reported, in abstract form, that inactivation of the MEN1 gene does not appear to participate commonly in the pathogenesis of parathyroid carcinoma (59).

Molecular pathogenesis

Over the past decade, evidence for the involvement of mutations of both oncogenes and tumor suppressor genes in the development of parathyroid tumors has accumulated. Cyclin D1 or PRAD1 (*pa*rathyroid *ad*enoma 1) is an oncogene located at chromosome band 11q13; its protein product is a cell cycle regulator. A chromosomal rearrangement of the cyclin D1 gene with the regulatory region of the PTH gene has been reported in 5% of parathyroid adenomas (60–62). In addition, the cyclin D1 oncoprotein is overexpressed in 18–40% of parathyroid adenomas (63–65). Overexpression of cyclin D1 protein is strikingly frequent in parathyroid carcinomas, having been identified in 91% of such tumors in one study (65) and in two of three in another (63). Although these data strongly suggest that cyclin D1 overexpression is a pervasive feature of parathyroid carcinoma, it remains to be determined whether this feature is causative or represents an association, and whether cyclin D1 might prove to be a therapeutic target for this disease.

Strong evidence exists for the presence of a gene on chromosome 13 whose acquired inactivation contributes to the development of parathyroid carcinoma. In 1994, Cryns *et al.* studied 9 parathyroid cancers for evidence of loss of a region on chromosome 13 containing the classic tumor suppressor gene RB (retinoblastoma) and for altered expression of RB protein. Together with cyclin D1, RB is important in cell cycle control. The cancers were compared with 21 parathyroid adenomas (66). All 11 parathyroid cancers lacked an RB allele, and most had complete absence of nuclear staining for the RB protein. In contrast, only 1 parathyroid adenoma lacked the allele, and none had abnormal staining for the RB protein. Subramaniam *et al.* (67) used a mouse monoclonal antibody to detect RB gene expression in 3 parathyroid carcinomas and 11 benign adenomas. Evidence of RB gene inactivation was observed in 2 of the 3 cancers and only 1 of 11 adenomas (67). Pearce *et al.* observed allelic deletions of the 13q12–14 region involving both the RB gene and the hereditary breast cancer susceptibility gene (BRCA2) in 3 of 19 parathyroid adenomas, all of which had aggressive clinical or histopathological features and 1 parathyroid cancer (68). Yoshimoto and colleagues demonstrated allelic dele-

tions on chromosome 13q in parathyroid adenomas from 2 members of a family with isolated primary hyperparathyroidism, 1 who also had parathyroid cancer and 1 with an adenoma (9). Allelic losses of RB or D13S71 at 13q14 in a parathyroid cancer were also reported by Dotzenrath *et al.* (69). Loss of 13q, as determined by comparative genomic hybridization, has been found frequently in parathyroid carcinomas (59, 70). These data strongly support the presence of a tumor suppressor gene on the long arm of chromosome 13, which is critical for the development of parathyroid carcinoma. However, in parathyroid carcinoma the deleted portion of chromosome 13 is large, and it remains to be determined (by direct search for mutations in the retained alleles) whether RB, BRCA2, or a different gene on 13q will prove to be the primary causative tumor suppressor.

Another important cell cycle regulator and frequent participant in human cancer, the p53 tumor suppressor gene, has been examined as a candidate for involvement in parathyroid cancers. However, the frequency of p53 allelic loss and abnormal p53 protein expression is low (31), and no coding region mutations were identified in one survey (71). Thus, it appears unlikely that p53 is a major contributor to the pathogenesis of parathyroid carcinoma.

Recently, several new locations for potentially important oncogenes or tumor suppressor genes were reported in 2 rather large series of parathyroid carcinomas (59, 70) and in 1 series of 10 carcinomas (72). Comparative genomic hybridization, validated in 1 study by molecular allelotyping of the same tumors (59), revealed several recurrent abnormalities that seem to be preferentially or exclusively found in carcinomas compared with adenomas. Tumor-specific gains or losses of chromosomal material suggested that oncogenes in locations including 1q, 5q, 9q, 16p, 19p, and Xq and tumor suppressor genes in locations including 1p, 3q, 4q, 13q, and 21q may be involved in the pathogenesis of parathyroid carcinoma. Moreover, as a number of the regions commonly lost in adenomas (including 11q, home of the MEN1 gene) were never or rarely lost in carcinomas, these results also support the hypothesis that parathyroid carcinomas tend to arise *de novo* rather than from preexisting adenomas.

Clarification of the molecular pathogenesis of parathyroid carcinoma will aid in diagnostically difficult cases and may provide important clues or biological targets for the development of new and more effective therapies.

Clinical features

The clinical features of parathyroid carcinoma (1–3, 11, 12, 14, 15, 17, 26–31, 34) are due primarily to the effects of excessive secretion of PTH by the functioning tumor rather than to infiltration of vital organs by tumor mass. Thus, signs and symptoms of hypercalcemia often dominate the clinical picture, with contributions from typical hyperparathyroid bone disease and features of renal involvement, such as nephrolithiasis or nephrocalcinosis. The challenge to the clinician rests upon differentiating between hyperparathyroidism due to parathyroid carcinoma and that due to its much more common benign counterpart. It is of great importance that parathyroid carcinoma be considered in the differential diagnosis of PTH-dependent hypercalcemia, as the morbid-

ity and mortality associated with this diagnosis are substantial, and optimal outcomes are associated with complete resection of the tumor at the time of the initial operation (1–3, 11, 12, 14, 15, 17, 26–31, 34, 73). All too often the diagnosis of parathyroid carcinoma is made in retrospect when hypercalcemia recurs due to local spread of tumor or distant metastases.

There are several presenting features of a patient with primary hyperparathyroidism that, when present, should suggest a malignant rather than a benign etiology. There is no association of gender with parathyroid carcinoma. The ratio of affected women to men is 1:1 in most series compared with primary hyperparathyroidism where there is a marked female predominance (ratio of 3–4:1). Most researchers have noted that the average age of the patient with parathyroid carcinoma is in the fifth decade, approximately 10 yr younger than typical patients with primary hyperparathyroidism, who most often present in their fifties or sixties. In contrast, a recent review of the Mayo Clinic experience (30) and that of the National Cancer Data Base indicated that the average age of their patients was somewhat greater (26), in the middle fifties. In any case, considerations of gender and age are of little help in evaluating the individual patient.

With the advent of the multichannel autoanalyzer in the late sixties, the clinical profile of primary hyperparathyroidism due to benign adenomatous or hyperplastic disease has changed. Today, primary hyperparathyroidism usually presents with mild hypercalcemia (within 1 mg/dL above the upper limit of normal) that is frequently asymptomatic and often discovered during a routine evaluation or during the investigation of an unrelated complaint (4–6). In contrast, the serum calcium level of most patients with parathyroid carcinoma is much higher, generally above 14 mg/dL or 3–4 mg/dL above the upper limit of normal (1–3, 11, 12, 14, 15, 17, 26–31, 34). Moreover, this more severe hypercalcemia is almost invariably associated with the typical signs and symptoms of hypercalcemia. The most frequent complaints are fatigue, weakness, weight loss, anorexia, nausea, vomiting, polyuria, and polydipsia. Other common presenting symptoms characteristic of a severely hyperparathyroid state include bone pain, fractures, and renal colic. When reported, PTH levels have ranged from 3–10 times above the upper limit of normal for the assay employed. Extremely high levels of PTH are unusual in primary hyperparathyroidism, in which circulating concentrations are commonly less than twice normal. Alkaline phosphatase is also higher in patients with parathyroid carcinoma than in those with primary hyperparathyroidism in whom levels are generally in the vicinity of the upper limit of the normal range (7). Patients with parathyroid carcinoma may have elevated levels of α- and β-subunits of hCG, whereas patients with primary hyperparathyroidism do not (74).

A palpable neck mass has been reported in 30–76% of patients with parathyroid carcinoma. This important clinical finding constitutes another striking difference between benign and malignant parathyroid disease, as a palpable neck mass is distinctly unusual in primary hyperparathyroidism (75). In addition, recurrent laryngeal nerve palsy in a patient with primary hyperparathyroidism who has not had previous neck surgery is also very suggestive of parathyroid cancer.

The classical target organs of PTH, kidney and skeleton, are affected with greater frequency and severity in parathyroid carcinoma (1, 2, 11, 12, 27, 30, 32, 33) than is commonly observed in the modern presentation of benign primary hyperparathyroidism. Most recent series of primary hyperparathyroidism report the prevalence of renal involvement, including nephrolithiasis, nephrocalcinosis, and impaired glomerular filtration, to be less than 20% (4, 7). In contrast, renal colic is a frequent presenting complaint of parathyroid carcinoma. The prevalence of nephrolithiasis was 56%, and the prevalence of renal insufficiency was 84% in one recent series (30). These figures are somewhat higher than previous reports in which the prevalence of renal involvement generally has ranged from 32–60%. Bone pain and pathological fractures are also common features of parathyroid cancer. Overt radiological signs of hyperparathyroid skeletal disease, such as osteitis fibrosa cystica, subperiosteal bone resorption, "salt and pepper" skull, and absent lamina dura as well as less specific signs such as diffuse spinal osteopenia are commonly seen in parathyroid carcinoma (44–91%). In contrast, patients with benign primary hyperparathyroidism rarely have skeletal complaints, and specific radiological signs are found in less than 5% (4, 5, 7). It is also important to note the high incidence of concomitant bone and stone disease that occurs in parathyroid cancer, whereas simultaneous renal and overt skeletal involvement is distinctly unusual in primary hyperparathyroidism. In addition to the kidneys and the skeleton, other organs are frequently affected. Recurrent severe pancreatitis, peptic ulcer disease, and anemia occur with greater frequency in patients with malignant disease than in those with benign primary hyperparathyroidism.

Parathyroid carcinoma shares many clinical features with acute primary hyperparathyroidism, sometimes called parathyroid crisis. In view of the marked elevations of serum calcium and PTH that are common in parathyroid crisis, the diagnosis of parathyroid cancer should be considered. Although the distinction between these two entities is not possible preoperatively, it is important to bear the diagnosis in mind because the surgical approach differs.

A summary of features that might lead one to suspect parathyroid cancer in a patient with hypercalcemia and elevated PTH levels is shown in Table 1. It should be noted however, that some patients with benign primary hyperparathyroidism present with more severe disease than is commonly seen today. In such patients, the distinction between benign and malignant disease may be even more difficult on clinical grounds, because profound hypercalcemia, renal disease, and osteitis fibrosa or diffuse osteoporosis may occur, and even concomitant kidney and bone disease may be present (73). However, it is preferable to have a high index of suspicion for parathyroid carcinoma when these features are present than to miss the opportunity for surgical cure by failing to consider it in the differential diagnosis.

Pathology

Several operative findings have been described that, when present, help to distinguish benign parathyroid adenomas from parathyroid carcinoma. The typical parathyroid ade-

TABLE 1. Parathyroid carcinoma and benign primary hyperparathyroidism: typical features

	Parathyroid carcinoma	Primary hyperparathyroidism
Female: male ratio	1:1	3.5:1
Average age (yr)	48	55
Asymptomatic (%)	<5	>80
Serum calcium (mg/dL)	>14	≤1, above upper limit of normal
PTH	Markedly elevated	Mildly elevated
Palpable neck mass	Common	Rare
Renal involvement (%)[a]	32–80	4–18
Skeletal involvement (%)[b]	34–91	<5
Concomitant renal and skeletal disease	Common	Rare

[a] Includes nephrolithiasis, nephrocalcinosis, and impaired renal function in absence of any other etiology.
[b] Includes osteitis fibrosa, subperiosteal resorption, "salt and pepper" skull, and diffuse osteopenia on plain radiographs.

noma is usually of soft consistency, round or oval in shape, and of a reddish-brown color. In contrast, parathyroid carcinoma is frequently described as a lobulated, firm to stony-hard mass. In about 50% of cases it is surrounded by a dense, fibrous, grayish-white capsule that adheres tenaciously to adjacent tissues and makes the tumor difficult to separate from contiguous structures. If there is gross infiltration of adjacent thyroid, nerve, muscle, or esophagus or obvious cervical node metastases, the diagnosis of carcinoma is not difficult. However, any one or all of these operative findings may be absent, and examination of frozen sections is of little value in distinguishing benign from malignant disease.

As is the case with many endocrine neoplasms, the histopathological distinction between benign and malignant parathyroid tumors is difficult. In 1973 Shantz and Castleman, based upon an analysis of 70 cases of parathyroid carcinoma, established a set of criteria for the pathological diagnosis of this malignancy (28). These histological features are 1) uniform sheets of (usually chief) cells arranged in a lobular pattern separated by dense fibrous trabeculae, 2) capsular or vascular invasion, and 3) mitotic figures within tumor parenchymal cells that must be distinguished from endothelial cell mitoses. Unfortunately, none of these features is pathognomonic of parathyroid carcinoma. Several features, namely, dense fibrous trabeculae, trabecular growth pattern, mitoses, and capsular invasion, have been found in parathyroid adenomas (75). Capsular and vascular invasion appear to correlate best with subsequent tumor recurrence.

Several other histological techniques have been investigated to improve further the accuracy of diagnosing parathyroid carcinoma. Electron microscopy of parathyroid cancer tissue reveals nuclear and mitochondrial alterations and evidence of increased secretory activity, but does not appear to be of value in distinguishing benign from malignant tumors (76–78). Nuclear diameter appears to be greater in parathyroid carcinomas than in adenomas (28, 76–80), but this index is not very useful in the individual case. Measurement of nuclear DNA content by flow cytometry may be of some value both in establishing the diagnosis of parathyroid carcinoma and in predicting the invasive potential of the tumor. Mean nuclear DNA content is greater, and an aneuploid DNA pattern is more common in parathyroid carcinoma than in adenomas; when present, aneuploidy appears to be associated with a poorer prognosis (33, 73, 81). Unfor-

tunately, however, aneuploidy occurs too frequently in parathyroid adenomas to be of great use in differentiating benign from malignant parathyroid lesions (34, 81, 82).

Some experts believe that the overall histological pattern is more useful than any single feature in the differentiation of parathyroid carcinoma from benign disease, and the presence of more than one in a lesion should raise the index of suspicion (32, 34). Bondeson and colleagues consider that cellular atypia, including nuclear pleomorphism and enlargement and macronucleoli, are associated with a greater likelihood of malignancy (83).

Immunohistochemical staining of RB protein may also prove useful in distinguishing benign from malignant parathyroid tumors. Cryn and colleagues were the first to report that staining for RB protein with polyclonal antibodies was commonly absent in parathyroid carcinomas and was almost always present in parathyroid adenomas (66). Other investigators have corroborated their results (67). In contrast, Farnebo et al., who used monoclonal antibodies directed against the RB protein, did not find immunostaining of RB protein to be useful in distinguishing between benign and malignant parathyroid tumors (84). However, these investigators did observe a trend for more intense immunostaining in parathyroid cancers of the cell cycle-associated antigen Ki-67, a marker for proliferative activity. In their hands, the technique was not useful for distinguishing carcinomas from adenomas (84), although Abbona et al. did find significant differences in Ki-67 staining between benign and malignant parathyroid disease (85). Further studies are necessary to assess the value of immunohistochemical stains for the differential diagnosis of parathyroid lesions.

Invasive growth of various neoplasms may be facilitated by tumoral secretion of proteolytic enzymes. One such enzyme is gelatinase A. Farnebo et al. recently reported that gelatinase A messenger ribonucleic acid was detected in 14 of 18 unequivocal and 4 of 13 equivocal parathyroid cancers (86). The strongest signal was detected in the fibroblasts and macrophages at the tumor border, rather than in the tumor cells themselves. This new technique may provide additional support for the diagnosis of malignancy.

Natural history

Parathyroid carcinoma is an indolent, albeit tenacious, tumor with rather low malignant potential. It tends to recur

locally at the operative site and spread to contiguous structures in the neck. Metastases occur late in the course of the disease with spread via both lymphatic and hematogenous routes. Cervical nodes (30%) and lung (40%) are involved most commonly, followed by liver (10%). Occasional involvement of bone, pleura, pericardium, and pancreas has been reported.

Management

Surgery. The single most effective therapy for parathyroid carcinoma is complete resection of the primary lesion at the time of the initial operation when extensive local invasion and distant metastases are less likely (1, 18, 27, 29, 34, 75). For this reason both preoperative suspicion and intraoperative recognition are of paramount importance. Patients whose clinical presentation is suggestive of parathyroid carcinoma warrant thorough exploration of all four parathyroid glands, as parathyroid carcinoma has been reported to coexist with benign adenomas or hyperplasia (10, 87). When the gross pathological findings suggest malignancy, the following steps should be taken: *en bloc* removal of the lesion together with the ipsilateral thyroid lobe and isthmus, and skeletonization of the trachea and removal of any contiguous tissues to which the tumor adheres. Great care must be exercised to avoid rupture of the capsule of the gland, which increases the likelihood of local seeding of the tumor. If the recurrent laryngeal nerve is involved with tumor, it must be resected. Tracheoesophageal, paratracheal, and upper mediastinal lymph nodes should be excised, but an extensive lateral neck dissection is indicated only when there is spread to the anterior cervical nodes.

The situation becomes more complex when the diagnosis is made in the early postoperative period on the basis of pathology. This is particularly so in view of the controversy that exists regarding the histopathological diagnosis of parathyroid carcinoma. If the gross characteristics of the lesion were typical of a parathyroid cancer and if the subsequent pathology appears to be aggressive with extensive vascular or capsular invasion or if the patient remains hypercalcemic, reexploration of the neck is indicated. The structures adjacent to the tumor site should be resected in the manner described above. If none of these features is present, but the diagnosis is made on the basis of the microscopic characteristics, immediate reoperation may not be necessary, as a simple complete resection of the tumor is often curative. Such a patient must be observed carefully with frequent measurements of PTH and serum calcium levels.

The postoperative management of a patient with parathyroid cancer must include careful attention to the serum calcium level. As calcium and phosphorus are deposited into the skeleton, symptomatic hypocalcemia (hungry bone syndrome) may ensue and should be regarded as a sign that the surgery has been successful. The hypocalcemia may be severe and protracted, requiring large doses of iv calcium. Sufficient supplemental calcium and calcitriol should be prescribed to maintain serum calcium at the low end of the normal range. As the bones heal and the remaining parathyroid glands recover, the requirement for calcium will decrease, permitting gradual reduction of the doses of calcium and calcitriol. After this point serum calcium and PTH levels should be monitored every 3 months.

The management of recurrent or metastatic parathyroid carcinoma reflects the rather indolent biology of this cancer and, in contrast to many other tumors, is primarily surgical (1, 11, 15, 18, 19, 26, 29, 30, 33, 88). As even very small tumor deposits may produce sufficient PTH to cause severe hypercalcemia, significant palliation may result from resection of lesions in the neck, lymph nodes, lungs, or liver (18). Many situations have been described in which resection of such lesions has resulted in periods of normocalcemia that range from months to years. Even though surgery is only palliative, amelioration of the hypercalcemia may also result making its control more amenable to medical therapies.

In patients with recurrent hypercalcemia, localization studies should be performed before reoperation. Careful palpation of the neck should be performed, as recurrence occurs earliest and most often at the original site, and such tumors are frequently palpable. Thallium 201-technetium 99m scanning is useful in locating tumors in the neck and upper mediastinum (89–91). Technetium 99m-sestamibi used concurrently with a hand-held, γ-detecting probe may also prove to be useful for the intraoperative localization of abnormal parathyroid tissue (22). Thallium 201 is also helpful for situations in which the thyroid has been partially or completely resected or when pulmonary metastases are suspected. Computerized tomography and magnetic resonance imaging are useful adjuncts to ultrasonography in evaluation of the neck and are superior for detection of distant metastases in the chest or abdomen. If noninvasive testing does not yield results, arteriography or selective venous catheterization may be useful. Fine needle aspiration biopsy in conjunction with ultrasonic localization and immunoperoxidase confirmation may be useful in localizing parathyroid tissue in patients with recurrent hyperparathyroidism (92). However, biopsy must be used with caution, if at all, in parathyroid carcinoma to avoid seeding the needle track with deposits of malignant tissue. Recurrent carcinoma in the neck should be treated with wide excision of the involved area, including the regional lymph nodes and other involved structures. Accessible distant metastases should also be resected when possible.

Radiation therapy. Parathyroid carcinoma is not a radiosensitive tumor. The use of radiation therapy to control tumor growth and decrease hormone production has been ineffective in the majority of cases in which it has been attempted (3, 28). In the occasional situation, radiation to the neck after surgery for recurrence may be helpful in preventing tumor regrowth (23, 75). An apparent cure (10 yr) of locally invasive parathyroid carcinoma by radiation therapy was reported by Wynne and colleagues (30). In addition, six patients who received adjuvant radiation therapy for microscopic residual disease have been followed for 12–156 months without recurrence (23).

Chemotherapy. Because of the rarity of parathyroid carcinoma, few investigators have sufficient numbers of patients to permit large scale clinical research trials. Thus complete investigations of the utility of a given therapy do not exist, and

experience is usually limited to scattered case reports. It is with these unavoidable limitations in mind that the following comments should be interpreted.

Attempts to control tumor burden with chemotherapy have been disappointing. Several regimens (nitrogen mustard; vincristine, cyclophosphamide and actinomycin D; adriamycin, cyclophosphamide, and 5-fluorouracil; and adriamycin alone) have been ineffective (87, 93, 94). Two patients have been treated with synthetic estrogens with some success (95, 96). A single patient with pulmonary metastases responded to treatment with dacarbazine, 5-fluorouracil, and cyclophosphamide with a decrease in PTH and normalization of serum calcium for 13 months (97). Another patient responded to dacarbazine alone with a brief, but significant, decline in her serum calcium level (98). An 18-month remission with regression of a mediastinal mass and pleural effusion was induced in a patient with a nonfunctioning parathyroid carcinoma by a regimen consisting of methotrexate, doxorubicin, cyclophosphamide, and lomustine (99). Such approaches warrant further investigation.

Management of hypercalcemia. When parathyroid carcinoma has become widely disseminated and surgical resection is no longer effective, the prognosis is poor. However, even at this juncture relatively prolonged survival is possible. The therapeutic goal at this point is to control the hypercalcemia, which because of the extremely elevated PTH levels and the intensity of the associated bone resorption, may be a difficult and frustrating task.

The acute hypercalcemia of parathyroid carcinoma is treated in the same way as hypercalcemia due to any other cause (100, 101). Management includes infusion of saline to restore fluid volume and enhance urinary calcium excretion, and loop diuretics to further increase calciuresis. Such measures rarely suffice, however, and addition of agents that interfere with osteoclast-mediated bone resorption is always necessary.

Bisphosphonates: The bisphosphonates are a group of drugs that inhibit osteoclast-mediated bone resorption. Several of these drugs have shown some promise in the therapy of parathyroid carcinoma. Clodronate (Cl$_2$MDP) lowers serum calcium in parathyroid carcinoma when administered iv (102–104). It is widely available in Europe and the United Kingdom, but it is not available in the United States. Etidronate has also been shown to lower serum calcium transiently in parathyroid cancer patients (105). It is administered iv over a 2-h period at a dose of 7.5 mg/kg and may be repeated daily or until the serum calcium falls to normal for a maximum of 7 days. Although the drug is available in an oral form, it is not effective in patients with parathyroid carcinoma, and even the iv preparation may not normalize the serum calcium.

A more potent bisphosphonate, pamidronate, is now widely available for iv use. When infused for periods ranging from 2–24 h and in doses ranging from 45–90 mg/day, pamidronate has been at least transiently effective in lowering serum calcium levels in several patients with parathyroid cancer (18, 20, 21, 106–108). New and more potent bisphosphonates (ibandronate and zoledronate) are being investi-

gated actively in the United States and soon may become available for the treatment of hypercalcemia of malignancy, including that due to parathyroid cancer.

Plicamycin: Plicamycin (mithramycin), another specific inhibitor of bone resorption, lowers serum calcium levels in parathyroid carcinoma (109). It is administered iv at a dose of 25 μg/kg over 4–8 h and may be repeated at daily intervals for up to 7 days until the serum calcium falls into an acceptable range (100, 101). Unfortunately, complete normalization of the serum calcium is often not achieved, and the effectiveness of the drug is not only transient but diminishes with repeated courses. Conversely, the toxic effects of plicamycin on the liver, kidney, and bone marrow increase with the number of exposures. Plicamycin therapy should be reserved for therapy of life-threatening hypercalcemia, unresponsive to iv bisphosphonates, while surgically accessible metastases are sought or for those patients whose hypercalcemia can be controlled in no other way.

Calcitonin: This agent both inhibits osteoclast-mediated bone resorption and increases urinary calcium excretion. However, it lowers serum calcium transiently, if at all, in most patients with parathyroid carcinoma (1, 97, 102, 110–112). It has been effective in a single patient when used in doses of 200–600 Medical Research Council units/day in combination with glucocorticoids (300 mg hydrocortisone) (113) and in occasional patients when used alone (114).

Gallium: Gallium nitrate appears to inhibit bone resorption by preventing dissolution of hydroxyapatite crystals (115). Gallium nitrate lowered serum calcium in two patients with parathyroid carcinoma (115) and was later reported to be effective in four of five patients (19). It is administered as a continuous 5-day infusion at a dose of 200 mg/m^2·day. Significant toxicities include elevation of the serum creatinine that is potentiated by volume depletion and the concomitant use of potentially nephrotoxic drugs. It remains unclear whether gallium nitrate will prove useful in the management of chronic hypercalcemia due to parathyroid cancer.

Calcimimetics: Under normal circumstances, PTH secretion is mediated by a cell surface calcium-sensing receptor, and this regulatory response is generally retained in benign parathyroid tumors. Recently, an allosteric modulator of the calcium receptor with calcimimetic properties has been shown to lower serum PTH and calcium concentrations in patients with primary hyperparathyroidism (116). This same agent was used to treat a patient with parathyroid carcinoma. Serum calcium was controlled for 2 yr without adverse effects (24). Such agents show promise in the management of parathyroid cancer.

WR-2721: WR-2721 [5-,2-(3-aminopropyl)amino]ethylphosphorothoric acid, is a hypocalcemic agent that acts by inhibiting PTH secretion and bone resorption. It has been shown to lower PTH levels and serum calcium levels in parathyroid carcinoma (117). Severe toxicities limit its use.

Octreotide: The long-acting somatostatin analog, octreotide, has also been reported to inhibit PTH secretion in a woman with parathyroid carcinoma metastatic to bone (118).

Immunization: Finally, a novel approach to therapy of hypercalcemia due to parathyroid cancer has recently been published in case report form (25). A patient with para-

thyroid carcinoma metastatic to lungs and pleura had severe hypercalcemia that was resistant to oral clodronate, iv pamidronate, octreotide, 5-fluorouracil, and streptozotocin. She was immunized with human and bovine PTH peptides, followed by booster doses at 4 and 11 weeks. Antibodies against PTH were detected at 4 weeks. Before therapy, serum calcium varied between 3.5 and 4.2 mmol/L. Serum calcium levels remained significantly lower (2.5–3.0 mmol/L) throughout the 6 months of observation. There was rapid improvement in her clinical condition, and no significant adverse effects were observed. If confirmed, this would seem to be a novel and relatively simple approach to the control of hypercalcemia in patients resistant to other measures.

Prognosis

The prognosis of parathyroid carcinoma is quite variable. No one characteristic correlates predictably with outcome. Early recognition and complete resection at the time of the initial surgery carry the best prognosis. The average time between surgery and the first recurrence is approximately 3 yr, although intervals of up to 20 yr have been reported. Once the tumor has recurred, complete cure is unlikely, although prolonged survival is still common under these circumstances with palliative surgery. Five-year survival rates vary from 40–86%. The National Cancer Database survey recently reported 10-yr survival to be approximately 49% (26).

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