Parathyroid Carcinoma, Atypical Parathyroid Adenoma, or Parathyromatosis?

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Supported in part by The Helen and Sanford Diller Foundation, the Gerald Heller Family Foundation, the Bell Charitable Foundation and Friends of UCSF/Mt. Zion Endocrine Surgery.

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Received February 1, 2007; revision received March 9, 2007; accepted March 12, 2007.

BACKGROUND. Parathyroid carcinoma, atypical parathyroid adenoma, and parathyromatosis can be differentiated relatively easily from typical parathyroid adenomas, but distinguishing them from each other is more difficult.

METHODS. A retrospective study of 28 consecutive patients with parathyroid carcinoma, 7 patients with atypical parathyroid adenoma, and 13 patients with parathyromatosis who were treated at the University of California at San Francisco Medical Center between 1966 and 2005 was performed. Patient demographics and clinical characteristics, indication for surgery, intraoperative findings, histopathologic characteristics, disease recurrence or persistence, site of invasion/metastases, and survival were compared in the 3 groups.

RESULTS. Parathyroid carcinoma (19 of 28 patients) and atypical adenoma (4 of 7 patients) were significantly more common in men, whereas parathyromatosis was more common in women (10 of 13 patients) ($P = .02$). A palpable neck mass and hoarseness were almost exclusively present in patients with parathyroid carcinoma. Prior to the first parathyroid surgery, patients with parathyroid carcinoma were found to have higher blood calcium levels ($\geq$14 mg/dL in 16 of 26 patients [62%]), whereas only 1 of 6 patients with atypical adenoma (17%) and no patients with parathyromatosis were found to have profound hypercalcemia ($P < .01$). Intraoperatively, patients with parathyroid carcinoma and atypical adenoma presented with single lesions, whereas patients with parathyromatosis had multiple small lesions. Histopathologic findings were well defined in parathyroid carcinoma, but some findings overlapped in the 3 tumors studied.

CONCLUSIONS. Patients with parathyroid carcinoma often differ from those with atypical parathyroid adenoma or parathyromatosis at the time of presentation because patients with parathyroid carcinoma have more profound hypercalcemia as well as invasive tumors. However, at times it is difficult to distinguish between these conditions both clinically and by final histologic examination. ***Cancer* 2007;110:255–64.** © *2007 American Cancer Society.*

KEYWORDS: parathyroid tumors, parathyroid carcinoma, atypical parathyroid adenoma, parathyromatosis, primary hyperparathyroidism, secondary hyperparathyroidism, recurrent hyperparathyroidism.

Hyperparathyroidism is a common endocrine disease that occurs in approximately 0.1 to 0.3% of the general population. Primary hyperparathyroidism (PHPT) is more common in women (1 in 500) than in men (1 in 2000).[1] Approximately 99% of patients with PHPT have benign tumors (85% with adenomas or atypical adenomas and 15% with hyperplasia or multiple abnormal parathyroid glands).[2] Less common causes of PHPT include double adenomas (4%), parathyroid carcinoma (<1%), and, rarely, parathyromatosis. Secondary hyperparathyroidism (SHPT) is a common problem in patients with chronic renal failure, nearly all of whom develop some degree of

DOI 10.1002/cncr.22790
Published online 8 June 2007 in Wiley InterScience (www.interscience.wiley.com).

parathyroid hyperplasia. Parathyroid carcinoma is rare in these patients, with only a few cases reported to date.[3,4] Patients with familial hyperparathyroidism and jaw tumor syndrome also have an increased risk of developing parathyroid carcinomas.[5] Some patients with PHPT have parathyroid tumors with some histologic characteristics of parathyroid cancer, but not enough to be diagnosed as cancer. These tumors are usually classified as "atypical adenomas." Parathyromatosis, a rare cause of recurrent or persistent hyperparathyroidism,[6] occurs most frequently after previous parathyroid surgery in patients with familial primary hyperparathyroidism, and in patients with secondary hyperparathyroidism due to chronic renal failure.[7–15] It also may occur de novo in patients who have not undergone previous parathyroid surgery.[11,16] Patients with parathyromatosis usually develop several nodules of hyperfunctioning parathyroid tissue in the neck and mediastinum. There are 3 theories regarding the origin of parathyromatosis: 1) it is a low-grade parathyroid malignancy,[17] 2) it results from seeding after the fracture of the parathyroid gland capsule during surgical removal of a parathyroid neoplasm,[6] or 3) it is an overgrowth of embryologic rests of parathyroid tissue.[16]

The purpose of the current retrospective investigation was to determine the clinical and histologic differences found in patients with parathyroid carcinoma, atypical adenoma, and parathyromatosis to properly diagnose patients with these tumors.

MATERIALS AND METHODS

We retrospectively analyzed the medical records and histologic findings of 28 patients with parathyroid carcinoma who were treated between 1966 and 2005, 7 of whom had atypical adenoma, and 13 patients with parathyromatosis who were treated between 1990 and 2005 at the University of California at San Francisco (UCSF) Medical Center. Nine of the 28 patients with parathyroid carcinoma received their initial treatment at UCSF, whereas the other patients were treated at another center. Seven patients underwent surgery for "atypical parathyroid adenomas," 5 of whom were treated initially at UCSF and 2 of whom were referred to UCSF with persistent PHPT. All 7 patients had parathyroid tumors with some atypical features found in parathyroid carcinoma, but not enough histologic criteria to make the diagnosis of parathyroid carcinoma. Thirteen patients were diagnosed and treated for parathyromatosis. Two underwent their initial surgery at UCSF and 11 were referred for recurrent or persistent hyperparathyroidism.

The histologic slides and reports of 26 patients with parathyroid carcinoma and for all patients with atypical parathyroid adenoma and parathyromatosis were rereviewed by 2 pathologists (E.K. and K.J.) who participated in the study. The diagnosis of parathyroid carcinoma was based on the macroscopic finding of a parathyroid tumor with a fibrotic capsule and surrounding adhesions, locally invasive tumor or distant metastasis, or histopathologic criteria (trabecular pattern, thick fibrous trabeculae, mitotic figures, capsular or vascular invasion, and lymph node invasion).[18] The diagnosis of "atypical adenoma" was made in patients with evidence of hyperparathyroidism who presented with large parathyroid tumors and surrounding fibrous tissue, and in those whose tumors had some histologic features suggesting parathyroid cancer but in whom a definitive diagnosis could not be made because not enough histologic features of parathyroid carcinoma were present. The diagnosis of parathyromatosis was made in patients with evidence of recurrent (10 patients) or persistent (2 patients) hyperparathyroidism and intraoperative findings of multiple small nodules of parathyroid tissue scattered in the neck and upper mediastinum. One patient had de novo parathyromatosis without having undergone a previous parathyroid surgery.

We compared the 3 diagnostic groupings with respect to patient age and gender at diagnosis, clinical manifestations, serum calcium and parathyroid hormone levels at initial diagnosis and at disease recurrence, indication for surgery and number of operations, intraoperative findings, histopathologic characteristics, time between first surgery and disease recurrence or persistence, site of invasion/metastases, and outcomes. First surgery was considered to occur at the time of the initial diagnosis of parathyroid carcinoma, atypical adenoma, or parathyromatosis. Recurrence was defined as evidence of disease recurrence (recurrent hypercalcemia with high serum parathormone levels), or evidence of locoregional or distant disease after a disease-free period of at least 6 months of normocalcemia. Persistent disease was defined as evidence of disease recurrence occurring within 6 months of the first parathyroid surgery. The disease-free interval was defined as the period of time from diagnosis or first parathyroid surgery to documentation of disease recurrence (patients with initial metastatic disease were excluded) and, in patients without disease recurrence, from the date of surgery until the last day of follow-up. Clinical information was obtained from UCSF Medical Center patient database, medical records, institutional Cancer Center Registry, and personal telephone contact when necessary.

TABLE 1
Gender and Age Distribution of Patients With Parathyroid Carcinoma, Atypical Adenoma, and Parathyromatosis

		Parathyroid carcinoma		Atypical adenoma		Parathyromatosis		
		n = 28	%	n = 7	%	n = 13	%	*P**
Gender	Male	19	67.9	4	57.1	3	23.1	
	Female	9	32.1	3	42.9	10	76.9	
M:F ratio		2.1:1		1.3:1		1:3.3		.02
Age at initial surgery, mean ± SD (range)		51.3 ± 13.9 (23–70)		55.8 ± 8.1 (46–66)		51.4 ± 10.8 (34–69)		NS

M indicates male; F, female; SD, standard deviation; NS, not significant.
* *P* values were determined using the chi-square test.

Informed consent from patients and institutional approval from the Committee of Human Research was obtained before the initiation of the study.

Results are expressed as the mean ± the standard deviation, proportions, and percentages (%). Analysis of variance (ANOVA) was used for comparison of continuous data between groups and chi-square tests were used for analysis of categoric variables. Survival was determined using Kaplan-Meier survival analysis.

RESULTS

Clinical Presentation

In the current series, more men than women had parathyroid carcinoma and atypical adenoma (Table 1). Although age at initial diagnosis was not found to be significantly different between the 3 groups, patients with atypical adenoma were slightly older than those with parathyroid carcinoma and parathyromatosis (Table 1).

A palpable neck mass and hoarseness were almost exclusively present in patients with parathyroid carcinoma, whereas psychiatric manifestations were surprisingly more common in patients with parathyromatosis. Other symptoms such as bone pain, fatigue, anorexia, and abdominal pain were comparable in the 3 groups (Table 2).

Blood calcium levels were $\geq$14 mg/dL prior to the first parathyroid surgery in 16 of 26 patients with parathyroid carcinoma, 1 of 6 patients with an atypical adenoma, and none of the patients with parathyromatosis ($P < .01$). Similar results were observed at the time of reoperation. Parathyroid hormone levels were similar in the 3 groups before the initial surgery and at the time of reoperation (Table 3).

The indication for surgery in the patients with parathyroid carcinoma was based on the diagnosis of PHPT together with severe hypercalcemia in the majority of patients (range, 11.1–24 mg/dL in 27 of 28 patients [96.4 %]). Only 1 of these patients was asymptomatic. One patient with parathyroid carcinoma had symptomatic SHPT with chronic renal failure. All but 1 patient with atypical parathyroid adenoma had symptomatic PHPT. One of these patients had a family history of hyperparathyroidism. Seven of 13 patients with parathyromatosis had symptomatic PHPT with hypercalcemia ranging from 10.9 to 13 mg/dL at the time of diagnosis. The other 6 patients had symptomatic SHPT due to chronic renal failure and their blood calcium levels ranged from 8.5 to 11 mg/dL.

Intraoperative Findings

We found that patients with parathyroid carcinoma (measuring 31.3 ± 17.8 mm) and atypical adenoma (measuring 29.4 ± 8.6 mm) had significantly larger lesions than those found in patients with parathyromatosis (measuring 11.7 ± 7.8 mm), ($P < .01$). A fibrous capsule with adhesions or invasion into the surrounding fibrofatty tissue or thyroid gland was identified in 23of the 28 patients with parathyroid carcinoma (82%). Fibrosis and scarring were also found in 12 of 13 patients with parathyromatosis because of previous parathyroid surgeries (92%). Surprisingly, a fibrous capsule was also found in 6 of 7 patients with atypical adenoma (86%). In contrast to parathyromatosis, in which there are usually several small tumors, parathyroid carcinomas usually presented as a single lesion. In 3 of our patients who presented with several nodules in the neck, a diagnosis of parathyromatosis was considered, but the final diagnosis was parathyroid carcinoma because of vascular invasion and multiple cervical lymph node metastases. In patients with parathyromatosis, we found up to 80 very small nodules or nests of parathyroid tissue that occasionally were microscopic; none of these patients presented with a solitary tumor. Patients with atypical adenomas always presented

TABLE 2
Clinical Manifestations of Patients With Parathyroid Carcinoma, Atypical Adenoma, and Parathyromatosis at the Time of Initial Diagnosis

	Parathyroid carcinoma		Atypical adenoma		Parathyromatosis		
Sign/symptom	n = 28	%	n = 7	%	n = 13	%	*P*
Bone pain	20	71.4	3	42.9	11	84.6	NS
Fatigue	22	78.6	3	42.9	10	76.9	NS
Kidney stones	11	39.3	0	0	3	23.1	NS
Anorexia	7	25	2	28.6	2	15.4	NS
Weight loss	6	21.4	0	0	2	15.4	NS
Hoarseness	3	10.7	0	0	0	0	NS
Abdominal symptoms (pain, dyspepsia, reflux)	7	25	1	14.3	3	23.1	NS
Psychiatric symptoms (depression, memory loss, decreased concentration)	9	32.1	2	28.6	6	46.2	.01
Palpable neck mass	9	32.1	0	0	1	7.7	<.01

NS indicates not significant.

TABLE 3
Laboratory Findings in Patients With Parathyroid Carcinoma, Atypical Adenoma, and Parathyromatosis Prior to the First Surgery and at the Time of Recurrent/Persistent Disease

1st surgery	Parathyroid carcinoma n = 26	Atypical adenoma n = 6	Parathyromatosis n = 11	*P*
Calcium (mg/dL), mean ± SD (range)	14.6 ± 2.7 (11.1–24)	13.5 ± 1.1 (13.5–20)	10.8 ± 1.1 (8.5–13)	<.01
PTH level (ng/L)* mean ± SD (range)	714.4 ± 1018 (97–4013)	374.5 ± 297 (140–941)	558 ± 462 (85–1231)	NS
Times elevated† (mean)	8.2	5.4	7.9	
2nd surgery (Recurrent/Persistent)	**n = 16**	**n = 2**	**n = 8**	***P***
Calcium (mg/dL) mean ± SD (range)	14.2 ± 2.5 (10.4–20.6)	12.25	10.9 ± 1.85 (8–14.7)	.01
PTH level (ng/L)‡, mean ± SD (range)	850.6 ± 540.8 (172–1800)	140	599.2 ± 525.2 (92–1321)	NS
times elevated† (mean)	13.8		8.7	

SD indicates standard deviation; PTH, parathyroid hormone; NS, not significant.

* PTH levels were present in 18 patients with parathyroid carcinoma, 6 with atypical adenoma, and 11 with parathyromatosis.

† PTH times upper limits were used to avoid differences in values between PTH assays.

‡ PTH levels were present in 12 patients with parathyroid carcinoma, 2 with atypical adenoma, and 7 with parathyromatosis.

with single lesions and in all of our patients, the surgeon suspected possible malignancy.

Among our 28 patients with parathyroid carcinoma, 5 were not suspected to have a malignant tumor and therefore underwent a more conservative initial surgery. Among the 23 patients in whom the intraoperative findings suggested possible parathyroid carcinoma, 21 underwent either unilateral or bilateral neck explorations with or without en bloc thyroid resection, cervical lymph node dissection, and thymectomy (Table 4). Four patients with atypical adenoma that was suspicious for malignancy because of adherence to adjacent tissues or a thick capsule were treated with a more aggressive approach, in which the surrounding tissues and thyroid lobes were removed (Table 4). Six of the 13 patients with parathyromatosis had multiple hyperplastic parathyroid nodules within the soft tissue of the neck, adherent to the thyroid gland or strap muscles or in the tracheoesophageal groove as well as intramuscularly. An en bloc resection was performed to remove the multiple implants. Different surgical approaches were used in the 7 other patients with parathyromatosis (Table 4). All but 1 patient underwent reoperation after previous parathyroidectomy. This patient had an adenoma, but on final histologic examination was found to have multiple microscopic nodules or implants of parathyroid tissue in the fibrofatty tissue surrounding this lesion (de novo parathyromatosis).

The average number of surgeries for hyperparathyroidism from the time of initial diagnosis was highest for the 28 patients with parathyroid carcinoma (2.11 ± 2.2), followed by the 13 patients with parathyromatosis (1.92 ± 0.9) and the 7 patients with atypical adenomas (1.28 ± 0.5).

TABLE 4
Type of Surgery and Postoperative Outcome in Patients With Parathyroid Carcinoma, Parathyromatosis, and Atypical Adenoma

	Parathyroid carcinoma n = 28			Atypical adenoma n = 7			Parathyromatosis n = 13		
Surgery	Persistent	Recurrent	Cured or NER at follow-up	Persistent	Recurrent	Cured or NER at follow-up	Persistent	Recurrent	Cured or NER at follow-up
FOC		2	2						2
UNIL	1	1	3		1*	1	1	3†	
UNIL or BIL + ITL (en bloc)	3	4	2	1		3	2		2
BIL	2	2	3			1			
BIL + CND, SMD or thymectomy	1	2					1		
BIL + TT + LCND or SMD								2	
Total no. of patients by subgroups (%)	7 (25)	11 (39.3)	10 (35.7)	1 (14.3)	1 (14.3)	5 (71.4)	4 (30.7)	5 (38.5)	4 (30.7)

NER indicates no evidence of disease recurrence; FOC, focused; UNIL, unilateral approach; BIL, bilateral approach; ITL, ipsilateral thyroid lobectomy; CND, central neck dissection; SMD, superior mediastinum dissection; TT, total thyroidectomy; LCND, left central neck dissection.

* Concurrent partial thyroidectomy.

† Concurrent thymectomy.

TABLE 5
Histopathologic Findings at the Time of First Surgery

	Parathyroid carcinoma		Atypical adenoma		Parathyromatosis	
Histologic characteristic	n = 26	%	n = 7	%	n = 13	%
Capsular invasion	19	73.1	0	0	0	0
Fibrous trabeculae	18	69.2	5	71.4	2	15.4
Trabecular pattern	16	61.5	2	28.6	2	15.4
Mitotic figures (>1 mitoses/10 HPF)	17	65.4	2	28.6	2	15.4
Nuclear pleomorphism	14	53.8	1	14.3	2	15.4
Vascular invasion	8	30.8	0	0	0	0
Lymph node invasion	5	19.2	0	0	0	0

HPF indicates high-power fields.

Concomitant parathyroid adenomas occurred in 4 of 28 patients with parathyroid carcinoma (14%), in 1 of 7 patients with atypical parathyroid adenoma (14%), and in 1 of 13 patients with parathyromatosis (8%).

Histopathologic Description

Histopathologic slides and reports were available and were rereviewed in 26 patients with parathyroid carcinoma and all the patients with atypical adenomas and parathyromatosis (Table 5). One patient previously considered to have parathyromatosis with multiple parathyroid nodules in the neck was reclassified as having parathyroid carcinoma because of the presence of a focus of vascular invasion. Not surprisingly, invasive behavior was a feature of malignancy. Capsular, vascular, and lymph node invasion, as well as distant metastasis, were found to be present only in the patients with parathyroid carcinomas (Fig. 1A). In our patients, atypical parathyroid adenomas had some histologic findings suggestive of cancer but not enough to make the diagnosis. Thus, a thick capsule, fibrous trabeculae, a trabecular growth pattern, and, occasionally, nuclear pleomorphism were present, but there was no local or vascular invasion, or lymph node or distant metastasis (Fig. 1B). In the recurrent hyperfunctioning nodules found in patients with parathyromatosis, there was invasion in the soft tissue of the neck and mitosis in 15.4% of the patients (Fig. 1C and D). None of these patients had vascular invasion, lymph node involvement, or distant metastasis.

Recurrent/Persistent Disease

Approximately one-third of the patients with parathyroid carcinoma and parathyromatosis and 5 of the 7 patients with atypical adenomas were cured or had no evidence of persistent or recurrent disease at the time of last follow-up (Table 4). In patients with parathyroid carcinoma, disease recurrence was more

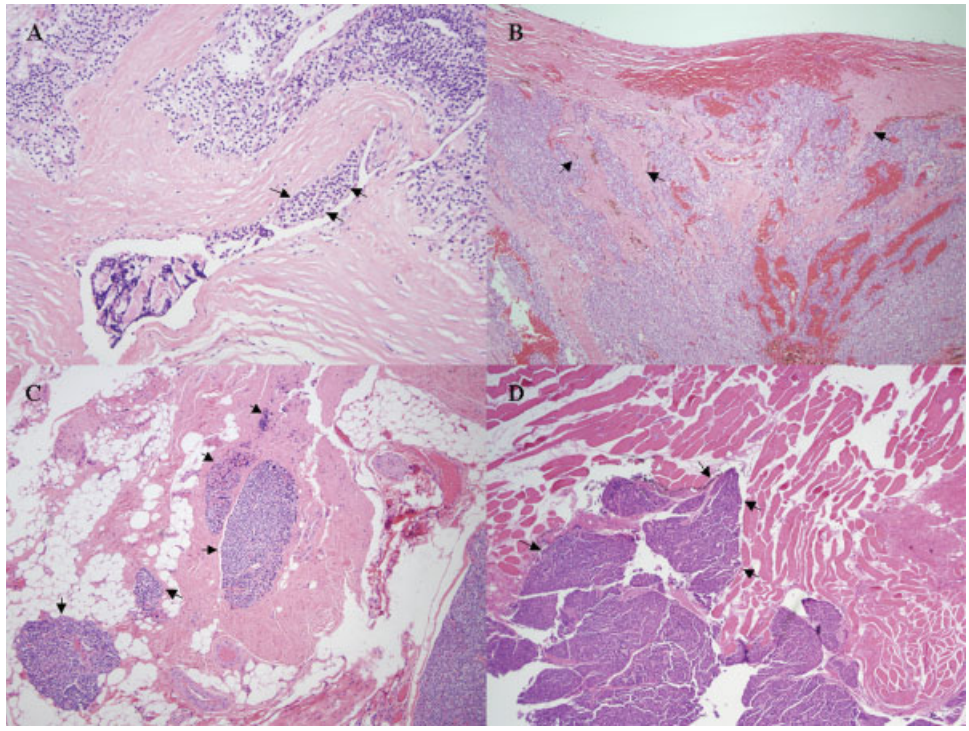

FIGURE 1. (A) Parathyroid carcinoma. Focus of vascular invasion (arrows). (H & E, original magnification ×100). (B) Atypical adenoma with a thick fibrous capsule and prominent fibrous trabeculae (arrows). (H & E, original magnification ×40). (C) Parathyromatosis. Multiple foci of parathyroid tissue infiltrating adipose and fibrous tissue (arrows). (H & E, original magnification ×40). (D) Parathyromatosis. Multiple foci of parathyroid tissue infiltrating skeletal muscle in the neck (arrows). (H & E, original magnification ×20).

common in men than in women (15 of 19 men vs 3 of 9 women; $P = .01$) and the men were younger (mean age, 50.2 ± 14 years vs 62.6 ± 5.5 years; $P = .03$). These differences were not present in patients with parathyromatosis or atypical adenomas. Recurrent and persistent disease were more common among patients with parathyroid carcinoma and parathyromatosis than those with atypical parathyroid adenoma (Table 4). Recurrence in both parathyroid cancer and parathyromatosis patients was documented because of an elevation of the parathyroid hormone and blood calcium levels and localization studies (ultrasound, technetium 99m sestamibi scan, magnetic resonance imaging, and computed tomography scan, and highly selective venous catheterization for parathyroid hormone when noninvasive localizing studies were equivocal or negative).

Among the patients with parathyroid carcinoma, disease recurred in all 5 patients who had lymph node metastasis at the time of initial surgery. Four of these 5 patients had a calcium level ≥14 mg/dL at the time of presentation. Seven of the 8 patients who had vascular invasion at the time of first surgery developed recurrent cancer, 6 of whom had a calcium level ≥14 mg/dL. Disease recurrence also occurred in 13 of the 17 patients who had >1 mitotic figure/10 high-power fields (HPFs), all of whom had a calcium level ≥14 mg/dL. Vascular and lymph node invasion were found exclusively in specimens of parathyroid carcinoma. Although capsular invasion was common and an inclusion criteria for the diagnosis of parathyroid carcinoma, only 11 of 19 patients with capsular invasion developed disease recurrence. Mitotic figures were observed in specimens from 2 patients with parathyromatosis and in 2 patients with atypical adenoma, with evidence of disease recurrence in 1 patient from each of the 2 groups.

The disease-free interval for patients with parathyroid carcinoma was 48%, 40%, and 32.1% at 24 months, 60 months, and 120 months, respectively. The disease-free interval was 83% at both 24 months and 60 months for patients with atypical adenomas, and was 46% at both 24 months and 60 months for patients with parathyromatosis (*P* value not significant) (Fig. 2).

Metastatic/Invasive Disease

The majority of patients (20 of 28 patients, 71.4%) with parathyroid carcinoma developed either locoregional or distant metastases during the course of their disease. At the time of diagnosis, 3 patients had

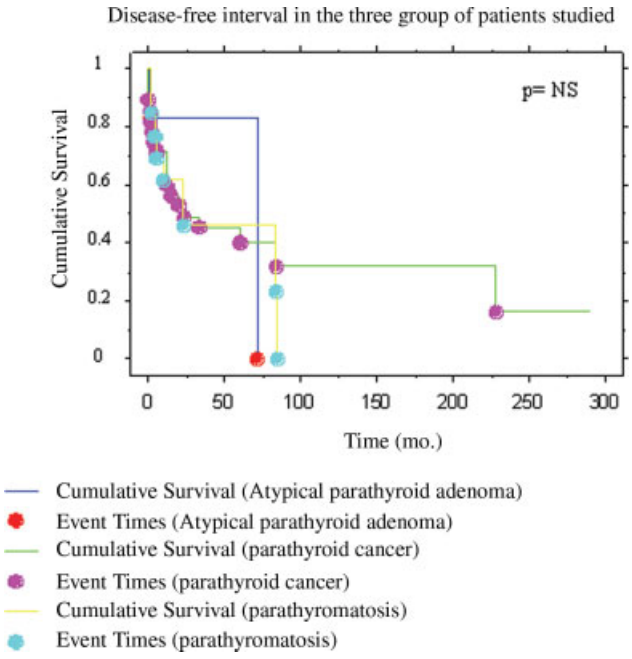

FIGURE 2. Kaplan-Meier disease-free interval curves for patients with parathyroid carcinoma, atypical adenoma, and parathyromatosis. NS indicates not significant.

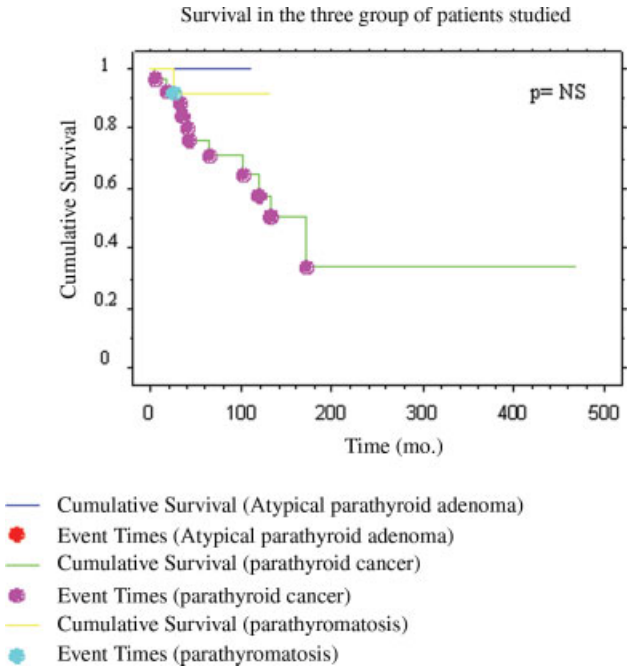

FIGURE 3. Kaplan-Meier survival curves for patients with parathyroid carcinoma, atypical adenoma, and parathyromatosis. NS indicates not significant.

metastatic disease located in the cervical lymph nodes, soft tissue of the neck, and strap muscles, and 1 patient also had metastases in the superior mediastinum. The other 17 patients developed clinical metastatic disease 3 to 96 months after their initial surgeries. Common sites of locoregional invasion were the fibrofatty tissue of the neck (80%); the strap muscles, thyroid, esophagus, and trachea (60%); and regional lymph nodes (40%). Distal metastasis was evident in the mediastinum (30%), lung (15%), bone (10%), and liver (5%).

The early development of metastasis was associated with a poor prognosis and death secondary to metabolic consequences of uncontrollable hypercalcemia, as was observed in 2 patients. All patients with parathyromatosis had foci of invasion near and in the original site of the parathyroid glands. The most common location for invasion was the fibrofatty tissue of the neck (92.3%); the strap muscles and the thyroid, esophagus, and trachea (61.5%); and the superior mediastinum (30.7%). None of the patients with atypical adenoma had evidence of tumor spread.

Follow-up and Survival

The average follow-up time was 98 months for patients with parathyroid carcinoma, 46 months for those with atypical adenomas, and 58 months for patients with parathyromatosis. One patient with parathyroid carcinoma and 1 patient with atypical parathyroid adenoma were lost to follow-up after their first surgeries. Eleven of the 27 patients with parathyroid carcinoma (41%) who had follow-up information died, 10 patients secondary to metastatic disease and uncontrollable hypercalcemia and 1 patient from respiratory distress and a cardiac arrest 1 day after undergoing surgery for his fifth recurrence of parathyroid cancer. Only 1 patient with parathyromatosis died during the follow-up period, secondary to complications of the uncontrollable hypercalcemia. All patients with atypical parathyroid adenomas were alive at the time of last follow-up.

The 24-month, 60-month, and 120-month cumulative survival rates were 92%, 76%, and 57%, respectively, for patients with parathyroid carcinoma. The cumulative survival rate was 100% at both 24 months and 60 months for patients with atypical parathyroid adenomas and was 100% at 24 months. and 92% at both 60 months and 120 months for patients with parathyromatosis. Although the overall survival rates were lowest for patients with parathyroid carcinoma, the differences between the groups were not significant (Fig. 3).

DISCUSSION

Parathyroid carcinoma, atypical parathyroid adenoma, and parathyromatosis are rare conditions that

account for approximately 2% of all patients with PHPT. The majority of patients with parathyroid carcinoma, atypical adenoma, and parathyromatosis can be easily differentiated from patients with "garden variety" primary hyperparathyroidism, but distinguishing these conditions from each other is more difficult because they lack precise clinical and histologic criteria.

In this retrospective series of 48 patients, we report that clinical and histopathologic presentation differs in patients with parathyroid carcinoma, atypical parathyroid adenoma, and parathyromatosis. Clinically, parathyroid carcinomas and atypical adenomas were significantly more common in men, whereas parathyromatosis was more common in women, a finding supported by others.[1,5,19,20]

Patients with parathyroid carcinoma usually have more profound hypercalcemia and metastases, and are more likely to die prematurely from metabolic complications.[21] In our patients with parathyroid carcinoma, blood calcium levels were found to be significantly higher ($\geq$14 mg/dL in 62% of patients) than the levels found in patients with atypical adenoma ($\geq$14 mg/dL in 17% of patients) and parathyromatosis (no patient had a blood calcium level $\geq$14 mg/dL). Blood calcium levels were lower in patients who had parathyromatosis and chronic renal failure than in patients with parathyromatosis and PHPT. Although blood parathyroid hormone levels were higher in patients with parathyroid carcinoma, there were no significant differences noted among the 3 groups. Another clinical difference was the presence of a palpable neck mass, which was found in approximately one-third of patients with parathyroid carcinoma, 1 patient with parathyromatosis, and none of the patients with atypical adenoma. We also found that patients with parathyromatosis had more depression, memory loss, and decreased concentration, which is surprising because their calcium and parathyroid hormone levels were generally lower than those of patients with parathyroid carcinoma. The presence of renal failure may have contributed to some of these symptoms.

Although parathyromatosis is most often associated with SHPT,[10] we found an even distribution of patients with primary and secondary hyperparathyroidism (53.8% vs 46.2%, respectively). Because the majority of our patients were referred to us from other medical centers because of recurrent or persistent hyperparathyroidism, this finding is likely the result of referral bias. Unlike parathyromatosis, parathyroid carcinoma is rarely found in patients with SHPT.[3,4] Only 1 of the patients with parathyroid carcinoma in the current study had evidence of SHPT and chronic renal failure at the time of presentation.

The main differential diagnosis of parathyromatosis is parathyroid carcinoma.[7,16,21] According to our experience, the distinction should be made between a locoregional metastatic parathyroid carcinoma with multiple implants and parathyromatosis. Parathyromatosis occurs primarily in patients who have had previous parathyroid surgeries during which $\geq$1 parathyroid glands are resected subtotally or fractured.[7,8,9,12,14,15] It has also been described after autotransplantation of the parathyroid gland in the forearm.[10,13] Parathyromatosis can also develop de novo in patients with no previous history of neck surgery or neck trauma.[11,16] Among the 28 patients in the current study with parathyroid carcinoma, 4 had previously had benign parathyroid tumors removed, but none of the others had undergone surgery previously.

The intraoperative findings are important for making the appropriate diagnosis. On macroscopic examination, as we and others have observed, parathyroid carcinomas are large, hard, whitish tumors surrounded by fibrous tissue. Intraoperative differentiation between a parathyroid carcinoma and an atypical adenoma can be difficult, especially at reoperation, because of the overlapping histologic characteristics found in each type of tumor. Parathyroid carcinomas and atypical adenomas are usually present as solitary tumors in patients with severe hypercalcemia. In contrast, lesions in patients with parathyromatosis are small and numerous, have a gray-tan color, and are often surrounded by adherent fibrous tissue, which gives some of these lesions the appearance of parathyroid carcinoma. In some cases, when the nests of parathyroid tissue are microscopic and located within the fat, muscle, thyroid, or thymus, the surgeon is often unaware of the presence of parathyromatosis until after microscopic histologic examination. There are exceptions to these observations, as evidenced by 3 patients in the current study with parathyroid carcinoma who had multiple nodules of locoregional metastatic disease without evidence of distal metastasis. Thus, intraoperative findings can be confusing for the surgeon trying to distinguish parathyromatosis from parathyroid carcinoma, but we recommend treating all such patients as if their lesion is cancerous because occult tumor can be present in both conditions.[8,16,19] Parathyroid carcinoma may be present in patients with parathyroid adenomas or hyperplasia.[4,22] Among our patients with parathyroid carcinoma, 4 had a coexistent benign parathyroid tumor. One of the current study patients with atypical adenoma and 1 patient with parathyromatosis also had a benign parathyroid tumor.

We and others recommend avoiding violation of the parathyroid tumor capsule, which results in the shedding of cells.[8–10] We recommend en bloc resection for both parathyroid carcinoma and parathyromatosis, including the ipsilateral lobe of the thyroid gland.[10,11,19,21,23–26] Among our patients with atypical parathyroid adenomas, the majority underwent en bloc resection with preservation of the recurrent laryngeal nerve because malignancy was suspected. Frozen section diagnosis unfortunately failed to confirm the diagnosis of cancer.

Histopathologic criteria to diagnose parathyroid carcinoma should unequivocally include a trabecular growth pattern; thick fibrous trabeculae; mitotic figures (>1/10 HPFs); capsular, vascular, and lymph node invasion; or distant metastasis.[18] Although some authors have reported the absence of these histologic criteria in patients with parathyromatosis,[7,9,10,16,19] some of our patients with parathyromatosis had several histologic features found in parathyroid carcinomas, such as trabecular growth pattern, fibrous trabeculae, mitotic figures, and nuclear pleomorphism, which made the diagnosis more difficult. Another histologic finding in parathyromatosis, in contrast to adenomas and primary parathyroid carcinomas, was evidence of poorly outlined cell borders and the absence of a real capsule in the nest of parathyroid tissue. Therefore, in patients with parathyromatosis, neither the absence nor the presence of some histologic features found in parathyroid carcinoma can be used as a reliable histologic criteria to distinguish these 2 entities.

Patients with parathyroid carcinoma and parathyromatosis have a greater chance of persistent or recurrent hyperparathyroidism than patients with solitary adenomas, double adenomas, or hyperplasia.[10,21,24,27] Unfortunately, in the current study, 65% of patients with parathyroid carcinoma and 69% of those patients with parathyromatosis, the majority of whom underwent surgery for recurrent or persistent disease, again developed recurrent and/or persistent hyperparathyroidism, whereas only 2 patients with an atypical adenoma did so. Parathyroid carcinoma most often recurs locally in the neck and mediastinum, but also in the lung, bone, and liver. As we and others have observed, parathyromatosis is usually localized in the fibrofatty and muscular tissues, the thyroid, and the superior mediastinum, generally on the side of the initial tumor resection.[6–8,10,16] Patients with parathyroid carcinoma usually die as a result of the metabolic complications of the hypercalcemia or from hypercalcemic crisis. Patients with parathyromatosis usually develop the neuropsychiatric and metabolic complications associated with hyperparathyroidism, but also occasionally profound hypercalcemia, as occurred in 1 of the current study patients.[7,10]

In conclusion, our investigation and review of the literature documents that patients with parathyroid carcinoma most often present with profound hypercalcemia (blood calcium levels $\geq$14 mg/dL), and it occurs either more frequently in men or equally in men and women. Parathyromatosis occurs more often in women. There is frequently a history of previous parathyroidectomy, and the majority of patients present with mildly increased blood calcium levels (1–2 mg/dL above the normal range) or normal calcium levels if the patient has chronic renal failure. Most patients with atypical adenoma have tumors that are found intraoperatively to be suspicious for malignancy. Our investigation also suggests that subtotal parathyroid gland resection should be performed with minimal shedding of parathyroid cells and that fracturing of parathyroid tumors should be avoided. The main genetic alteration (HRPT2 mutations) responsible for parathyroid carcinoma are known, whereas to our knowledge, the genetic changes responsible for atypical parathyroid adenoma and parathyromatosis are not. A future study of their molecular pathogenesis may contribute toward a better understanding of these diseases and the development of a better way to distinguish and diagnosis them.

REFERENCES

1. Lal G, Clark OH. Diagnosis of primary hyperparathyroidism and indications for parathyroidectomy. In: Clark OH, Duh QY, Kebebew E, editors. Textbook of Endocrine Surgery. Philadelphia: Elsevier; 2005:384–392.
2. Clark OH. How should patients with primary hyperparathyroidism be treated? *J Clin Endocrinol Metab.* 2003;88: 3011–3014.
3. Takami H, Kameyama K, Nagakubo I. Parathyroid carcinoma in a patient receiving long-term hemodialysis. *Surgery.* 1999;125:239–240.
4. Berland Y, Olmer M, Lebreuil G, Grisoli J. Parathyroid carcinoma, adenoma and hyperplasia in a case of chronic renal insufficiency on dialysis. *Clin Nephrol.* 1982;18:154–158.
5. Hundahl SA, Fleming ID, Fremgen AM, Menck HR. Two hundred eighty-six cases of parathyroid carcinoma treated in the U.S. between 1985–1995: a National Cancer Data Base Report. *Cancer.* 1999;86:538–544.
6. Palmer JA, Brown WA, Kerr WH, Rosen IB, Watters NA. The surgical aspects of hyperparathyroidism. *Arch Surg.* 1975;110: 1004–1007.
7. Fitko R, Roth SI, Hines JR, Roxe DM, Cahill E. Parathyromatosis in hyperparathyroidism. *Hum Pathol.* 1990;21:234–237.
8. Rattner DW, Marrone GC, Kasdon E, Silen W. Recurrent hyperparathyroidism due to implantation of parathyroid tissue. *Am J Surg.* 1985;149:745–748.

9. Kollmorgen CF, Aust MR, Ferreiro JA, McCarthy JT, Van Heerden JA. Parathyromatosis: a rare yet important cause of persistent or recurrent hyperparathyroidism. *Surgery*. 1994;116:111–115.
10. Stehman Breen C, Muirhead N, Thorning D, Sherrard D. Secondary hyperparathyroidism complicated by parathyromatosis. *Am J Kidney Dis*. 1996;28:502–507.
11. Lee PC, Mateo RB, Clarke MR, Brown ML, Carty SE. Parathyromatosis: a cause for recurrent hyperparathyroidism. *Endocr Pract*. 2001;7:189–192.
12. Baloch ZW, Fraker D, LiVolsi VA. Parathyromatosis as cause of recurrent secondary hyperparathyroidism: a cytologic diagnosis. *Diagn Cytopathol*. 2001;25:403–405.
13. Falvo L, Catania A, Sorrenti S, D'Andrea V, Santulli M, De Antoni E. Relapsing secondary hyperparathyroidism due to multiple nodular formations after total parathyroidectomy with autograft. *Am Surg*. 2003;69:998–1002.
14. Lentsch EJ, Withrow KP, Ackermann D, Bumpous JM. Parathyromatosis and recurrent hyperparathyroidism. *Arch Otolaryngol Head Neck Surg*. 2003;129:894–896.
15. Evans CF, Mansfield L, Sharma AK. Recurrent hyperparathyroidism caused by parathyromatosis. *Hosp Med*. 2005; 66:424–425.
16. Reddick RL, Costa JC, Marx SJ. Parathyroid hyperplasia and parathyromatosis. *Lancet*. 1977;1:549.
17. Barnes BA, Cope O. Carcinoma of the parathyroid glands: report of 10 cases with endocrine function. *JAMA*. 1961;178: 556–559.
18. Schantz A, Castleman B. Parathyroid carcinoma. A study of 70 cases. *Cancer*. 1973;31:600–605.
19. Sokol MS, Kavolius J, Schaaf M, D'Avis J. Recurrent hyperparathyroidism from benign neoplastic seeding: a review with recommendations for management. *Surgery*. 1993;113: 456–461.
20. Holmes EC, Morton DL, Ketcham AS. Parathyroid carcinoma: a collective review. *Ann Surg*. 1969;169:631–640.
21. Wang CA, Gaz RD. Natural history of parathyroid carcinoma. Diagnosis, treatment, and results. *Am J Surg*. 1985; 149:522–527.
22. Shapiro DM, Recant W, Hemmati M, Mazzone T, Evans RH. Synchronous occurrence of parathyroid carcinoma and adenoma in an elderly woman. *Surgery*. 1989;106:929–933.
23. Anderson BJ, Samaan NA, Vassilopoulou Sellin R, Ordonez NG, Hickey RC. Parathyroid carcinoma: features and difficulties in diagnosis and management. *Surgery*. 1983;94: 906–915.
24. Cohn K, Silverman M, Corrado J, Sedgewick G. Parathyroid carcinoma: the Lahey Clinic experience. *Surgery*. 1985;98: 1095–1100.
25. Vetto JT, Brennan MF, Woodruf J, Burt M. Parathyroid carcinoma: diagnosis and clinical history. *Surgery*. 1993;114: 882–892.
26. Kebebew E, Arici C, Duh QY, Clark OH. Localization and reoperation results for persistent and recurrent parathyroid carcinoma. *Arch Surg*. 2001;136:878–885.
27. Shortell CK, Andrus CH, Phillips CE Jr, Schwartz SI. Carcinoma of the parathyroid gland: a 30-year experience. *Surgery*. 1991;110:704–708.