1-1-2019

Effect Of Marital Status On Survival In Parathyroid Cancer Patients In The Usa – A Seer Database Study

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Completed – 2019

Degree Awarded – 2019

Master of Public Health

Yale School of Public Health, Chronic Disease Epidemiology

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ABSTRACT

INTRODUCTION: To evaluate the influence of marital status on the survival outcomes of patients diagnosed with parathyroid cancer.

MATERIALS and METHODS: The Surveillance, Epidemiology, and End Results (SEER) database was used to identify patients diagnosed with parathyroid cancer between 1975 and 2016. Survival analysis was performed using Kaplan-Meier method and multivariate Cox regression analysis, to evaluate the association between marital status and parathyroid cancer survival, controlling for potential confounders. Overall mortality and parathyroid cancer-specific mortality rates were calculated for 5-year and 10-year follow-up periods.

RESULTS: The final cohort from SEER consisted of 611 patients. 373 (61.05%) were married and 238 (38.95%) were unmarried. 315 were male (51.55%) and 286 were female (48.45%). Married patients were older (Mean age 56.98 years; 95% CI 55.66-58.31) compared to unmarried patients (Mean age 54.72 years; 95% CI 52.69-56.75). Married patients had better overall 5-year survival (94.3% vs 86.4%; p=0.0532), and better overall 10-year survival (86.4% vs 72.2%; p=0.0061). Marital status was not associated with cancer-specific survival. Older age at diagnosis (HR 1.62; p=0.0254), distant metastases (HR 2.75; p<0.0001), no surgery (HR 2.57; p=0.0172) all independently predicted 5-year survival. Unmarried patients had a significantly higher risk of 10-year mortality (HR 1.43; p=0.0335).

CONCLUSIONS: Marital status is an independent predictor of 10-year overall survival in patients with parathyroid cancer. It is not a statistically significant independent predictor for parathyroid cancer specific survival.

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INTRODUCTION:

Parathyroid cancer is a rare malignancy of the parathyroid gland, accounting for <1% of all cases of hyperparathyroidism in the United States, [1-3]. The incidence is very low, with only 11 cases per 10 million people since 2001 [4], and a prevalence of approximately 0.005% of all cancers [5]. Patients present with hyperparathyroidism as the main feature, but parathyroid cancer only accounts for <1% of all the cases of hyperparathyroidism [1-3]. Compared to even other rare cancers, literature about the characteristics and epidemiological factors of parathyroid cancer is sparse.

The parathyroid glands are four small, pea-sized glands, located in the neck on the thyroid glands. They secrete the hormone parathormone (PTH) which is essential to maintain the calcium level in the blood. Calcium is required for the normal functioning of almost every cell in the body. Increased activity of the parathyroid gland is called hyperparathyroidism. It usually occurs due to benign tumors of the parathyroid gland, called adenomas [7], and rarely due to malignancy of the parathyroid glands. The increase in PTH causes increase in the calcium level in the blood (called Hypercalcemia) by increasing the absorption of calcium in the intestine from the food ingested, and resorption of calcium from the bones into the blood. The hypercalcemia caused by hyperparathyroidism a serious and life-threatening condition, and treating it is as important as treating the cancer [7]. The metabolic complications (renal complications, bone disease, pancreatitis, peptic ulcer disease) that occur due to parathyroid cancer is the main cause of morbidity and mortality in parathyroid cancer patients, more than the tumor itself [8].

Demographic characteristics such as a patient's age, sex, race, family history, educational status, income level have all been proven to be associated with various cancers and their outcomes. Marital status also affects survival rates in various cancers. The pioneering study by Durkheim in 1897 [9] on suicide demonstrated that marriage plays a beneficial role in survival. Several studies have established that married cancer patients have better survival rates than unmarried or divorced/separated patients in various other cancer types such as prostate cancer, breast cancer, colo-rectal cancer, urothelial cancer, and gallbladder cancer [6, 10-14]. Marital status is commonly used as a marker of social and emotional support [15]. Married patients may have better financial resources compared to those patients who aren't married and may have better social support [16], have a better quality of life [17], and tend to lead a healthier lifestyle [17]. Such patients might also have better access to treatment, compared to other patients.

Marital discord or disruption of marriages may contribute to stress. The associated behavioral response patterns to stress and resultant neurohormonal changes, have been linked to cancer development and metastasis [18-19]. Marital quality has also been established as a predictor of poor immune function, which could also play a role in cancer development and progression [20].

Despite the plethora of research articles analyzing the relationship between marital status and survival in patients with other types of cancer [6, 10-14], there hasn't been any study yet analyzing this relationship in parathyroid cancer patients. Although it would be reasonable to assume that a similar beneficial and protective effect of marriage might exist in parathyroid cancer patients as well, it would be wrong to accept it as fact without a proper analysis. The aim

of this study is to analyze this relationship in parathyroid cancer patients, to determine if the hypothesis that a similar beneficial relationship exists, is true.

OBJECTIVES:

The objectives of this study include – (1) Creating a database of parathyroid cancer patients for analysis; (2) Analyze the demographic characteristics including marital status among the married and unmarried patients in the database; (3) Calculate overall survival rates and cancer-specific survival rates in the two groups; (4) Perform a multivariate Cox regression analysis to calculate the hazard ratios for other possible confounding factors, selected from other literature about parathyroid cancer epidemiology.

Since parathyroid cancers are rare, individual institution data might be sparse, and hence population-based registries are the best resources to provide data on a large number of parathyroid cancer cases for meaningful analysis. For the purpose of this study, we used information from the national Surveillance, Epidemiology, and End Results (SEER) database, which provides information for parathyroid cancer patients from the participating registries since 1973, and is probably one of the best databases currently available for parathyroid cancers. Other studies that used data from the SEER registry to analyze the association between marital status and cancer survival have also found that married patients have better survival outcomes for other cancer types such as colon cancer [6], gall bladder [10], prostate cancer [11], breast cancer [12], bladder urothelial carcinoma [13], but no study has been published till date analyzing this association with parathyroid cancer.

ETHICS APPROVAL:

Since this study does not involve human participants, or studies with animals, ethics approval is not required.

MATERIALS & METHODS:

The SEER Database:

This is an observational study, using data from the SEER database. The SEER database is a publicly available cancer database created by the National Cancer Institute in 1973 and currently includes 18 tumor registries nationwide [21], representing 18 geographic regions within the United States, and encompassing approximately 26% of the entire general population. The geographical areas represented in the SEER registry include Connecticut, Iowa, New Mexico, Utah, Hawaii, Los Angeles, the metropolitan areas of Detroit and San Francisco-Oakland, Kentucky, Greater California, Louisiana, Georgia, New York, Massachusetts, Wisconsin, Idaho, Seattle-Puget Sound, Cherokee Nation, Arizona Indians, and the Alaska Native Tumor Registry. It is one of the largest publicly accessible tumor registries in the US with information on various demographic characteristics such as age, sex, county of residence, date of diagnosis, cause of death, and tumor characteristics such as tumor size, stage and date of the disease, treatment provided etc. Numerous research articles have been published analyzing the relationship between various demographic and tumor characteristics, and cancer outcome in parathyroid cancer. Association between marital status of the patient and cancer survival has been studied in other cancers such as breast, colo-rectal, gallbladder cancers etc., but has not been previously studied in patients with parathyroid cancer.

Data Collection:

Data collection from the SEER database was done using the SEER*STAT software version 8.3.5, made available by the National Cancer institute. The case listing session was used with the variables of interest selected, to obtain a database of patients for the study. Within the SEER database, the 'Incidence – SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2018 Sub (1975-2016) varying' database was selected for data retrieval. This is the most recent database available in SEER, and included cases from 1975 until 2016, with follow-up data until the end of 2016.

Patient population & variables:

From the SEER database, we identified patients diagnosed with parathyroid cancer (primary site code C75.0 – parathyroid gland; ICD-O-3 histology codes 800 (neoplasm), 801 (carcinoma, not otherwise specified), 802 (carcinoma, undifferentiated, not otherwise specified), 814 (adenocarcinoma, not otherwise specified), 829 (Oxyphilic adenoma), 831 (Clear cell adenocarcinoma) and 832 (Water clear cell adenocarcinoma)) from 1988 to 2009. We excluded patients coded with ICD-10 codes consistent with metastatic disease originating from other organ sites. The database contains information on cases diagnosed until 2016, and follow-up data until the end of 2016. The variables that were obtained for each patient included age, race, sex, marital status, age at diagnosis, month of diagnosis, vital status, survival in months, cause of death, surgery performed, diagnostic confirmation, histologic type, SEER summarized staging, and grade. As tumors of the parathyroid glands are small, the standard AJCC TNM tumor staging data, which is used to stage most other cancers, is not applicable for

staging parathyroid cancers, and hence was not available in the SEER database for these patients. Instead, a summary SEER staging system was available in SEER, and was included in the study.

Exclusion criteria:

Only patients for whom information on all the variables of interests were available in the SEER database were included. Since marital status and survival period are the main variables of interest, patients with missing data for these two variables, and patients under the age of 18 were excluded, as the legal age of marriage is 18 years in 48 out of the 50 states in the USA. Patients were excluded if the vital status and the cause of death were recorded only from death certificates. Patients with ICD-O-3 codes other than 800, 801, 802, 814, 829, 831 and 832 were excluded. Only patients in whom the diagnosis was confirmed by a positive histology were included in the study. The last exclusion criteria used was patients in whom the vital status (dead/alive) and cause of death were not collected by active follow-up.

Description of variables:

Marital status for patients in the SEER database is categorized into five groups – 'single (never married)', 'married', 'widowed', 'separated' and 'divorced'. For the purpose of this study, all patients were grouped into two categories - 'married' or 'unmarried'. The unmarried group included the widowed, divorced and single (never married) patients. The marital status data refers to the status at the time of cancer diagnosis. Any change in the marital status after diagnosis is not available.

Race data in the SEER database is coded as White, Black, Hispanic, Asian or Pacific Islander (API), Native American/Alaskan, and other unspecified. The Asian & Pacific Islander, Native American/Alaskan, and Other categories were grouped together into a single group, and termed 'Other'.

Parathyroid glands are small, and the tumors are also usually small compared to other solid tumors. Hence, the TNM staging system is not used in parathyroid cancers, although the standalone T, N and M staging information can be useful. For this reason, tumor data in the SEER database is not classified according to the standard AJCC TNM staging, and hence not included. Instead, the SEER database includes a category termed 'SEER Summary Stage', which uses available information on the primary tumor characteristics, lymph node status, and metastasis if any, to arrive at a 'Summary Stage'. This staging methodology stages the cancer in each patient into 6 categories – 'Localized', 'Regional extension only', 'Regional extension with lymph nodes involvement', 'Regional Lymph node involvement only', 'Distant metastasis', and an 'Unknown/Unstaged' category. For this study, we grouped the 3 regional stages together to arrive at a final 4 stage classification – 'Localized', 'Regional', 'Distant metastasis', and the 'Unknown/Unstaged' categories.

Surgical status was extracted as a dichotomous variable. Data on whether patients had a surgery or not was available in the SEER database, but data on the type of surgery performed was not available for many patients, and hence surgical status was coded dichotomously as 'Yes' and 'No', and not stratified on the type of surgery performed.

Based on the histological characteristics, grade was assigned as Grades I, II, III and IV (Grade I – Well differentiated; Grade II – Moderately differentiated; Grade III – Poorly differentiated; and Grade IV – Undifferentiated or Anaplastic). For a majority of the patients (n=531, 86.9%) the information was incomplete. Data on the grade of the tumor was included in the demographic characteristic table, but was not included in any of the analyses., due to lots of missing data.

STATISTICAL ANALYSIS:

Baseline demographic characteristics were calculated using the t-test for continuous variables such as age, survival months, year of diagnosis. Chi-square test was used to calculate the descriptive statistics for categorical variables such as sex, race, stage of the disease, grade and surgery performed. The Kaplan-Meier method was used to generate survival curves, and to compare the death rates due to parathyroid cancer and the overall death rate. Hazard ratios were calculated using the multivariate Cox regression analysis to calculate the risk of parathyroid cancer specific mortality and overall mortality among the two groups. The covariates included in the Cox regression analysis were age at diagnosis (two groups - ≤57 and >57 years), year of diagnosis, sex, race, marital status and stage of the cancer. Hazard ratios and survival rates were calculated for both groups for 5-year follow-up and 10-year follow-up periods.

All calculations were performed using the JMP Pro analytical software, version 13.

Table 1. Demographic Characteristics			
	MARRIED (n=373)	UNMARRIED (n=238)	p-value
AGE AT DIAGNOSIS			
- Mean	56.98 (55.66-58.31)	54.72 (52.69-56.75)	**<0.001**
- Median	58 yrs	55 yrs	
- Range	25-87 yrs	20-89 yrs	
- Age ≤57 yrs	178 (47.7%)	137 (57.6%)	**0.0176**
- Age >57 yrs	195 (52.3%)	101 (42.4%)	
SURVIVAL (Months)	107.34	92.96	**<0.001**
RACE			
- White	251 (67.3%)	134 (56.3%)	**<0.001**
- Black	39 (10.5%)	56 (23.5%)	
- Hispanic	48 (12.9%)	33 (13.9%)	
- Other	35 (9.4%)	15 (6.3%)	
SEX			
- Male	208 (55.8%)	107 (45.0%)	**0.0092**
- Female	165 (44.2%)	131 (55.0%)	
STAGE			
- Localized	228 (61.1%)	132 (55.5%)	0.2261
- Regional Spread	116 (31.1%)	76 (31.9%)	
- Distant metastasis	15 (4.0%)	16 (6.7%)	
- Unstaged	14 (3.8%)	14 (5.9%)	
SURGERY			
- Yes	367 (98.4%)	227 (95.4%)	**0.0272**
- No	6 (1.6%)	11 (4.6%)	
GRADE			
- I	38 (10.2%)	21 (8.8%)	0.3084
- II	12 (3.2%)	3 (1.3%)	
- III	2 (0.5%)	1 (0.4%)	
- IV	3 (0.8%)	0 (0.0%)	
- Unstaged	318 (85.3%)	213 (89.5%)	

RESULTS:

DEMOGRAPHIC CHARACTERISTICS:

The final database from SEER consisted of 611 patients with parathyroid cancer, diagnosed between the years 1975 and 2016, a 42-year study period. Follow-up data was available until the end of 2016, so all patients had a minimum follow-up period of at least a year, except those who died within a year of diagnosis. All the demographic characteristics stratified by marital status is represented in table 1.

AGE: The median age at diagnosis of all the patients, both male and female, was 57 years. So, patients were grouped into either one of two groups, ≤57 and >57 years. The mean age at diagnosis of the married patients was 56.98 years (95% CI 55.66-58.31) and for the unmarried patients, it was 54.72 years (95% CI 52.69-56.75). The median age of the married and unmarried patients was 58 years and 55 years respectively. With the overall median age of 57 years as the cutoff value, a majority of the married patients were over 57 years of age at the time of diagnosis (52.3%), whereas the majority of the unmarried patients were younger than 57 years at the time of diagnosis (57.6%). Overall, unmarried patients were slightly younger than the married patients.

SEX: Of the 611 patients, 315 were male (51.55%) and 286 were female (48.45%). Among the male patients, a majority were married (n=208; 66% married vs unmarried n=107; 34%), and a majority of the female patients were also married at the time of diagnosis (n=165; 57.7% married vs unmarried n=131; 42.3%).

RACE: A majority of parathyroid cancer patients in both groups were white. In the married group, 251 patients were white (67.3%), 39 patients were black (10.5%), 48 patients (12.9%) were Hispanic and 35 patients (9.4%) belonged to other racial groups. Among the unmarried patients, 134 patients (56.3%) were white, 56 patients (23.5%) were black, 33 (13.9%) were Hispanic, and the remaining 15 patients (6.3%) belonged to other minority racial groups.

MARITAL STATUS: 373 patients (61.05%) were married and 238 (38.95%) were unmarried when they were diagnosed with parathyroid cancer. A majority of the married cancer patients were male (55.8%) whereas a majority of the unmarried patients were female (55.0%)

SURVIVAL MONTHS: The average length of survival overall in the married patients group is 9 years (107.34 months), and 7 years and 9 months (92.96 months) in the unmarried group. Limiting the follow-up to five years, the average lengths of survival are 4 years (48.54 months) and 3 years 9 months (45 months) for married and unmarried patients respectively. With a ten-year follow-up, the survival periods are 6 ½ years (77.64 months) and 6 years (72.04 months) respectively.

SUMMARY STAGE: In a majority of patients in both the groups, the cancer was localized (n=228, 61.1% in married patients; n=132, 55.5% in unmarried patients). In 116 married patients (31.1%) and 76 unmarried patients (31.9%) the tumor had spread regionally. Distant metastasis was present in 4% of married patients (n=15) and 6.7% of unmarried patients (n=16)

at the time of diagnosis. The tumors were unstaged in 3.8% of the married patients (n=14) and 5.9% of unmarried patients (n=14).

An overwhelming majority of patients in both the groups had surgery to treat the cancer. Surgery had been performed in 98.4% of married patients (n=367) and 95.4% of unmarried patients (n=227).

A grade was not assigned to a majority (85.3% in the married group; 89.5% in the unmarried group) of the patients. Instead, the summary stage data was used for comparison.

KAPLAN MEIER SURVIVAL CURVES:

The overall 5-year survival rate (Figure 1) was higher in the married group (94.3%) compared to the unmarried group (86.4%), and the difference is marginally significant (p=0.0532). The 5-year cancer-specific survival rate was also better in the married group (97.8%) compared to the unmarried group (95.3%), but the difference was not statistically significant (p=0.2205).

The 10-year overall survival and cancer-specific survival rates were also measured (Figure 2). Married patients had statistically significant better rate of surviving 10 years after being diagnosed with parathyroid cancer (86.4%) compared to unmarried patients (72.2%) (p=0.0061).

The 10-year cancer-specific survival rate was also better in the married group (95.2%) compared to the unmarried group (90.4%), but the difference was not statistically significant (p=0.5671).

Figure 1: Kaplan-Meier estimates of overall mortality stratified by marital status

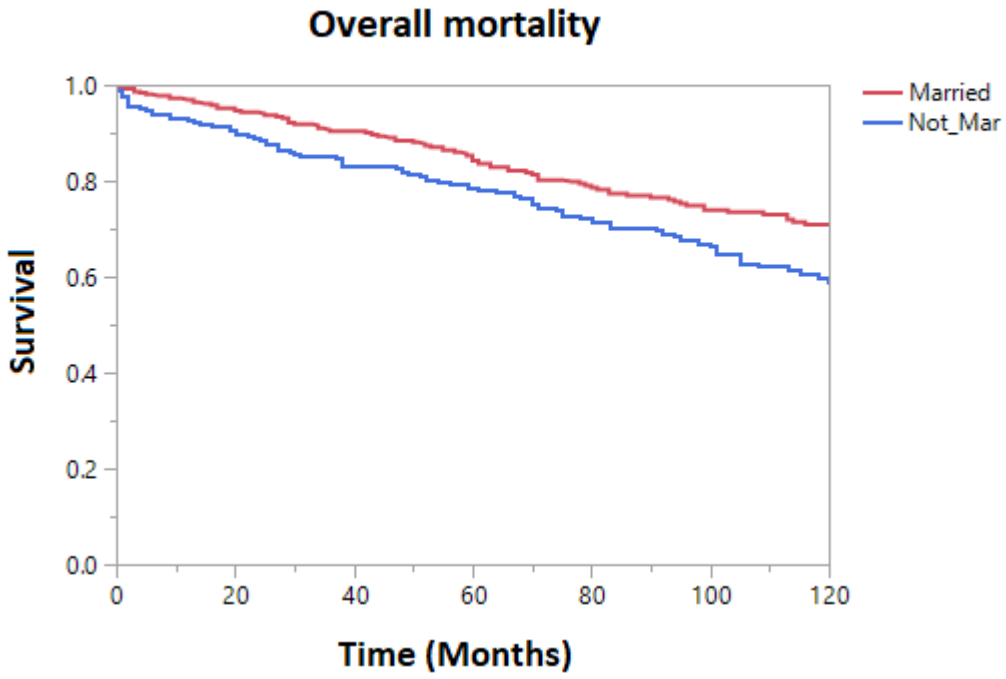
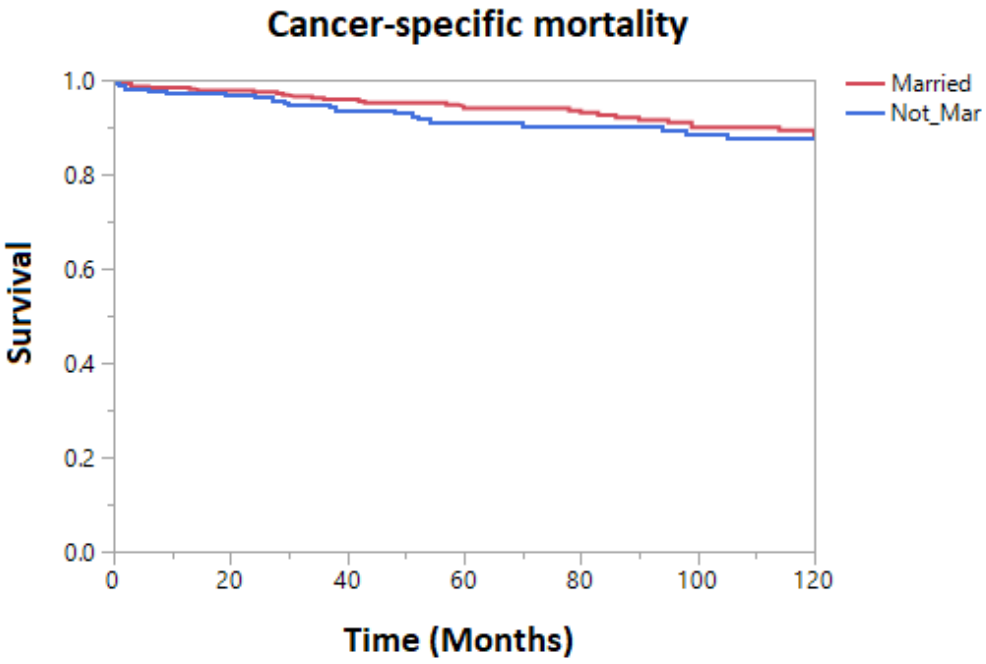


Figure 2: Kaplan-Meier estimates of cancer-specific mortality stratified by marital status



COX PROPORTIONAL HAZARDS ANALYSIS:

5-year follow-up: Patients who were 57 years or older at the time of diagnosis (HR 1.62; 95% CI 1.06-2.48; p=0.0254), and patients with distant metastasis at presentation (HR 3.75; 95% CI 2.04-6.90; p<0.0001) had statistically significant worse 5-year survival, after controlling for other possible confounders. Patients who subsequently underwent surgery (HR 2.57; 95% CI 1.15-5.58; p=0.0172) had statistically significant better overall survival rates after five years, compared to those who did not undergo surgery. These three characteristics are strong, independent predictors of survival. Unmarried patients have an increased risk of mortality within five years after cancer diagnosis compared to married patients (HR 1.35; 95% CI 0.88-2.06; p=0.1642) after controlling for age, race, sex, surgery, summary stage, and year of diagnosis, but it was not statistically significant (Table 2). The cancer-specific mortality was slightly lower in unmarried patients compared to married patients (HR 0.93; 95% 0.46-1.89; p=0.8505) but not statistically significant.

10-year follow-up: With a ten-year follow-up period, multivariate Cox regression analysis shows the following variables to be strong, independent predictors of overall survival – (1) Age <57 years (HR 1.97; 95% CI 1.42-2.73; p<0.0001); (2) Black population (HR 1.66; 95% CI 1.12-2.45; p=0.0114); (3) Unmarried patients (HR 1.43; 95% CI 1.02-1.99; p=0.0335); (4) Distant metastasis at presentation (HR 3.57; 95% CI 2.16-5.91; p<0.0001). **Unmarried patients have a statistically significant higher risk of overall mortality compared to married patients**. The Hazard ratio for cancer-specific mortality rate in the unmarried patient group is lower than that in the married group, but is not statistically significant (HR 0.82; 95% CI 0.45-1.52; p=0.5339).

The only statistically significant independent predictors of higher cancer-specific mortality are the presence of distant metastasis, and the unstaged group.

Table 2: Multivariate Cox regression analysis of variables associated with 5-year overall and 5-year cancer-specific mortality.

	OVERALL MORTALITY			PARATHYROID Ca SPECIFIC MORTALITY		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
YEAR OF DIAGNOSIS	0.99	0.967-1.010	0.2602	0.99	0.955-1.020	0.4407
AGE at Diagnosis						
- ≤57 yrs	1.00	Reference		1.00	Reference	
- >57 yrs	**1.62**	1.06-2.48	**0.0254**	1.29	0.64-2.59	0.4736
SEX						
- Male	1.00	Reference		1.00	Reference	
- Female	0.71	0.47-1.07	0.1057	1.15	0.57-2.31	0.6945
RACE						
- White	1.00	Reference		1.00	Reference	
- Black	1.43	0.86-2.38	0.1713	1.88	0.88-4.04	0.1041
- Hispanic	0.61	0.26-1.43	0.2590	0.31	0.04-2.36	0.2603
- Others	1.05	0.48-2.46	0.9133	0.59	0.08-4.48	0.6076
MARITAL STATUS						
- Married	1.00	Reference		1.00	Reference	
- Unmarried	1.35	0.88-2.06	0.1642	0.93	0.46-1.89	0.8505
STAGE						
- Localized	1.00	Reference		1.00	Reference	
- Regional Spread	1.07	0.66-1.72	0.7946	1.33	0.54-3.25	0.5368
- Distant mets	**3.75**	2.04-6.90	**<0.0001**	**12.27**	5.26-28.65	**<0.0001**
- Unstaged	1.80	0.79-4.09	0.1583	3.15	0.84-11.77	0.0874
SURGERY						
- Yes	1.00	Reference		1.00	Reference	
- No	**2.57**	1.18-5.58	**0.0172**	2.82	0.98-8.11	0.0538

Table 3: Multivariate Cox regression analysis of variables associated with 10-year overall and 10-year cancer-specific mortality.

	OVERALL MORTALITY			PARATHYROID Ca SPECIFIC MORTALITY		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
YEAR OF DIAGNOSIS	0.98	0.967-1.016	0.0705	0.98	0.955-1.011	0.2348
AGE at Diagnosis						
- ≤57 yrs	1.00	Reference		1.00	Reference	
- >57 yrs	**1.97**	1.42-2.73	**<0.0001**	1.54	0.85-2.79	0.1545
SEX						
- Male	1.00	Reference		1.00	Reference	
- Female	0.76	0.55-1.05	0.0928	1.18	0.65-2.14	0.5838
RACE						
- White	1.00	Reference		1.00	Reference	
- Black	**1.66**	1.12-2.45	**0.0114**	1.63	0.81-3.30	0.1746
- Hispanic	0.76	0.41-1.39	0.3747	0.47	0.11-2.00	0.3072
- Others	0.93	0.47-1.86	0.8423	1.22	0.36-4.13	0.7514
MARITAL STATUS						
- Married	1.00	Reference		1.00	Reference	
- Unmarried	**1.43**	1.02 -1.99	**0.0335**	0.82	0.45-1.52	0.5339
STAGE						
- Localized	1.00	Reference		1.00	Reference	
- Regional Spread	1.05	0.73-1.51	0.8067	1.39	0.66-2.92	0.3859
- Distant mets	**3.57**	2.16-5.91	**<0.0001**	**13.35**	6.24-28.58	**<0.0001**
- Unstaged	1.71	0.87-3.35	0.1196	**4.63**	1.62-13.23	**0.0043**
SURGERY						
- Yes	1.00	Reference		1.00	Reference	
- No	1.65	0.81-3.35	0.1682	1.92	0.70-5.28	0.2064

Discussion:

This study shows that parathyroid carcinoma patients who were married at the time of diagnosis have better overall survival rates compared to unmarried patients, at both 5 year and 10-year follow-up time periods from the date of diagnosis. This observation, however, is statistically significant at the 10-year follow-up period, but not at the 5-year follow-up period. The results are similar to survival statistics in patients in other types of cancer stratified by marital status. The presence of distant metastasis at diagnosis is a strong independent predictor of poor survival in both marital groups, in both the 5-year and 10-year follow-up periods. Patients in both groups who underwent surgery had significantly better overall and cancer-specific survival statistics at the 5-year follow-up end point, though this benefit is not significant at the 10-year follow-up end point. This inference adds to the already established fact that marriage plays a beneficial role in survival in patients with cancer.

It would have been more insightful to further stratify marital status into further groups - divorced, separated, widowed etc., but owing to the relatively small sample size, the marital status was only stratified into two groups – married and unmarried.

There are some limitations to our study. First, parathyroid carcinoma is a rare cancer with a low prevalence. But the available sample size had to be further reduced due to missing information on one or more variables of interest in some of the patients. Coding of the variables also different for different time periods, so patients with mismatched coding information also limited the sample size.

The sample size of the study is small compared to other studies of other carcinomas using data from the SEER database. This is because parathyroid cancer is relatively rare. Yet, since the SEER database is one of the largest cancer databases available, and previously published studies about parathyroid cancer epidemiology used smaller databases, this study would be utilizing one of the largest available cohorts of parathyroid cancer patients currently available anywhere.

Third, there is a possibility of selection bias, as patients who lived longer probably had more time to get married, hence enabling them to benefit from any potential protective and supportive effects of marriage.

Fourth, data on marital status in the SEER database only reflects the status at the time of cancer diagnosis. Information on whether a patient remained married, or became widowed, separated or divorced after the diagnosis is not available, and it would be reasonable to assume that a change in marital status after diagnosis would have an effect on the personal well-being and support structure of the patient. Hence it is not possible to treat marriage as a time-varying covariate. Information on the quality of the marriage is also not available, and would be potential confounder. Marital distress has been reported to have a variety of deleterious effect on health and immunity of an individual [20]. Patients might be married but the marriage might be harming the mental and emotional health of the patient. Religion might also play a role. Divorce is not permitted in certain religions. Some patients might remain legally married despite it breaking down, and unable to separate due to religious restrictions.

Data on serum calcium levels are not available, and hence cannot be adjusted for in predicting the cancer-specific survival. Although an elevated serum calcium level at the time of diagnosis is not a predictive factor for survival, monitoring serum calcium levels after surgery can help detect elevated levels, which are associated with an increased rate of recurrence of the cancer and hence survival [21].

Finally, this study is a retrospective cohort study. As an observational study, there could be other previously unknown confounding factors that were not accounted for in the initial data collection. Despite all these limitations, the data from the SEER database would still have been collected and stored with rigorous quality control measures by the National Cancer Institute, and provides an excellent and the most exhaustive source for demographic studies on parathyroid cancer outcomes.

Conclusion:

Marital status is a predictor of overall survival in patients with parathyroid cancer. It is not a statistically significant independent predictor for parathyroid cancer specific survival. Future research using a larger cohort and comprehensive data is needed to explore the relationship between marital status and survival among patients with parathyroid cancer.

REFERENCES:

1. Fujimoto Y, Obara T, Ito Y, Kanazawa K, Aiyoshi Y, Nobori M. **Surgical treatment of ten cases of parathyroid carcinoma: importance of an initial en bloc tumor resection**. World J Surg., 1984 Jun;8(3):392-400.
2. Hakaim AG, Esselstyn CB Jr. **Parathyroid carcinoma: 50-year experience at The Cleveland Clinic Foundation**. Cleve Clin J Med. 1993 Jul-Aug;60(4):331-5.
3. Koea JB, Shaw JH. **Parathyroid cancer: biology and management**. Surg Oncol. 1999 Nov;8(3):155-65.
4. Lo WM, Good ML, Nilubol N, Perrier ND, Patel DT. **Tumor Size and Presence of Metastatic Disease at Diagnosis are Associated with Disease-Specific Survival in Parathyroid Carcinoma**. Ann Surg Oncol. 2018 Sep;25(9):2535-2540.
5. Goswamy J, Lei M, Simo R. **Parathyroid carcinoma**. Curr Opin Otolaryngol Head Neck Surg. 2016 Apr;24(2):155-62.
6. Wang L, Wilson SE, Stewart DB, et al. **Marital status and colon cancer outcomes in US Surveillance, Epidemiology and End Results registries: does marriage affect cancer survival by gender and stage?** Cancer Epidemiol 2011;35:417–22.
7. National Cancer Institute. **Parathyroid Cancer Treatment (PDQ®)–Patient Version**. (2019, April 9). Retrieved from National Cancer Institute: https://www.cancer.gov/types/parathyroid/patient/parathyroid-treatment-pdq
8. Lee PK, Jarosek SL, Virnig BA, Evasovich M, Tuttle TM. **Trends in the incidence and treatment of parathyroid cancer in the United States**. Cancer. 2007 May 1;109(9):1736-41.
9. Durkheim E. **Suicide: A study in Sociology**. New York: Free Press; 1897.

10. Bai DS, Chen P, Qian JJ, et al. **Effect of marital status on the survival of patients with gallbladder cancer treated with surgical resection: a population-based study**. Oncotarget 2017;8:26404–13.

11. Tyson MD, Andrews PE, Etzioni DA, et al. **Marital status and prostate cancer outcomes**. Can J Urol 2013;20:6702–6.

12. Croft L, Sorkin J, Gallicchio L. **Marital status and optimism score among breast cancer survivors**. Support Care Cancer 2014;22: 3027–34.

13. Niu Q, et al. **The effect of marital status on the survival of patients with bladder urothelial carcinoma: A SEER database analysis**. Medicine. 2018 Jul;97(29):e11378.

14. Li Q, Gan L, Liang L, Li X, Cai S. **The influence of marital status on stage at diagnosis and survival of patients with colorectal cancer**. Oncotarget 2015;6:7339–47.

15. Lindstrom M. **Social capital, economic conditions, marital status and daily smoking: a population-based study**. Public Health 2010;124:71–7.

16. Gritz ER, Demark-Wahnefried W. **Health behaviors influence cancer survival**. J Clin Oncol 2009;27:1930–2.

17. Merrill RM, Johnson E. **Benefits of marriage on relative and conditional relative cancer survival differ between males and females in the USA**. J Cancer Surviv 2017;11:578–89.

18. Moreno-Smith M, Lutgendorf SK, Sood AK. **Impact of stress on cancer metastasis**. Future Oncol 2010;6:1863–81.

19. Antoni MH, Lutgendorf SK, Cole SW, et al. **The influence of biobehavioural factors on tumour biology: pathways and mechanisms**. Nat Rev Cancer 2006;6:240–8.

20. Jaremka LM, Glaser R, Malarkey WB, Kiecolt-Glaser JK. **Marital distress prospectively predicts poorer cellular immune function**. Psychoneuroendocrinology. 2013 Nov;38(11):2713-9.

21. National Cancer Institute. **About the SEER Registries**. (2019) Retrieved from https://seer.cancer.gov/registries/

22. Harari A, Waring A, Fernandez-Ranvier G, et al. **Parathyroid carcinoma: a 43-year outcome and survival analysis**. J Clin Endocrinol Metab. 2011 Dec;96(12):3679-86.