Parathyroid carcinoma survival: improvements in the era of intact parathyroid hormone monitoring?

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Abstract

The intact parathyroid hormone (iPTH) assay is a critical test in the diagnosis and management of PTH-mediated hypercalcemia, including parathyroid carcinoma (PCa). We hypothesized that the survival of patients diagnosed with PCa has improved since adoption of the iPTH assay into clinical practice. We identified all confirmed cases of PCa within the Surveillance, Epidemiology and End Results database from 1973 to 2006. Patients were categorized into two eras based upon introduction of the iPTH assay: 1973 to 1997 (era I) and 1997 to 2006 (era II, when the iPTH assay was in standard use). We estimated overall survival (OS) and disease-specific survival (DSS) using the Kaplan-Meier method, with differences among survival curves assessed via log rank. Multivariate Cox proportional hazards models compared the survival rates between treatment eras while controlling for patient age, sex, race/ethnicity, tumor size, nodal status, extent of disease, and type of surgery. Multivariate models included patients undergoing potentially curative surgery and excluded those with distant metastases. Risks of overall and disease-specific mortality were reported as hazard ratios with 95% confidence intervals. Study criteria were met by 370 patients. Median survival was 15.6 years. Five-year rates of OS and DSS were 78% and 88% for era I and 82% and 96% for era II. On multivariate analysis, age, black race, and unknown extent of disease predicted an increased risk of death from any cause. Treatment era did not predict OS. No factor predicted PCa-specific mortality. In multivariate analysis, neither OS nor DSS have improved in the current era that utilizes iPTH for the detection and management of PCa.

Introduction

Parathyroid carcinoma (PCa) is a rare endocrine malignancy representing only 0.005% of all cancers.[1] It accounts for <1% of patients with primary hyperparathyroidism in Europe and the United States. There are limited data regarding prognostic factors and long-term outcome.[2,3] Indeed, there is no accepted staging system for this malignancy, although some have been propose.[4] The American Joint Committee on Cancer does not advocate the use of its TNM system for PCa due to its' low incidence and rarity of lymph node metastasis.[1] Rather, patients are usually staged clinically, according to whether their primary tumor is confined to the parathyroid gland, extraglandular, or associated with distant metastases. No clear prognostic role has been attributed to tumor size or to the presence or number of lymph node metastases. Prior population-based studies have yielded few additional prognostic factors.[1,5,6] In the absence of definitive data, *en bloc* resection with an associated central neck dissection of level VI lymph nodes is currently recommended for all patients with localized PCa, though only 27- 39% of patients receive it.[5-7]

The intact parathyroid hormone (iPTH) assay has evolved into a critical test in the diagnosis and management of parathyroid hormone (PTH)-mediated hypercalcemia, including PCa. The first assay to detect PTH was developed in the 1970's, eventually winning the Nobel prize for one of its creators.[8] The immunochemiluminometric assay (ICMA) in use today was first described in 1988.[8] The advantages of this method over the immunoradiometric assay (IRMA) are the speed with which the sample can be processed (~15 min) along with the decreased toxicity and increased shelf-life of the reagents and the ability to measure the *bioactive* (1-84) portion of the PTH. Newer assays have decreased the cross reactivity with the N-truncated form (7-84) of the peptide.[9] The iPTH assay for intraoperative use was described by Nussbaum in 1988 pointing toward its usefulness regarding the extent of neck exploration.[10] Irvin adapted a *quick* IRMA assay for use in the operating room in 1991 in a series of 21 patients and studied this utility further using ICMA in 1994.[11,12] The Nichols Chemiluminescence Intra-operative Intact PTH Kit was the first intra-operative intact PTH kit to be FDA approved in December of 1996. It is unknown if the widespread adoption of this improved assay has led to the earlier diagnosis or improved treatment of patients with PCa, but high iPTH levels and severe hypercalcemia does raise suspicion for the disease.[3,13] In this study, we hypothesize that there have been recent improvements in survival of patients diagnosed with PCa associated with time period of adoption of the iPTH assay into clinical practice. Furthermore, since there is a paucity of known prognostic factors, we investigated clinical, demographic, and treatment-related factors which may be associated with PCa outcomes.

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Materials and Methods

We used the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute to identify histologically confirmed cases of PCa diagnosed between 1973 and 2006. Patients who were not diagnosed by histopathology and those who were diagnosed by death certificate or autopsy were excluded from our analysis. Approximately 26% of cancer cases in the United States population are currently represented by one of 17 population-based cancer registries that provide cancer incidence and survival data to SEER. The database provides information on patient demographics, primary tumor site, tumor morphology, stage at diagnosis, first course of treatment, and follow-up vital status. Current SEER registries include the states of Connecticut, Hawaii, Iowa, Kentucky, Louisiana, New Jersey, New Mexico, and Utah; the metropolitan areas of Atlanta, Detroit, San Francisco-Oakland, Seattle-Puget Sound, and San Jose-Monterey; the Alaska Native Tumor Registry, rural Georgia, Greater California, and Los Angeles County. SEER data are de-identified and therefore exempt from Institutional Review Board approval.

Human PTH was sequenced in the 1970s.[8] The Nichols Chemiluminescence Intra-operative Intact PTH Kit was the first intra-operative intact PTH kit to be FDA approved at the end of

1996. Given that new technologies take time before being incorporated into common use, we elected to sue 1 year after this date, 1997, as the cut-off date between groups. We categorized patients into two groups according to the era in which they were diagnosed and treated: 1973 to 1997 (Era I) and 1998 to 2006 (Era II).[14] We also know that an intact PTH assay has been the standard laboratory measure technique since 1990.[1] Era I included the time-period prior to, and Era II the time-period after, the widespread adoption of iPTH assays. We compared differences in patients from each era using Chi-square testing for categorical variables and proportions.

Covariates

Patient, tumor, and treatment covariates of known or potential prognostic importance were obtained from SEER and included: patient age (median =56 years; ≤56 years *vs.* >56 years), sex, race/ethnicity (Asian, black, Hispanic, native American, white, other), tumor size (0-2 cm, 2.1-4 cm, >4 cm, unknown), nodal status (positive, negative, unknown), metastasis (M0, M1, MX), extent of disease (glandular, extra-glandular, metastatic, unknown), and type of surgery [none, debulking, local excision, radical resection, surgery not otherwise specified (NOS), unknown].

Analyses

Survival was calculated as the number of completed months between the date of diagnosis and whichever occurred first: date of death,

Table 1. Patient, tumor, and treatment-specific characteristics.

Characteristics	N (%)
Age (years)	
≤56	192 (51.9)
>56	178 (48.1)
Sex	
Male	184 (49.7)
Female	186 (50.3)
Race	
White	251 (67.8)
Black	54 (14.6)
Hispanic	38 (10.3)
Asian	24 (6.5)
Native American	3 (0.8)
Tumor size (cm)	
0 to 2 cm	69 (18.7)
2.1 to 4 cm	94 (25.4)
>4 cm	30 (8.1)
Unknown	177 (47.8)
Lymph nodes	
Negative	78 (21.1)
Positive	10 (2.7)
Unknown	282 (76.2)
Extent of disease	
Glandular	212 (57.3)
Extra-glandular	116 (31.4)
Metastasis	19 (5.1)
Unknown	23 (6.2)
Grade	
I	32 (8.7)
II	12 (3.2)
III	1 (0.3)
IV	1 (0.3)
Unknown	324 (87.6)
Surgery	
None	7 (1.9)
Biopsy/debulking (3 biopsies, 1 debulking surgery)	4 (1.1)
Local Excision	248 (67)
Radical Resection	38 (10.3)
Surgery NOS	66 (17.8)
Unknown	7 (1.9)
Radiation	
Yes	33 (8.9)
No	333 (90)
Unknown	4 (1.1)
Treatment Era	
Era I: 1973-1997	142 (38.4)
Era 2: 1998-2006	228 (61.6)

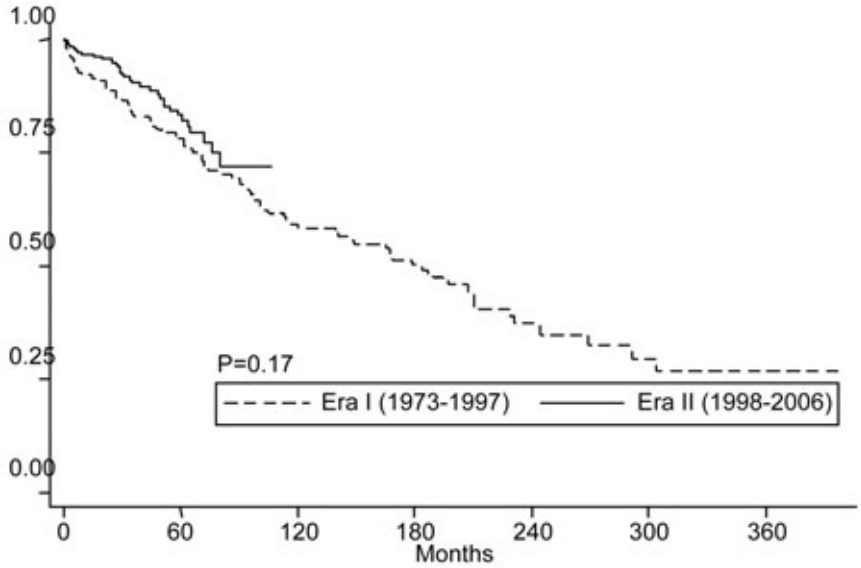

Figure 1. Overall survival according to treatment era in parathyroid carcinoma patients.

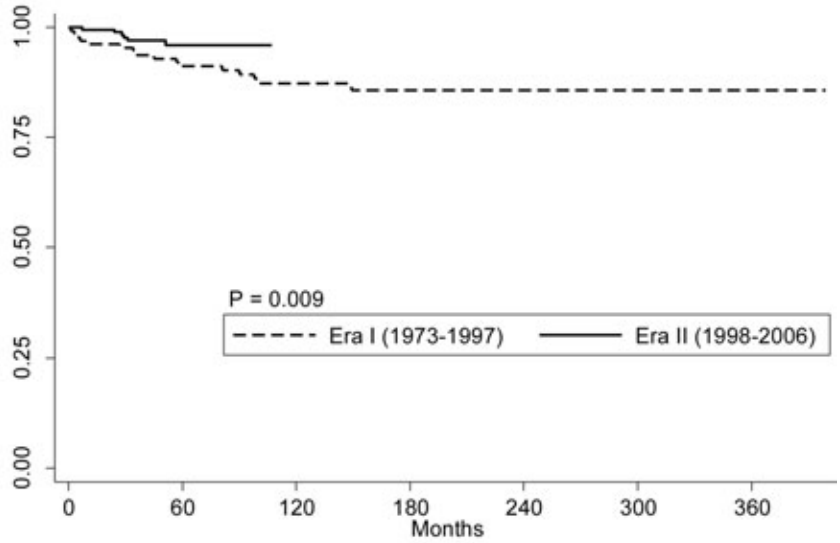

Figure 2. Disease-specific survival according to treatment era in parathyroid carcinoma patients.

date last known to be alive, or December 31, 2006. The survival endpoints for the present study were disease specific survival (DSS) and overall survival (OS). Patients who were lost to follow-up or survived beyond December 31, 2006 were coded as censored observations. Additionally, those dying from causes other than PCa were coded as censored observations in the calculation of DSS.

Univariate analysis of OS and DSS by each covariate and treatment era was performed using the Kaplan-Meier method. Statistical differences among or between survival curves were assessed via the log-rank test. Multivariate Cox proportional hazards models compared rates of OS and DSS between treatment eras while controlling for the covariates of patient age, sex, race/ethnicity, tumor size, nodal status, extent of disease, and type of surgery. In the multivariate models, age was analyzed as a continuous variable, while all other covariates were treated as categorical variables. To avoid potential bias, we excluded patients with distant metastases and those not undergoing potentially curative surgery for PCa from the multivariate analyses. Risks of overall and disease-specific mortality were reported as hazard ratios (HR) with 95% confidence intervals (CI); significance was set at P≤0.05. All statistical analyses were performed using STATA version 11 (College Station, TX, USA).

Results

We identified 370 cases of PCa within the SEER registry from 1973-2006. Demographic characteristics of these cases are summarized in Table 1. The median age was 56 years and equivalent numbers of men and women were affected. More white patients were in the registry than other race groups. There were a number of cases in which the lymph node status (76.2%), tumor size (47.8%) and grade of tumor (87.6%) were unknown. Only 5.1% of tumors presented with distant metastasis. Sixty-seven percent of the surgical procedures performed were local excisions. In this series, a minority of patients (9%) had radiation treatment. After dividing the cohort into eras based on the date of diagnosis, 142 (38.4%) of the cases were in era I (1973-1997), while 228 (61.6%) of cases were in era II (1998-2006). Between the treatment eras, we observed significant differences in tumor size (P=0.003), extent of disease (P=0.013) and type of surgery (P<0.001) (Table 2). However, age, sex, race, lymph node positivity, tumor grade and use of radiation did not differ by era. The median OS for the population as a whole was 15.6 years and the ten-year OS for the cohort was 61.2%. Five-year DSS rates were 88% in era I and 96% in era II. Ten year DSS for the cohort was 88.8%. In unadjusted analyses, no significant difference in OS was observed between the two treatment eras (P=0.17) (Figure 1 and Table 3). The five-year rate of OS was 78% in era I and 82% in era II. The unadjusted DSS in era II was significantly better than in era I (P=0.009) (Figure 2 and Table 3). In univariate analyses of OS, patient age (P<0.001), extent of disease (P<0.001), and type of surgery (P<0.001) were significant factors (Table 3). Additionally, the univariate analyses of DSS revealed that the extent of disease (P<0.001) and type of surgery (P<0.001) were also significant factors (Table 3). Nodal status (P=0.05) and tumor size (P=0.07) approached statistical significance.

Increasing age (HR 1.06, CI 1.04-1.08; P<0.001), black race (HR 1.91, CI 1.08-3.38; P=0.03), and unknown extent of disease (HR 2.80, CI 1.26-6.21; P=0.01) were predictive of an increasing risk of death from any cause on multivariate analysis (Table 4). We did not identify any significant predictor of DSS on multivariate analysis. There was no significant improvement in either OS (HR 0.72, P=0.29)

Table 2. Patient characteristics according to treatment era.

Characteristics	Era I (%) 1973-1997	Era II (%) 1998-2006	P value
Age (years)	≤ 56	74 (52.1)	118 (51.8)
0.95			
> 56	68 (47.9)	110 (48.3)	
Sex			
Male	64 (45.1)	120 (52.6)	0.16
Female	78 (54.9)	108 (47.4)	
Race			
White	102 (71.8)	149 (65.4)	0.40
Black	21 (14.8)	33 (14.5)	
Hispanic	9 (6.3)	29 (12.7)	
Asian	9 (6.3)	15 (6.6)	
Native American	1 (0.7)	2 (0.9)	
Tumor size (cm)			
0 to 2 cm	26 (18.3)	43 (18.9)	0.003
2.1 to 4 cm	22 (15.5)	72 (31.6)	
>4 cm	12 (8.5)	18 (7.9)	
Unknown	82 (57.8)	95 (41.7)	
Lymph nodes			
Negative	22 (15.5)	56 (24.6)	0.12
Positive	4 (2.8)	6 (2.6)	
Unknown	59 (100)	51 (72.9)	
Extent of disease			
Glandular	78 (54.9)	134 (58.8)	0.013
Extra-glandular	41 (28.9)	75 (32.9)	
Metastasis	14 (9.9)	5 (2.2)	
Unknown	9 (6.3)	14 (6.1)	
Grade			
I	14 (9.9)	18 (7.9)	0.20
II	2 (1.4)	10 (4.4)	
III	1 (0.7)	0 (0)	
IV	1 (0.7)	0 (0)	
Unknown	124 (87.3)	200 (87.7)	
Surgery			
None	0 (0)	7 (3.1)	<0.001
Debulking	3 (2.1)	1 (0.4)	
Local excision	55 (38.7)	193 (84.7)	
Radical resection	17 (12)	21 (9.2)	
Surgery NOS	60 (42.3)	6 (2.6)	
Unknown	7 (4.9)	0 (0)	
Radiation			
Yes	15 (10.6)	18 (7.9)	0.60
No	125 (88)	208 (91.2)	
Unknown	2 (1.4)	2 (0.9)	

or DSS (HR 0.52, P=0.49) between era II and era I in the multivariate analysis.

Discussion

Dividing the SEER data into pre- and post-iPTH eras allowed us the opportunity to explore the hypothesis that the widespread adoption of this test for the evaluation of PTH-mediated hypercalcemia might lead to earlier diagnosis, improved treatment, and better outcomes for patients. While DSS is improved in the more recent era in unadjusted analyses, this improvement did not remain after controlling for clinical, demographic and treatment factors in multivariate analysis. Indeed, the distribution of tumor size, extent of disease and type of surgery were significantly different in era II (Table 2). Despite being one of the largest analyses of PCa patients to date, no predictor of DSS could be identified in this cohort.[7]

Five year OS and DSS are similar to other published studies as are the 10-year survival rates for OS and DSS for the cohort.[1,5] These were not largely different by era. As in other case series, younger patients had better OS, patients that had surgical intervention had better OS and DSS than those that did not and those patients with less disease burden and absence of distant metastasis had better OS and DSS.[6,15] There was a trend toward a significant difference in the nodal status and DSS. Using cytometric assessments of parathyroid gland DNA for diagnosis is controversial. The classic histopathologic features (fibrous bands, trabecular pattern, mitotic figures, and capsular and vascular invasion) for diagnosis are similarly contentious. None of these factors are available in the SEER database, however. On multivariate analysis, age ≥56, black race and unknown extent of disease were predictive of decreased OS. As the risk of death from all causes is expected to increase with advancing age, the association with age and poorer OS is entirely expected. Black race was noted to be a risk factor for death from all causes, but not PCa-related death. This would most likely indicate that our Black patients were dying from other factors. Black patients are known to have higer rates of hypertension, diabetes, and coronary artery disease than white patients. It is likely that the Black patients in our study died from their comorbid conditions. SEER does not provide information on patient comorbidities, so this assumption can not be confirmed. Finally, our model indicated an increased risk of all-cause mortality with unknown extent of disease. It is possible that unknown extent of disease serves as a proxy for locally advanced but hard to quantify disease. If this was so, however, we would expect for this to predict poorer disease, specific survival as well, and this was not found. It is likely an aberrant finding. Patients with parathyroid carcinoma most commonly die as a result of uncontrolled hypercalcemia. Despite modest advances in the treatement of hypercalcemia over the thirty three years of our study, such as the use of bisphosphonates and cinacalcet, our

Table 4. Multivariate Cox proportional hazards models for overall survival and disease-specific survival in parathyroid carcinoma patients without distant metastases undergoing potentially curative surgical resection.

	Overall survival		Disease-specific survival	
	Hazard ratio (95% confidence interval)	P value	Hazard ratio (95% confidence interval)	P value
Age (years)	1.06 (1.04-1.08)	<0.001	1.01 (0.97-1.06)	0.57
Sex				
Female (referent)	*	*	*	*
Male	1.31 (0.85-2.03)	0.22	1.14 (0.39-3.36)	0.81
Race				
White (referent)	*	*	*	*
Black	1.91 (1.08-3.38)	0.03	0.48 (0.06-3.93)	0.50
Hispanic	0.80 (0.29-2.24)	0.67	0.64 (0.08-5.07)	0.67
Asian	1.15 (0.48-2.74)	0.75	NA	NA
Native American	NA	NA	NA	NA
Tumor size (cm)				
0 to 2 cm (referent)	*	*	*	*
2.1 to 4 cm	0.73 (0.34-1.57)	0.42	0.79 (0.12-5.26)	0.81
>4 cm	0.94 (0.36-2.44)	0.90	2.79 (0.34-22.96)	0.34
Unknown (referent)	0.98 (0.51-1.87)	0.95	0.60 (0.10-3.59)	0.57
Nodal status				
Negative (referent)	*	*	*	*
Positive	2.70 (0.81-9.05)	0.11	7.18 (0.54-94.96)	0.13
Unknown	1.28 (0.65-2.52)	0.48	3.22 (0.33-31.28)	0.31
Extent of disease				
Glandular (referent)	*	*	*	*
Extra-glandular	1.06 (0.66-1.71)	0.80	1.93 (0.61-6.07)	0.26
Unknown	2.80 (1.26-6.21)	0.01	5.02 (0.86-29.42)	0.07
Surgery				
Local excision (referent)	*	*	*	*
Radical resection	1.28 (0.59-2.79)	0.60	1.73 (0.30-10.01)	0.54
Surgery NOS	0.88 (0.46-1.67)	0.38	2.05 (0.43-9.71)	0.37
Treatment era				
Era I, 1973-1997 (referent)	*	*	*	*
Era II, 1998-2006	0.72 (0.40-1.31)	0.29	0.58 (0.14-2.36)	0.45

*Referent population. NA, not applicable; too few patients to analyze.

study did not demonstrate a difference in either OS or DSS by era. It is possible that despite earlier detection and treatment of hypercalcemia in these patients, we were unable to detect a benefit. A limited multivariate analysis that excluded patients with an unknown surgical procedure and unknown extent of disease did not alter findings for disease-specific survival. Only in this more limited analysis were male sex (HR 2.09, CI 1.19-3.68; P<0.001) and node positive status (HR 3.59, CI1.04-12.40; P=0.04) significantly associated with poorer OS. A number of limitations of our analysis warrant discussion. First, this was a registry study with cases diagnosed and annotated over a period of 30 years during which procedures for staging and evaluation may have changed. The dataset contained a large number of cases with unknown LN status, tumor size, extent of disease and type of surgery. These data would be important to know, since *en bloc* resection has been associated with a favorable prognosis.[7] Furthermore, our data set does not have equal representation of all populations due to the rarity of PCa overall. Even more rare are nonfunctioning parathyroid carcinomas with <30 cases reported.[16] The results of this study therefore holds true for functioning carcinomas and nonfunctioning tumors likely do not contribute to the lack of improvement in survival. While the use of iPTH has become much more common in the recent decades, it is not known whether it was used to assist in preoperative diagnosis of PTH-mediated hypercalcemia and data regarding its perioperative use in the management of cases is era II are not available. Lastly, we were unable to reveal 10 year survival rates on the more recent data from Era II.

Conclusions

After accounting for demographic, clinical, and treatment factors, we found no significant difference in the DSS or OS between patients diagnosed with PCa in a more contemporary time period compared to those diagnosed prior to 1997. Additionally, we could not identify independent predictors of PCa DSS. Further research is needed to improve diagnostic strategies and improve patient outcomes in this uncommon disease.

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