Trends in the Incidence and Treatment of Parathyroid Cancer in the United States

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BACKGROUND. Parathyroid cancer is a rare cause of hyperparathyroidism. The objectives of this study were to determine the patterns of disease, treatment trends, and outcomes among patients with parathyroid cancer by using a population-based data source.

METHODS. Surveillance, Epidemiology, and End Results (SEER) cancer registry data were used to identify patients who were diagnosed with parathyroid cancer from 1988 through 2003. To assess whether the incidence rate, treatment, tumor size, and cancer stage changed over time, the Cochrane-Armitage trend test was used, and Cox proportional-hazards modeling was used to identify the factors associated with an improved overall survival rate.

RESULTS. From 1988 through 2003, 224 patients with parathyroid cancer were reported in the SEER data. Over that 16-year study period, the incidence of parathyroid cancer increased by 60% (1988–1991, 3.58 per 10,000,000 population; 2000–2003, 5.73 per 10,000,000 population). Most patients (96%) underwent surgery (parathyroidectomy, 78.6% of patients; en bloc resection, 12.5% of patients; other, 4.9% of patients). The rate of surgical treatment increased significantly during the study period. The 10-year all-cause mortality rate was 33.2%, and the 10-year cancer-related mortality rate was 12.4%. Patient age ($P < .0001$), sex ($P = .0106$), the presence of distant metastases at diagnosis ($P = .0004$), and the year of diagnosis ($P = .0287$) were associated significantly with the overall survival rate. Tumor size, lymph node status, and type of surgery were not associated significantly with the overall survival rate.

CONCLUSIONS. Although parathyroid cancer is rare, the incidence increased significantly in the United States from 1988 through 2003. Young age, female gender, recent year of diagnosis, and absence of distant metastases were associated significantly with an improved survival rate. ***Cancer*** **2007;109:1736–41.** © *2007 American Cancer Society.*

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Parathyroid cancer is a rare disease, accounting for <1% of all cases of hyperparathyroidism[1–3] and for only 0.005% of all cancers.[4] Most parathyroid cancers secrete parathyroid hormone (PTH) and cause hypercalcemia. In fact, the morbidity and mortality from parathyroid cancer usually are caused by metabolic complications (bone disease, renal disease, pancreatitis, peptic ulcer disease) rather than tumor burden.

No staging system for parathyroid cancer has been adopted universally, because 1) it is a very rare disease, 2) tumor size and lymph node status generally do not correlate with survival, and 3) the disease rarely is diagnosed preoperatively or even intraoperatively.[1–5] Surgical resection is the only curative treatment. Postoperatively, the clinical course of patients with parathyroid cancer is quite variable.

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The most common site of recurrence is within the neck; however, systemic metastases to the bone and lung can also occur.[5–9]

With such a rare cancer, population-based registries offer a large base to estimate incidence rates, patterns of treatment, and survival. We used the national Surveillance, Epidemiology, and End Results (SEER) database, which offers site-specific surgery codes and, beginning with cancers diagnosed in 1988, includes tumor size for parathyroid cancer.[10] The main objectives of our study were 1) to evaluate recent trends in the incidence, treatment, and outcomes of patients diagnosed with parathyroid cancer in the United States and 2) to identify factors that may influence the overall survival rate.

MATERIALS AND METHODS

We used data from the SEER cancer registry to conduct our study. The SEER Program, which is a collection of tumor registries, is headed by the National Cancer Institute. Nine of the 16 current registries (Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Utah, Seattle-Puget Sound, and Atlanta) began between 1973 and 1975. Since then, the remaining 7 registries (San Jose, Los Angeles, Rural Georgia, Alaska Natives [in 1992] and Greater California, Kentucky, Louisiana and New Jersey [in 2000]) were added. The SEER database contains information on tumor characteristics, including date of diagnosis, tumor size, cancer stage and grade, and surgery and radiation for the first course of treatment. Patient characteristics include age, sex, and county of residence. Follow-up information, such as date and cause of death, also is included.

For the current study, we examined patients with parathyroid cancer reported by the SEER registries since 1988, the year that SEER began reporting information on tumor size. Patients aged <21 years were excluded from our analysis. Incidence rates were calculated using SEER county-level population estimates. Crude incidence rates were calculated using SAS software (SAS for Windows 9.1.3; SAS Institute Inc., Cary, NC). All incidence rates are reported per 10,000,000 population; the 4-year rates reflect the average annual incidence over a 4-year period.

To assess whether incidence rates, tumor size, cancer stage, and treatment changed over time, we used the Cochrane-Armitage trend test. To evaluate variables associated with increased hazard of death, while taking censoring into account, we used Cox proportional-hazards regression. Age at diagnosis and year of diagnosis were analyzed as continuous variables, whereas the other variables (sex, treatment, cancer stage, tumor size, and lymph node status) were analyzed as categorical variables. En bloc resection was compared with all other surgeries and with no surgery. Because our study used preexisting data with no personal identifiers, the Human Subjects Committee of the University of Minnesota's Institutional Review Board determined that it was exempt from review.

TABLE 1
Crude Incidence Rates of Parathyroid Cancer by Four-year Groupings, 1988–2003 (N = 224)

Incidence (per 10,000,000 population)				
1988–1991	1992–1995	1996–1999	2000–2003	*P**
3.58	3.11	4.57	5.73	.046

* Cochrane-Armitage trend test.

RESULTS

From 1988 through 2003, a total of 224 patients with parathyroid cancer were identified by the SEER registries. The incidence of parathyroid cancer was very low (<1 per million population per year). Over the 16-year study period, the incidence increased significantly by 60%: from 3.58 per 10,000,000 population during 1988 to 1991 to 5.73 per 10,000,000 population during 2000 to 2003 (Table 1). Parathyroid cancer was distributed evenly among men and women (Table 2). The median patient age was 56 years (range, 23–90 years). The reported histopathology of the majority of cases was nonspecific (carcinoma-not otherwise specified [NOS], 88%; adenocarcinoma-NOS, 2.7%; and malignant neoplasm, 1.8%).

Parathyroid cancer was localized (confined to the parathyroid gland) in 51.8% of patients. Potentially important pathologic information often was not recorded (tumor size, 43.8%; lymph node status, 32.9%; and tumor grade, 87.7%). In fact, the proportion of patients with unrecorded tumor size increased significantly during the 16-year study period (1988, 33.3%; 2003, 46.7%) (Table 3). Unrecorded tumor size was not associated with the type of surgery. When recorded, lymph node metastases were present in 6% of patients. Significant trends in cancer stage were not observed over study the period; however, the proportion of patients with large tumors (≥4 cm) decreased significantly (Table 3). In addition, the proportion of patients with negative lymph nodes increased significantly.

Most patients (78.6%) underwent a simple parathyroidectomy, and another 12.5% of patients underwent en bloc resection (Table 2). Few patients (4%)

TABLE 2
Characteristics and Treatment of Patients with Parathyroid Cancer, 1988–2003 (N = 224)

Characteristic	No.	%
Sex		
Men	112	50
Women	112	50
Race		
White	176	78.6
Black	29	13
Other	19	8.5
Age, y		
<45	49	21.9
45–59	87	38.8
60–69	46	20.5
70–79	35	15.6
≥80	7	3.1
Cancer stage		
Localized*	116	51.8
Regional disease	80	35.7
Distant metastases	10	4.5
Unstaged	18	8
Lymph node status		
Negative	141	63.1
Positive	9	4
Not reported	74	32.9
Size of tumor, cm		
0–1.9	36	16.1
2–3.9	69	30.8
≥4	21	9.4
Not reported	98	43.8
Treatment		
None	8	3.6
Surgical treatment		
None	9	4.0
Parathyroidectomy	176	78.6
En bloc resection	28	12.5
Other†	11	4.9
Radiation therapy		
No	202	90.2
Yes		
Without surgery	1	0.4
With surgery	21	9.4

* Confined to the parathyroid gland.
† Others included debulking surgery and surgery not otherwise specified.

underwent no surgical treatment. Fewer than 10% of patients received radiation therapy after surgery; only 1 patient received radiation without surgery.

The proportion of patients that did not undergo surgical treatment decreased significantly during the study period (Table 3). Among surgically treated patients, the parathyroidectomy rate increased significantly; however, the rate of en bloc resection decreased (statistical significance not reached). The rate of radiation therapy did not change.

The 10-year all-cause mortality rate was 33.2% (1-year all-cause mortality, 7.5%; 5-year all-cause mortality, 16.1%), and the 10-year cancer-related mortality rate was 12.4% (1-year cancer-related mortality, 4.4%; 5-year cancer-related mortality, 9%) (Fig. 1). The Cox proportional-hazards model indicated that older age, male gender, distant metastases at diagnosis, and early year of diagnosis were associated significantly with a worse overall survival rate (Table 4). The type of surgical procedure, tumor size, and lymph node status were not associated significantly with the overall survival rate. However, given the small number of patients and deaths in our study, statistical power was very limited; therefore, we were unable to determine significant differences in the overall survival rate.

DISCUSSION

The incidence of parathyroid cancer increased significantly in the United States during our 16-year study period (1988–2003). To our knowledge, this increase has not been reported previously; it may be secondary to increased serum calcium screening, which may have identified more patients with asymptomatic parathyroid cancer. In 2002, the National Institutes of Health recommendations for parathyroidectomy for asymptomatic hyperparathyroidism became less stringent compared with previous recommendations. For example, in 1990, parathyroidectomy was recommended for patients with serum calcium levels from 1.0 mg/dL to 1.6 mg/dL above normal reference; in 2002, the recommended level was 1.0 mg/dL above normal reference.[11] Consequently, we expect that, in the future, even more patients will undergo parathyroidectomy, and even more cancers will be detected.

Surgical resection is the only curative treatment for patients with parathyroid cancer. The 2 most commonly performed resections are simple tumor excision (parathyroidectomy) and en bloc resection (including ipsilateral thyroid lobectomy and any adjacent tissues that are invaded by tumor). Some nonrandomized, retrospective studies have reported improved outcomes with en bloc resection, whereas others have reported no difference.[5–7,9,12] In our study, en bloc resection was not associated with improved survival; however, our analysis was limited by the small number of patients and potential selection bias (en bloc resection may be performed more frequently on patients with aggressive tumors). It is noteworthy that patients who experience tumor recurrence after parathyroidectomy often require multiple subsequent operations to control tumor burden and to reduce the morbidity of recurrent hyperparathyroidism.[5] Radical lymph node dissection is not recommended, because the incidence of cervical lymph node metastases from parathyroid cancer is low. (In our study, only 6% of all

TABLE 3
Trends in Parathyroid Cancer Staging and Treatment by Four-year Groupings, 1998–2003 (N = 224)

Characteristic	No. of patients (%)				Total	*P**
	1988–1991	1992–1995	1996–1999	2000–2003		
Cancer stage						
Localized†	14 (58.3)	15 (46.9)	23 (47.9)	64 (53.3)	116	.485
Regional disease	7 (29.2)	14 (43.8)	19 (39.6)	40 (33.3)	80	.379
Distant metastases	1 (4.2)	2 (6.3)	2 (4.2)	5 (4.2)	10	.403
Unstaged	2 (8.3)	1 (3.1)	4 (8.3)	11 (9.2)	18	.255
Size of tumor, cm						
0–1.9	7 (29.2)	5 (15.6)	6 (12.5)	18 (15)	36	.096
2–3.9	5 (20.8)	10 (31.3)	15 (31.3)	39 (32.5)	69	.176
≥4	4 (16.7)	3 (9.4)	7 (14.6)	7 (5.8)	21	.043
Not reported	8 (33.3)	14 (43.8)	20 (41.7)	56 (46.7)	98	.135
Lymph node status						
Negative	13 (54.2)	17 (53.1)	28 (58.3)	83 (69.2)	141	.029
Positive	1 (4.2)	2 (6.3)	1 (2.1)	5 (4.2)	9	.466
Not reported	10 (41.7)	13 (40.6)	19 (39.6)	32 (26.7)	74	.032
Surgical treatment						
None	1 (4.2)	3 (9.4)	4 (8.3)	1 (0.8)	9	.032
Parathyroidectomy	17 (70.8)	23 (71.9)	35 (72.9)	101 (84.2)	176	.024
En bloc resection	5 (20.8)	5 (15.3)	3 (6.3)	15 (12.5)	28	.165
Other‡	1 (4.2)	1 (3.1)	6 (12.5)	3 (2.5)	11	.279
Radiation therapy						
No	22 (91.7)	28 (87.5)	44 (91.7)	108 (90)	202	.494
Yes	2 (8.3)	4 (12.5)	4 (8.3)	12 (10)	22	.485

* Cochrane-Armitage trend test.

† Confined to the parathyroid gland.

‡ Includes parathyroidectomy, debalking surgery, and surgery not otherwise specified.

patients who had their lymph node status recorded had lymph node metastases).

The rate of surgical treatment increased significantly during the 16-year study period. We observed that 96% of patients with parathyroid cancer underwent surgical treatment. Although many authors advocate en bloc resection, only 12.5% of patients in our study underwent this treatment compared with 78.6% of patients who underwent parathyroidectomy alone. In an analysis of the National Cancer Data Base (NCDB) from 1985 through 1995, Hundahl et al. reported that 95.5% of patients with parathyroid cancer underwent surgical treatment.[4]

Some investigators have suggested that radiation therapy reduces the local recurrence rate after surgery.[8,13] Chow et al. reported a 0% local recurrence rate in 7 patients who underwent surgery and received radiation therapy at Princess Margaret Hospital in Toronto.[13] Only 9.8% of patients in our study and 6.3% of patients in the NCDB study received radiation therapy.[4] The use of radiation therapy did not change significantly during our 16-year study period and was not associated with an improved survival rate. Other investigators have reported that chemotherapy does not improve the outcomes of patients with parathyroid cancer.[8] However, we were unable to assess whether our study patients underwent chemotherapy.

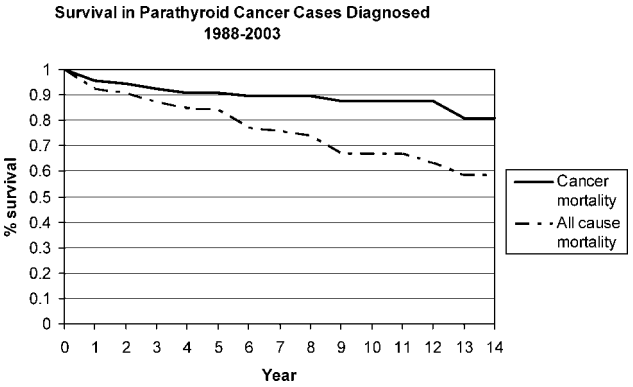

FIGURE 1. Survival rates for patients diagnosed with parathyroid cancer from 1988 to 2003.

In our study, from 1988 through 2003, the 10-year overall survival rate was 67.8%. The 10-year overall survival rate from the NCDB study was 49.1%.[4] Sandelin et al. reported a 10-year overall survival rate of 70% for 95 patients from the Swedish Cancer Registry database.[5] Despite the relatively high survival rate for patients with parathyroid cancer, the reported tumor

TABLE 4
Cox Proportional Hazards Model Predicting Time to Death

Characteristic	HR	*P*
Age at diagnosis*	2.23	<.0001
Year of diagnosis*	0.90	.017
Sex		
Women	1.00	
Men	2.37	.013
Surgical treatment		
En bloc resection	0.55	.357
All other surgeries†	1.00	
Radiation therapy		
No	1.00	
Yes	2.40	.060
Cancer stage		
Localized‡	1.00	
Regional disease	0.59	.237
Distant metastases	11.62	<.0001
Unstaged	2.02	.238
Size of tumor, cm		
0–1.9	1.00	
2–3.9	1.13	.828
≥4	1.18	.786
Not reported	1.25	.672
Lymph node status		
Negative	1.00	
Positive	2.84	.227
Not reported	1.33	.425

HR indicates hazard ratio.

* Continuous variable.

† Includes parathyroidectomy, debulking surgery, and surgery not otherwise specified.

‡ Confined to the parathyroid gland.

recurrence rate is approximately 40% to 60% after surgery.[5,8,9]

We observed that young age, recent year of diagnosis, female gender, and the absence of distant metastases were associated significantly with an improved overall survival rate. Like what was reported in the NCDB study, tumor size and lymph node status were not prognostic factors in our study.[4] Sandelin et al. identified patient age, type of surgery, and histopathologic results as significant prognostic factors.[5] Single-institutional studies have indicated that patient age, sex, preoperative calcium and PTH levels, tumor size, and tumor grade are not associated with overall survival.[8,9,14] However, all analyses, including our own, are limited by the rarity of parathyroid cancer.

Potentially important pathologic prognostic information, such as lymph node status (current study, 32.9% of patients; NCDB, 63.3% of patients) and tumor size (current study, 43.8% of patients; NCDB, 39.2% of patients) often is missing from large database studies.[4] Because most patients with parathyroid cancer are not diagnosed preoperatively or even intraoperatively, tumors often are removed in a piecemeal fashion; consequently, exact determination of tumor size often is impossible.[4] Nevertheless, tumor size and lymph node status are not associated with the overall survival rate.

Our study used cancer registry data; thus, detailed patient and tumor information was not available. Specifically, we did not have serum calcium and PTH levels, genetic testing results for multiple endocrine neoplasia testing, detailed surgical and radiation therapy information, or location of the parathyroid cancer (ie, which gland). In addition, cause of death was determined from death certificate data, which may not capture all cancer-related deaths (eg, hypercalcemia crisis). However, SEER is population-based and provides data on large numbers of patients that would not be available from individual institutional studies. Consequently, we were able determine important patterns of disease, treatment trends, and outcomes of patients with this rare malignancy. According to our current results, the incidence of parathyroid cancer in the United States increased significantly (by 60%) from 1988 through 2003. Most patients (78.6%) were treated with simple parathyroidectomy. Several clinical factors (young age, female gender, recent year of diagnosis, and absence of distant metastases) were associated significantly with an improved overall survival rate.

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