
PARATHYROID CARCINOMA: A 22-YEAR EXPERIENCE

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Abstract: *Purpose.* Because parathyroid carcinoma is rare, clear consensus is not available regarding the optimal management of patients with this condition. Treatment strategies generally derive from clinical and anecdotal experiences. We report our experience with this entity.

Methods. We included all patients with parathyroid carcinoma seen at The University of Texas M. D. Anderson Cancer Center since January 1, 1980. The medical records and pathology specimens were reviewed and verified in all cases.

Results. Since 1980, 27 patients (16 men and 11 women) registered at M. D. Anderson Cancer Center with parathyroid carcinoma and a minimum follow-up of 2 years. The age at initial diagnosis (mean \pm SD) was 46.7 \pm 15.3 years. All patients were

seen with hypercalcemia (mean calcium, 13.4 \pm 1.5 mg/dL). Eighteen patients had locally invasive disease, eight had localized disease, and one had distant metastasis. Parathyroid cancer was treated with complete surgical excision with curative intent in 18 patients. In the other nine patients, who had clinical and/or radiographic evidence of soft tissue extension, the tumor was treated by comprehensive "en bloc" soft tissue resection. Of six patients who received adjuvant radiotherapy after initial surgery, only one had a local relapse. In contrast, of 20 patients who did not receive adjuvant radiotherapy, 10 had a local relapse, excluding the one patient who had distant metastases. The 5-year survival was 85%, and the 10-year survival was 77%. Five patients died of parathyroid carcinoma; all deaths were hypercalcemia related.

Conclusions. Parathyroid carcinoma can be an indolent disease with morbidity and mortality related to hypercalcemia. Adjuvant radiotherapy may improve local control and limit the occurrence of local relapse. A comprehensive multidisciplinary approach with surgery, radiation therapy, and medical treatment for hypercalcemia is needed to optimize patient outcome. © 2004 Wiley Periodicals, Inc. *Head Neck* 26: 716–726, 2004

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Parathyroid carcinoma is rare, accounting for 0.4% to 5%¹⁻⁵ of all cases of parathyroid hormone–induced hypercalcemia. It is the least common endocrine malignancy,⁵⁻⁹ with a prevalence of 0.005%,¹⁰ of all cancers. Because the disease is so uncommon, our knowledge regarding the natural history and prognostic factors in parathyroid carcinoma remains limited. With the exception of the Mayo Clinic report,¹¹ many previous case series are small or based on data from multiple institutions over variable time periods.^{7,10,12} Over time, diagnostic tools have evolved significantly, rendering it difficult to compare data regarding disease stage and clinical outcomes, such as disease-related morbidity and mortality. In this article, we report our institution's experience during the past 22 years; during this interval, diagnostic imaging and biochemical analysis technology have been relatively constant and comparable. We review the outcomes of these patients, focusing on clinical features and interventions that may affect them.

METHODS

In this retrospective review, we included all patients who were evaluated and treated for parathyroid carcinoma at The University of Texas M. D. Anderson Cancer Center since January 1, 1980, and had a minimum follow-up of 2 years since disease diagnosis. We focused the analysis on patients who received their diagnosis after 1980 for three reasons: first, the use and improvement of radiologic studies, such as CT scans, ultrasound, and nuclear scans, for the diagnosis and follow-up of cancer had become fairly standard in our institution by that time; second, improvements in parathyroid hormone measurement methods over the past 20 years have simplified the diagnosis of parathyroid disease¹³; and third, one of the authors (RVS) was available throughout and had the opportunity to participate in the care of most patients and the deliberations regarding treatment guidelines for the disease. The patient population was identified through a search of the Tumor Registry database maintained by the Department of Medical Informatics. Institutional review board approval was obtained before the initiation of this study.

Patient Characteristics. The cohort comprised 27 patients with pathologically confirmed parathyroid carcinoma. Clinical information was derived from the institutional patient database and a thorough review of the medical records. Twelve patients had their initial surgery at M. D. Anderson Cancer Center; the others were referred to the cancer center for further management after pathologic confirmation of malignancy or at a later date when they had a recurrence develop; thus, all patients had at least part of their evaluation and treatment at M. D. Anderson.

Pathologic diagnosis was confirmed by one of the authors (AEN) who re-reviewed all slides and reports. In all patients, the diagnosis of parathyroid carcinoma was made on the basis of histopathologic criteria, local invasiveness (microscopic or macroscopic), metastasis, or the combination of these criteria. The histopathologic criteria established by Shantz and Castleman in 1973¹⁴ have been used at M. D. Anderson to characterize parathyroid carcinoma throughout. These criteria include the presence of sheets of tumor cells arranged in a lobular pattern separated by dense fibrous trabeculae, capsular or vascular invasion, necrosis, and/or mitotic figures.

Demographic, etiologic, pathologic, and clinical presentation data were recorded and analyzed as described in "Statistical Analyses." Details of surgical and adjuvant therapies (ie, chemotherapy, radiation), along with their clinical and biochemical outcomes, were reviewed. Finally, a complete description of acute and chronic complications of this disease and its outcomes was compiled.

Laboratory Analyses. Biochemical abnormalities, including hypercalcemia, hypophosphatemia, elevation of serum alkaline phosphatase, and parathyroid hormone (PTH) levels were recorded at initial presentation and during follow-up. Hypercalcemia was categorized¹⁵ as follows: mild hypercalcemia, calcium level <12 mg/dL; moderate hypercalcemia, calcium level between 12 mg/dL and 13.5 mg/dL; and severe hypercalcemia, calcium level >13.5 mg/dL. Assays for the measurement of amino and carboxyl terminal fragments of PTH were available before 1990. Since 1990, an intact PTH assay (iPTH) has been the standard laboratory measure technique. From 1990 to 1996, iPTH samples were sent from M. D. Anderson to an outside reference laboratory. Then from 1996 to 2000, iPTH samples were tested at M. D. Anderson by the immunoradiometric assay method (IRMA), and from 2000 to the present,

iPTH measurements were done locally in the M. D. Anderson laboratory by use of the immunochemiluminescent assay (ICMA) performed by Nichols Institute Advantage instrument (Nichols Institute, San Clemente, CA).

Staging. All 27 patients were categorized by extent of disease and were placed in one of three groups as follows: group 1, localized disease, histologically defined as carcinoma but confined to the parathyroid gland; group 2, locally invasive disease defined as microscopic or macroscopic disease extension outside the parathyroid gland involving adjacent tissues such as adipose, striated muscle, thyroid, and esophagus; and group 3, metastatic disease defined as tumor spread to distant organs.

Clinical Course. Disease-free interval (DFI) was defined as the period of time in months from diagnosis to documentation of disease relapse (usually identified with recurrence of hypercalcemia). In all analyses for DFI and relapses, the one patient who was seen with metastases was excluded. Potential prognostic factors including clinical, biochemical, and treatment modalities were also analyzed.

Radiation Therapy. Adjuvant radiation therapy was defined as treatment within 2 months after the initial surgery. All irradiated patients completed a full course of postoperative radiotherapy (PORT). Indications for treatment were positive resection margins, local invasion, or multiple recurrences. Mean total dose delivered was 60 Gy. Patients were treated with ^{60}Co or 6-mV linear accelerator. Initial parallel-opposed anteroposterior–posteroanterior (AP-PA) fields were used to spinal cord tolerance, and then alpha cord conformal setup was used.

Statistical Analyses. STATISTICA for Windows version 6.0 (STAT Soft, Tulsa, OK) was used to perform statistical analyses. Descriptive statistics, including frequencies, percentages, means, standard deviations (SDs), and ranges were used to describe the cohort. Chi-square tests, correlation associations, and univariate analyses were performed as deemed appropriate in subgroup comparisons. Survival and disease-free interval analyses were done with the survival module based on Kaplan-Meier survival analyses. Power analyses were performed in consideration of effect size with Cohen's method.

RESULTS

Patient Characteristics. Twenty-seven patients were followed for a minimum of 2 years since the time of diagnosis (by design) to a maximum of 21 years, with an average of 7.9 years follow-up. The group included 16 men (59%) and 11 women (41%); the male–female ratio was 1.5:1. The mean age \pm SD at initial diagnosis was 46.7 ± 15.3 years (range, 16–75 years). Figure 1 depicts the distribution of patient age and sex.

Two patients had a recorded history of neck irradiation for hemangioma and chronic tonsillitis 34 and 40 years before the diagnosis of parathyroid carcinoma, respectively. No patient was thought to have multiple endocrine neoplasia syndromes. One patient had hereditary hyperparathyroidism–jaw tumor syndrome, and two patients had a family history of parathyroid adenoma; none had a family history of parathyroid carcinoma as described in some reports.^{16,17} Table 1 depicts the characteristics and clinical course of the 27 patients.

Clinical Presentation. Nineteen patients were initially seen with constitutional symptoms such as fatigue, weight loss, anorexia, memory deficit, and paresthesias in upper and lower extremities. Eight patients were asymptomatic despite hypercalcemia; one of these had severe hypercalcemia (14.5 mg/dL) at presentation, and three patients had moderate hypercalcemia. The clinical features of the 27 patients are presented in Table 2 (several patients had more than one symptom).

Twelve patients exhibited renal complications of primary hyperparathyroidism, including nephrolithiasis in seven patients, renal failure in seven patients, and nephrocalcinosis in three patients. Metabolic bone disease was observed radiologically in six patients; among four patients with osteopenia on plain films, three also had osteitis fibrosis cystica. One patient had pancreatitis.

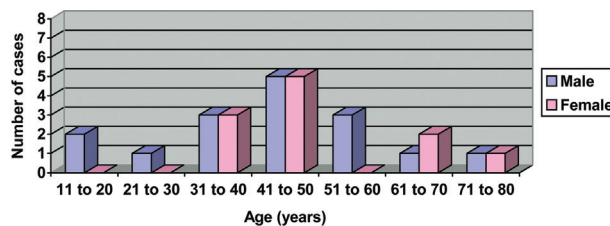


FIGURE 1. Distribution of the 27 patients with parathyroid carcinoma by sex and age at diagnosis. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Table 1. Clinical characteristics of 27 patients with parathyroid carcinoma.

Patient	Sex-age at diagnosis	Stage	Surgery	Adjuvant radiation therapy	DFI (months)	FU (months)	Outcome
1	F-62	Local	CE	–	252	252	A/FOD
2	M-46	Local	CE	–	18	30	DOD
3	M-37	Distant	EB	–		10	DOD
4	F-52	Invasive	CE	+	228	228	A/FOD
5	F-73	Invasive	EB	–	24	24	D/other
6	F-36	Invasive	CE	–	84	84	A/FOD
7	M-75	Invasive	CE	–	108	108	D/other
8	M-46	Invasive	EB	+	121	121	A/FOD
9	M-56	Invasive	CE	–	121	121	D/other
10	M-16	Invasive	CE	–	144	144	A/FOD
11	M-53	Invasive	EB	+	30	30	A/FOD
12	F-45	Invasive	EB	–	10	23	DOD
13	M-48	Local	CE	–	84	108	DOD
14	F-32	Local	CE	–	108	108	A/FOD
15	M-16	Local	CE	–	48	192	A/FOD
16	F-68	Invasive	EB	+	36	36	A/FOD
17	F-49	Invasive	CE	+	84	84	A/FOD
18	F-41	Local	CE	–	72	72	A/FOD
19	M-46	Invasive	EB	–	36	96	A/FOD
20	M-27	Invasive	CE	–	60	84	A/WD
21	F-49	Invasive	CE	–	60	60	A/FOD
22	M-33	Local	CE	–	168	216	A/WD
23	M-39	Local	EB	–	132	216	A/WD
24	F-39	Invasive	CE	–	30	30	A/FOD
25	M-69	Invasive	EB	+	12	20	DOD
26	M-60	Invasive	CE	–	6	36	A/WD
27	M-47	Invasive	CE	–	24	40	A/WD

Abbreviations: F, female; CE, complete excision; A/FOD, alive and free of disease; M, male; DOD, dead of disease; EB, en bloc; D/other, dead from other causes; A/WD, alive with disease.

Physical examination was abnormal in five patients: four had a cervical mass and one had a brown tumor of the right maxilla.

Laboratory Findings. All 27 patients had hypercalcemia at the time of diagnosis as documented in the medical records. The exact calcium level was available in 18 patients; the mean concentration was 13.4 ± 1.9 mg/dL (range, 10.4–17.7 mg/dL). Eight (44%) of the 18 patients were initially seen with severe hypercalcemia (as defined in “Methods”), five (28%) had moderate hypercalcemia, and five (28%) had mild hypercalcemia. For the other nine patients, it was clear from the medical records that hypercalcemia was present initially, although the exact calcium level was not in the M. D. Anderson record.

Hypophosphatemia was not a common finding. It was present in five of 15 patients who had phosphorus measured at their initial visit. Alkaline phosphatase was elevated in seven of 11 patients. Initial PTH values (N terminus, C terminus, or iPTH) were available for 16 patients; 14 had elevated PTH values, and two had normal

levels despite hypercalcemia. Initial PTH values were not in the M. D. Anderson medical record for the remaining 11 patients.

Staging. Eight patients (30%) were considered to have localized disease, as defined in the “Methods”

Table 2. Presenting symptoms in 27 patients with parathyroid carcinoma.

Symptom	No. of patients
Asymptomatic	8/27
Fatigue	9/27
Bone pain	8/27
Headaches	7/27
Joint pain	6/27
Weight loss	4/27
Dyspepsia	4/27
Muscular pain	4/27
Memory deficit	2/27
Constipation	2/27
Paresthesias	3/27
Polyuria	2/27
Polydipsia	2/27
Neck pain	1/27

section, 18 patients (67%) had locally invasive disease, and one patient had evidence of metastatic disease at the time of presentation. No patients had regional spread to cervical lymph nodes at the time of presentation.

Surgery. On the basis of the presumptive preoperative diagnosis of benign disease, 18 patients initially had complete surgical excision with curative intent. The diagnosis of malignancy was made postoperatively in 14 of these patients by surgical pathology based on histologic criteria. The other four patients remained with the diagnosis of parathyroid adenoma for a number of years, while being cared for at outside institutions, until local recurrence or metastatic disease manifested 2 to 15 years later.

Nine patients with preoperative suspicion of parathyroid carcinoma on the basis of clinical and/or radiographic evidence of soft tissue extension underwent comprehensive “en bloc” soft tissue resection; this usually included thyroid lobectomy, excision of the strap musculature, and adjacent soft tissues as required^{10,18} without sacrifice of a normally functioning recurrent laryngeal nerve unless circumferentially involved by malignancy. A recurrent laryngeal nerve was resected only if the tumor was grossly invading and macroscopically surgically inseparable from the nerve. In this series, finding a laryngeal nerve truly at risk was distinctly uncommon. In one of these cases, the final pathologic analysis showed the tumors to be localized; the others, indeed, had locally invasive disease (among them, one patient had distant disease at diagnosis). Hypercalcemia abated within 1 day after surgery in all the patients except the one patient who had distant metastases.

Pathology. On the basis of clinical and histopathologic criteria, 19 of the 27 patients met the criteria for the diagnosis of locally invasive parathyroid carcinoma; the most common sites of local invasion were adipose tissue and muscle in nine patients, esophagus in four patients, thyroid gland in three patients, recurrent laryngeal nerves in three patients, and trachea in three patients (more than one site was involved in some cases). Of these 19 patients, 18 had locally invasive cancer limited to the primary site, and one patient also had distant metastases. In the remaining eight patients, five patients had histopathologic characteristics for malignancy, but the tumors were contained within the gland, and they were,

therefore, considered to have localized disease. The other three patients were initially diagnosed with benign parathyroid adenomas in outside institutions and manifested clinically as carcinoma on the basis of the histopathology of tissue samples obtained from reoperation. They were considered to have localized disease on the basis of their initial histopathologic diagnosis.

Table 3 outlines the most prominent pathologic features. The primary tumor was found in the inferior parathyroid glands in 15 patients and in the superior parathyroid glands in three patients. Only one tumor was found in the mediastinum. The exact site of the primary tumor was not clear in eight patients who initially underwent surgery elsewhere. Other investigators^{19–22} have also noted the apparent predilection of parathyroid cancers for the inferior parathyroid glands. The average tumor size was 3 cm. Three patients were given an initial diagnosis of benign adenoma in outside institutions but were later seen at M. D. Anderson with confirmed metastases; the initial slides for these patients were not available for review. A fourth patient had an initial diagnosis of parathyroid adenoma, and years later, the patient was seen at M. D. Anderson with a local relapse; the initial pathologic findings were reviewed and reclassified as parathyroid carcinoma.

Radiation Therapy. Six of 18 patients with the diagnosis of locally invasive disease received adjuvant radiation therapy within 2 months after initial surgery. The radiation therapy dose ranged between 50 and 63 Gy in all six patients. Two patients had undergone complete surgical excision, whereas four patients had been treated with comprehensive “en bloc” soft tissue excision. None of the eight patients with pathologic diagnosis of localized disease received adjuvant radiation therapy. Although no formal algorithms for postoperative adjuvant radiation therapy exist for this disease, this modality is generally added for

Table 3. Histology of parathyroid carcinoma.

Histology	No. of patients (%)
Fibrous bands	12 (44)
Mitoses	11 (40)
Vascular invasion	10 (37)
Capsular invasion	7 (26)
Trabeculae	3 (11)
Lymphatic invasion	3 (11)

patients who are considered at increased risk for recurrence on clinical grounds. It is, therefore, of interest that only one of six patients had disease recurrence (a lower apparent frequency than nonirradiated patients; a discussion of recurrence follows).

The patient who had local relapse after adjuvant radiation had recurrent hypercalcemia develop 6 months later and died of this complication within 2 years.

Two other patients received postoperative radiation therapy after reoperation for regional recurrence. One 32-year-old man had, in the course of 5 years, two reoperations for locally recurrent parathyroid cancer and persistent hypercalcemia throughout before coming to M. D. Anderson, where he had another operation followed by radiation therapy. With his last surgery, the iPTH decreased from 986 pg/mL to 513 pg/mL; 6 months after radiation therapy, the iPTH was 66 pg/mL. One year later, iPTH was still normal (66 pg/mL); when the patient returned to M. D. Anderson 2 years later (3 years after radiation therapy), the iPTH was once again elevated (238 pg/mL).

Another, 55-year-old man had, in the course of 25 years, three reoperations for locally recurrent parathyroid cancer before coming to M. D. Anderson, where he had another operation followed by radiation therapy. With surgery, the iPTH decreased from 1256 pg/mL to 279 pg/mL. After radiation therapy, the iPTH declined further over

the course of 3 years to a nadir value of 88 pg/mL (which represents his latest level).

Disease Relapses As They May Relate to Stage and Initial Therapy.

Excluding the patient with distant metastases, 15 patients remain disease free after initial surgery, and 11 patients have had at least one relapse after surgery. Figure 2 presents an overview and juxtaposes the pathology, surgery, radiation therapy, and recurrence profile of the group.

Eight patients with pathologically localized disease received surgery alone without adjuvant radiation, and five patients had a local relapse; whether the extent of surgery played a role in relapse cannot be defined because of the small number of cases.

Among the 18 patients with pathologically locally invasive disease, 11 patients had complete surgical excision. Two of these patients received adjuvant radiation and have had no relapse; the other nine patients did not receive adjuvant radiation, and three have had a regional relapse. Of the seven patients with locally invasive disease who received extensive “en bloc” soft tissue resection, regional relapse has occurred in one of four who had adjuvant radiation and in two of three who did not. Although the small number of patients precludes quantitative analysis of the impact of adjuvant radiation, it would seem that adjuvant radiation might decrease the risk of regional recurrence.

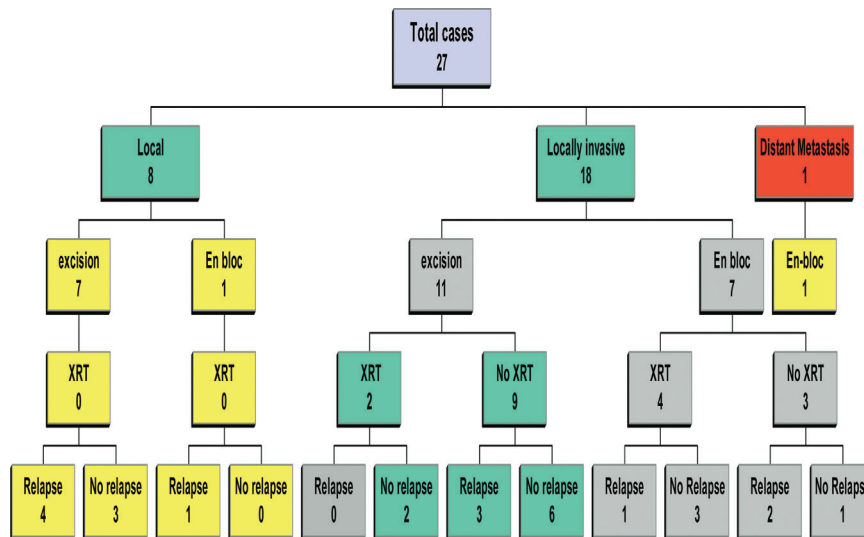


FIGURE 2. Schematic outline of presentation, treatment, and outcomes in patients with parathyroid carcinoma at The University of Texas M. D. Anderson Cancer Center. XRT, radiotherapy. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Metastases. Six patients had distant metastases develop in the lungs, bones, and liver during the course of their disease, whereas only one patient initially was seen with metastatic disease. The treatment modalities for metastases varied. One patient had surgical resection for lung metastasis, two patients received radiation therapy for bony metastases, and four patients received chemotherapy; the chemotherapeutic agents used included: doxorubicin; bleomycin, carboplatin, 5-fluorouracil (5-FU), and taxol. Chemotherapy was not considered clinically efficacious.

Disease-Free Interval. The 60-month DFI was 68%, and the 120-month DFI was 62% (Figure 3). One of 11 women versus 10 of 16 men has had a relapse, but the DFI was not statistically different by sex. In patients who had disease recurrence, the DFI after initial surgery was 12 to 252 months. Neither extent of disease nor extent of surgical intervention made any difference to DFI ($p = .7$ and 0.4 , respectively). Radiation therapy seems to increase DFI, but the difference is not significant ($p = .5$).

Survival of Patients with Parathyroid Carcinoma.

Of the 27 patients, five (19%) have died of the malignancy. Four died of severe hypercalcemia in the context of advanced disease. The fifth patient had a rare variant of this cancer known as sarcomatous parathyroid carcinoma²³ and died of chemotherapy-related neutropenic infection; this patient had diffuse lung metastases develop and had a relatively short survival of 23 months.

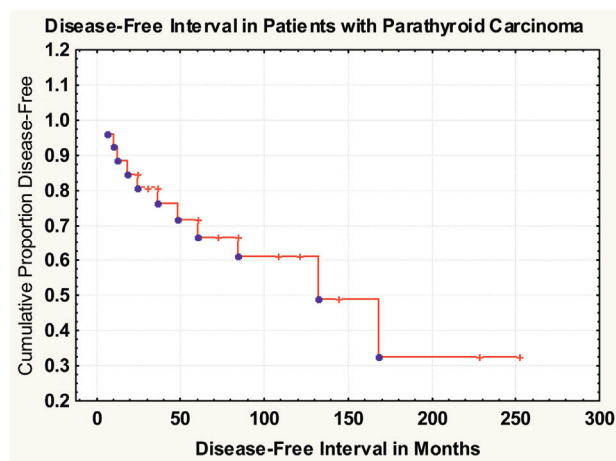


FIGURE 3. Disease-free interval in patients with parathyroid carcinoma. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Three other patients died of unrelated conditions (lung carcinoma, congestive heart failure, and cerebrovascular accident). These three patients had no evidence of parathyroid carcinoma at the time of death. Nineteen patients are still alive. The 5-year survival rate was 85%, and the 10-year survival rate was 77%, according to the Kaplan-Meier survival analyses (Figure 4).

Prognostic Factors. We did not observe any statistically significant differences in survival by sex, age at diagnosis, tumor size, or preoperative calcium level. However, patients with preoperative serum calcium levels >13.5 mg/dL were significantly younger than those with lower calcium levels (37.8 ± 13.9 years vs 52.6 ± 12.7 years, $p = .03$). Although not statistically significant, there was a trend toward shorter survival in patients with severe hypercalcemia; indeed, all patients with a preoperative serum calcium level <13.5 mg/dL are still living. It seems that men who had a clinical profile characterized by younger age and more severe hypercalcemia were at an increased risk of death from the disease.

Associated Conditions. Four patients had embolic phenomena. Two patients had pulmonary embolism; one had no other risk factors, and the other had experienced a recent hip fracture. Another patient had widespread metastatic disease, and bone marrow embolism was found in the lungs at autopsy. The fourth patient had a central-line-associated deep vein thrombosis.

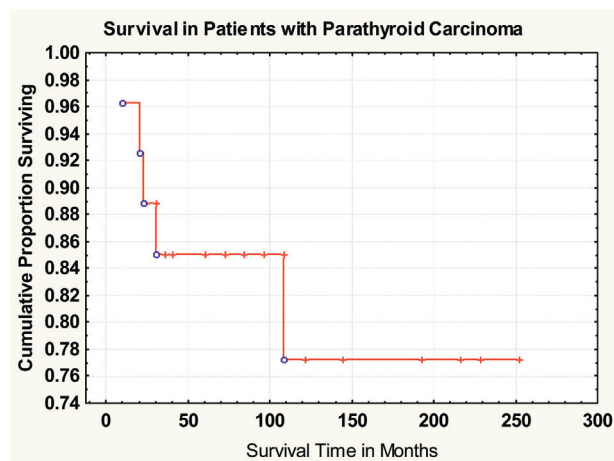


FIGURE 4. Total survival in patients with parathyroid carcinoma. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Five patients had additional malignancies (thyroid, colon, melanoma, chondrosarcoma, and lung).

DISCUSSION

This series represents our institution's experience with parathyroid carcinoma during the past 22 years. Table 4 illustrates a comparative summary of other single-institutional experiences with the disease.^{7,20,24} As in other series, the diagnosis is most often made during the fifth decade; in our patients, the mean age at diagnosis was 46.5 years, almost one decade earlier than benign parathyroid adenomas.^{2,7,11,20,25}

Radiation exposure has been implicated in reports of carcinoma occurring within an adenoma or hyperplastic gland²⁶⁻²⁸; we had two patients with a history of neck irradiation many decades before the diagnosis of parathyroid carcinoma.

Wynne et al¹¹ described pulmonary embolism in association with parathyroid carcinoma, and, interestingly, four of our patients experienced embolic phenomena during the course of their disease. We believe it would be premature at this point to suggest a causal relationship.

The diagnosis of parathyroid carcinoma in the absence of regional or distant metastases is a challenging issue. High calcium values (>13.5 mg/dL) and high iPTH values raise the suspicion of this disease.^{7,18} Gross invasion and adherence at the time of surgery, recurrences, or the classic histopathologic criteria are available other clues to assist in diagnosis. Pathologic criteria also may not definitively differentiate parathyroid carcinoma from the more common adenoma. Previous reports have identified aneuploidy and nuclear DNA content as a discriminating factor indicating more aggressive tumors.^{18,29} Availability of specific immunohistochemical staining, such as inactivating mutations in tumor suppressor genes, may in the future help to better define parathyroid carcinoma.^{10,18,30}

Oftentimes, the malignant potential of parathyroid tumors is not appreciated even postoperatively, until the histopathologic examination is complete or later when a relapse occurs. Identifying a parathyroid cancer before surgery would enable the surgeon to perform a presumably preferred extensive "en bloc" soft tissue resection³¹ that would be more likely to secure clear surgical margins, whereas such an approach would not be justified for most patients with benign adenomas.³²

There are no accepted staging criteria for parathyroid carcinoma. The usual TNM staging system cannot be applied to this disease for two reasons. First, parathyroid carcinoma is not a disease that frequently metastasizes to lymph nodes,^{8,10} and, second, tumor size does not seem to play a role in prognosis.¹⁰ In our series, we chose to use staging criteria on the basis of clinical and histopathologic invasiveness of the tumor. In most of our patients (19 of 27 cases), the tumors were locally invasive, similar to the Princess Margaret Hospital experience.²⁵ Whether this represents a referral bias to tertiary cancer referral centers or a true representation of the disease is unclear. We did not demonstrate a relationship between initial extent of disease, regional invasiveness, and likelihood of recurrence. This is perhaps because of the small number of patients with this disease or may, indeed, reflect the disease biology.

Surgery remains central in the management of patients with parathyroid cancer.^{11,33-36} The extent of resection that is required to optimize clinical outcome, however, is not entirely clear. For example, the type of initial surgery did not have a statistically significant effect on DFI or overall survival. The extent of resection was empirically selected on the basis of preoperative assessment, prevailing opinions over time, and institutional preference. Prospective criteria could be developed and studied, although the rarity of the disease and the generally prolonged survival are significant logistic hurdles. Because none of the patients had regional lymph node metastases initially, routine lymph node dissection does not seem warranted.

Role of Radiation Therapy. Adjuvant radiation therapy seemed to effectively decrease the local relapse rate. Radiation therapy has been reported to improve the DFI, especially in high-risk patients.²⁵ Whether adjuvant radiation therapy should become the standard of care in these patients remains a subject of discussion. In our patients, the local relapse rate seemed lower if adjuvant radiation was applied after initial surgery independently of the type of surgery and disease stage. For example, one would have expected that patients with cancer confined to the gland (localized) would be less likely to have a recurrence, yet five of eight patients did, including the one patient who was treated with comprehensive resection. It should be noted that none had adjuvant radiation in this group. At the same time, one would also expect that patients

Table 4. Comparison of a few published single institution's experiences with parathyroid carcinoma.

	UCSF ³¹	Cleveland Clinic ⁶	Mayo Clinic ¹¹	M. D. Anderson Cancer Center 1983 ³²	M. D. Anderson Cancer Center 2003
Period of review	1966–1999	1938–1988	1920–1990	1968–1982	1980–2002
No. of patients	18	7	43	14	27
Male/female	13/5	4/3	21/22	7/7	16/11
Mean age, y	46.1	45	54	51	46.7
Mean calcium, mg/dL	13.7	15.3	14.6	16.8	13.4
Recurrence rate	78%	86%	67%	86%	42%
Death	4/18 (22%) at 10 y (parathyroid carcinoma related)	6/7 (86%) Not related to local complications of recurrence	17/39 (44%) parathyroid carcinoma related 4/39 (9%) other causes	11/14 (79%) at 12 y	5/27 (19%) parathyroid carcinoma related 3/27 (11%) other causes
Survival	N/A	85% at 5 y 57% at 10 y 14% at 20 y	69% at 5 y	21% at 12 y	85% at 5 y 77% at 10 y
Metastatic sites	Lungs, bones	Lung	14 patients (45%)	Lung, bones, brain 4 patients (29%)	Lung, bones, brain 4 patients (15%)
Neck masses	N/A	No	Yes	N/A	Yes
Pulmonary embolism	N/A	N/A	6 patients for recurrent or metastatic disease	1 adjuvant, disease free	6 adjuvant, 5 disease free
Radiotherapy	2 patients, unknown results	2 patients for recurrent disease, no response	4/6 no response 1/6 no data 1/6 disease free after 11 y	1 for recurrent disease, no response	2 for recurrent disease, 1 no response and 1 prolonged response
Chemotherapy	1 patient unknown result	1 patient transient response	6 patients no effect	3 no effect	4 patients no effect

with locally invasive cancer would be more likely to have a recurrence. Yet only six of 18 recurred, three after complete resection and three after comprehensive resection. It should be noted that only one of six patients who received adjuvant radiation in this group had a recurrence independently of the extent of surgery. Although the small number of patients precludes formal quantitative analyses, it is intriguing to suggest that adjuvant radiation may play an important role in local disease control.

In accordance with other reports,^{6,11,31,32} chemotherapy did not seem to have a clinically significant effect in our patients.

Parathyroid cancer has a tendency to relapse. Fifty-six percent of our patients had at least one recurrence over a 5- to 10-year period, which is slightly higher than the previously reported 40% recurrence rate in series by Sandelin and Shane.^{18,33} These relapses were mainly regional to the neck and surrounding tissues. Because patients with this disease are at relatively high risk of multiple relapses over, often, prolonged time periods, they should be monitored for life. In most instances, hypercalcemia was the initial sign of recurrence. Because most of these tumors are functional, serum calcium and iPTH levels are very useful tumor markers.

Patients with persistent or recurrent disease manifesting as elevated iPTH and calcium should have localizing studies that may include sonography, CT, MRI, sestamibi scans, or (more recently) positron emission tomography scans, which have seemed promising. In the absence of measurable disease, "blind" neck re-exploration has been disappointing.

Parathyroid carcinoma is a disease with an often indolent but progressive course. A more aggressive disease course with a shorter DFI tended to be present in men who were younger and tended to present with higher calcium values.

The morbidity and mortality associated with parathyroid carcinoma is generally because of PTH secretion and hypercalcemia, rather than the tumor burden itself. Treatment modalities for hypercalcemia, especially in patients with unresectable disease or without measurable disease, becomes of utmost importance. Conventional treatment with IV fluids, diuretics, and antiresorptive agents such as bisphosphonates, gallium, or mithramycin help to control or ameliorate the hypercalcemia. However, therapies such as calcimimetic agents that focus on decreasing PTH secretion may better prevent complications and

improve survival in patients with no curable disease.³⁴

Our 5-year survival rate of 85% was consistent with that of previous reports,⁶ but our 10-year survival is somewhat higher at 77%.³² Because the data are derived from patients diagnosed in the past 22 years only, the difference in long-term survival seen in this series compared with others' and our previous series may relate to improvements in overall general supportive medical care and prevention of fatal hypercalcemia. This has been accomplished through advances in diagnostic localization techniques (allowing for the identification and removal of cancer deposits) and the availability of more effective pharmacologic therapies for the treatment of hypercalcemia.

An interdisciplinary team approach involving endocrinologists, surgeons, radiation therapists, and pathologists must be used to offer patients the best option for cure of this rare disease.³⁵

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