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ORIGINAL ARTICLE

Men in the US with Solid Pseudopapillary Carcinomas of the Pancreas Have Compromised Survival: A Population-Level Study of Outcomes

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ABSTRACT

Objective Studies of pancreatic solid pseudopapillary neoplasms are limited to institutional series. Outcomes and predictors of survival on a population-level remain unclear. **Methods** Patients with solid pseudopapillary carcinomas of the pancreas were selected from the SEER database (2000-2010), and incidence, characteristics, and survival evaluated. Data were analyzed with $\chi 2$ tests, ANOVA, the Kaplan Meier method, log-rank tests, logistic regression, and Cox proportional hazards. **Results** The diagnosis of SPCs has increased within the last decade. Men had a trend towards larger tumors (7.3 cm vs. 6.2 cm, P=0.282) with higher rates of extrapancreatic extension (37.5% vs. 25.3%, P=0.338), nodal metastasis (25.0% vs. 3.6%, P=0.076) and distant metastasis (18.8% vs. 9.5%, P=0.376) in comparison to women, although the differences failed to reach statistical significance. 5-year disease-specific survival in men was compromised in comparison to women (74.1% vs. 91.7%, P=0.026). After adjustment for age, gender, race, surgery, radiation, tumor location, tumor size, and extrapancreatic extension, nodal metastasis (hazard ratio 41.4, 95% confidence interval 2.3-753.1) and distant metastasis (hazard ratio 9.0, 95% confidence interval 1.8-45.4) remained independent predictors of disease-specific survival. Subset analysis of patients with distant disease revealed a trend towards decreased 5-year disease-specific survival in men in comparison to women (20.0% vs. 71.4%, P=0.072). **Conclusions** Solid pseudopapillary carcinomas are an increasingly diagnosed entity. Even with malignant disease, prognosis is excellent in women; however, men in the US with solid pseudopapillary carcinomas have compromised survival, possibly due to higher rates of nodal and distant metastasis. Treatment and follow-up strategies should be tailored accordingly.

INTRODUCTION

Solid pseudopapillary neoplasms (SPNs) of the pancreas are rare tumors accounting for 1-3% of pancreatic malignancies [1]. Well circumscribed lesions frequently exhibiting cystic degeneration, hemorrhage, and necrosis, SPNs are microscopically characterized by small uniform cells arranged in pseudopapillae due to cellular degeneration around a fibrovascular stalk [2-6]. The largest American surgical series of SPNs from Johns Hopkins University and Memorial Sloan-Kettering Cancer Center captured 51 and 45 patients, respectively, while a meta-analysis summarized the experience of 718 patients in the English literature [7-9]. Approximately 85% of patients with SPNs are female with a mean age in the 30s [7-9]. Patients most commonly present with abdominal pain, and on axial imaging, lesions are round or oval, well-circumscribed, and encapsulated with frequent calcifications [8]. Prognosis is generally excellent with low recurrence rates, while reports of mortality are rare [2-8, 10, 11]. Resection of SPNs using laparoscopic and robotic techniques has been described with success [12-14].

Previously referred to as solid pseudopapillary tumors, solid cystic tumors, papillary cystic tumors, solid and papillary epithelial neoplasms, or Frantz tumors, SPNs have undergone multiple changes in naming and classification since its first description by Frantz in 1959 [1, 15]. As recently as the World Health Organization (WHO) 2000 classification, SPNs were classified as either benign (solid pseudopapillary neoplasm, ICD-O-3 code 8452/1) or malignant (solid pseudopapillary carcinoma, SPC, ICD-O-3 code 8452/3), although strict criteria for malignancy have never been established [16]. However, recent advances in the molecular pathogenesis of SPNs have undermined the distinction between benign and malignant disease. Nearly all SPNs have been shown to exhibit abnormal nuclear and cytoplasmic accumulation of β-catenin caused by missense mutations in exon 3 of the *CTNNB1*, inhibiting phosphorylation and degradation of β-catenin [17, 18]. Therefore, the distinction between benign and malignant SPNs has been replaced by the belief that all SPNs are malignant. This is reflected in the fourth edition of the WHO 2010 classification, which only recognizes ICD-O-3 code 8452/3 as the proper designation for SPNs of the pancreas.

While most patients with SPNs have excellent outcomes, a subset of patients has compromised survival. Characterization of this population has been limited by

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sample size, and predictors of survival have not been analyzed. Studies of outcomes through surgical series are limited by the excellent prognosis afforded by resectable disease, and although the relation between male gender and aggressive behavior in SPNs has been studied with mixed conclusions, an association with prognosis has never been made [2, 7, 8]. The most recent edition of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database captures data from 1973 to 2010 and is restricted to malignant tumors. As such, only tumors with aggressive behavior classified as solid pseudopapillary carcinomas (SPCs) were captured by SEER during this time period. While the distinction between benign and malignant disease in SPNs no longer exists, our study nevertheless represents the largest series of SPNs with aggressive behavior to date and the first to analyze these tumors on a population-level with a specific focus on the impact of gender on characteristics and survival.

METHODS

Data Source and Study Participants

The data sources for this study include the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, which provides population-based data on cancer incidence and survival from 18 registries throughout the United States and represents 28% of the United States population [19].

Patients were selected from all 18 registries using the ICD-O-3 code 8452/3 ("solid pseudopapillary carcinoma"). Our study was further restricted to patients diagnosed with SPCs on histology from 2000-2010 in order to maintain consistency in diagnosis over the study period. Because the SEER database is restricted to tumors with an ICD-O-3 behavior code of 2 (in situ) or 3 (malignant), SPNs classified as benign were necessarily excluded from our study. Incidence data were obtained from the SEER 18 registries, which offer the most complete incidence data for this time period. Data regarding demographic, clinical, and pathologic variables of interest were collected. Data on tumor grade was only available for 28.2% of patients and was deemed insufficient for analysis. Extrapancreatic extension was defined as tumor extension into peripancreatic tissue or adjacent organs or vessels. Distant metastasis reflects metastasis discovered at the time of diagnosis. Patients were classified as having localized, regional, or distant disease based on SEER historic stage. In this system, localized disease is defined as tumors confined entirely to the pancreas. Regional disease is defined as tumors with extrapancreatic extension, metastasis to regional lymph nodes, or both. Distant disease is defined as tumors with spread to parts of the body remote from the primary tumor. Survival time was calculated as time in years from diagnosis until death, date last known to be alive, or December 31, 2010, whichever came first.

Statistical Analysis

Summary statistics were used to describe baseline characteristics. Chi square tests and analysis of variance were used to analyze categorical and continuous variables, respectively. Fischer's exact test was used for analyze categorical variables with expected values less than 5. Survival was analyzed using the Kaplan-Meier method, and the log rank test was used to determine differences in survival that were statistically significant. Cox proportional hazards was used to identify factors independently associated with survival. Binary logistic regression was used to identify predictors of extrapancreatic extension, nodal metastasis, and distant metastasis. Variables with a level of significance of $P<0.1$ on univariate analysis were included in multivariate analysis. All tests were two-sided, and $P<0.05$ was considered statistically significant. Data with missing values were excluded from statistical analysis.

Incidence and trend analysis were performed by SEER*Stat version 8.1.2 obtained from SEER (Bethesda, MD). All other analysis was performed with SPSS version 19 (SPSS, Inc., Chicago, IL). Because SEER data is publicly available and institutional data was recorded without identifiers, our study was deemed to be exempt from institutional review board approval.

RESULTS

Incidence

110 cases of SPC were recorded in the SEER 18 registries from 1973 to 2010, 100 of which were diagnosed based on histology from 2000 to 2010. The number of cases of SPC diagnosed annually in the SEER 18 registries is shown in **Figure 1**. In 2010, SPCs accounted for 0.15% (16 of 10,681) of pancreatic malignancies identified in the SEER 18 registries. Patients were followed for up to 22 years, with a mean follow-up of 3.73 years.

Characteristics

Demographic, clinical, and pathologic characteristics are summarized in Tables 1 and 2. 84.0% of patients were women. Mean age at diagnosis was significantly higher in men in comparison to women (48.4 *vs.* 36.8 years, P=0.008). 52.0% were of non-white race (Hispanic, Asian, black, or other). Men also had a trend towards larger tumors (7.3 cm *vs.* 6.2 cm, P=0.282) with higher rates of extrapancreatic extension (37.5% *vs.* 25.3%, P=0.338), nodal metastasis (25.0% *vs.* 3.6%, P=0.076) and distant metastasis (18.8% *vs.* 9.5%, P=0.376) in comparison to women, although the differences failed to reach statistical significance. No significant differences between men and women were observed with respect to race or tumor location. No significant predictors of extrapancreatic extension, nodal metastasis, or distant metastasis were identified.

Survival

The disease-specific mortality rate in our cohort was 8.0%, 25.0% in men and 5.3% in women. 5-year disease-specific survival (DSS) in men was compromised in comparison to women (74.1% *vs.* 91.7%, P=0.026). After adjustment for age, race, surgery, radiation, tumor location, tumor size,

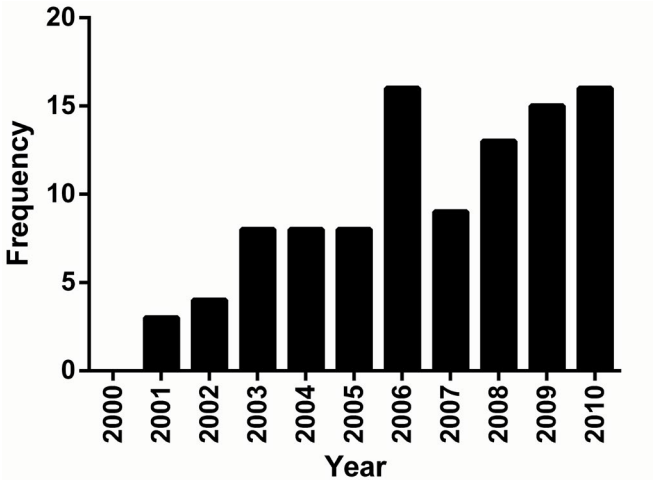

Figure 1. Cases of SPC diagnosed by year (SEER 18 registries, 2000-2010); SPC, solid pseudopapillary carcinoma, SEER, Surveillance, Epidemiology, and End Results database

extrapancreatic extension, and nodal metastasis, male gender (hazard ratio [HR] 4.7, 95% confidence interval [CI] 1.0-16.5) and distant metastasis (HR 4.7, 95% CI 1.3-16.8) remained independent predictors of OS. Age ≥65 years, male gender, no surgery, extrapancreatic extension, nodal metastasis, and distant metastasis were predictors of disease-specific survival (DSS) on univariate analysis (**Figure 2**). However, after adjustment, male gender was not a predictor of survival, and only nodal metastasis (HR 41.4, 95% CI 2.3-753.1) and distant metastasis (HR 9.0, 95% CI 1.8-45.4) remained independent predictors of DSS (Table 3). No significant differences in overall (P=0.501) or disease specific survival (P=0.401) were observed with various extents of resection including enucleation, partial pancreatectomy, pancreaticoduodenectomy, or total pancreatectomy.

Subset analysis of patients with localized, regional, and distant disease respectively revealed no significant differences in DSS between men and women with localized (P=0.677) or regional (P=0.480) disease. However, a trend towards decreased 5-year DSS was observed in men in comparison to women (25.0% *vs.* 71.4%, P=0.073) in patients with distant disease (**Figure 3**).

DISCUSSION

While the distinction between benign and malignant disease in SPNs no longer exists, our study nevertheless represents the largest series of SPNs with aggressive behavior to date and the first to analyze these tumors on a population-level. In addition to highlighting that the diagnosis of these tumors is being made with increasing frequency, we observed a trend towards more aggressive features in men in comparison to women. Even in the setting of malignant disease, we observed that prognosis is excellent in women; however, men classified as having SPCs had compromised OS and DSS.

The changing classification of SPNs has greatly impacted how these tumors are recorded in SEER. Because the SEER database is restricted to malignant tumors, data regarding "benign" SPNs were not recorded during the study period, and therefore our cohort is comprised of tumors deemed to be "malignant". Admittedly, strict criteria to define malignancy in SPNs were never established. While the WHO 2000 classification of SPNs suggested perineural invasion, angioinvasion, or deep invasion into surrounding tissue indicated malignancy, a study from Memorial Sloan Kettering Cancer Center (MSKCC) defined malignancy by local unresectability, regional or distant metastasis, or disease recurrence. [7, 16] Although it is impossible to derive from SEER what criteria for malignancy were utilized for each patient in our cohort, the low relative incidence of SPCs in our study (0.15% of pancreatic malignancies in 2010 in SEER) and poorer outcomes observed in comparison to the SPN literature confirm that our study captures a subpopulation of patients with SPNs with aggressive behavior and represents the largest analysis of these patients to date.

With respect to incidence, various institutional series have

Table 1. Demographic and Clinical Characteristics of SPCs in men *vs.* women, SEER 2000-2010

	Male, n=16 n (%)	Female, n=84 n (%)	P value
Age			0.008
Mean (SEM)	48.4 (4.1)	36.8 (1.7)	
Age < 18	0 (0)	8 (9.5)	
Age 18-44	6 (37.5)	52 (57.1)	
Age 45-64	6 (37.5)	28 (31.0)	
Age ≥65	4 (25.0)	2 (2.4)	
Race			0.381
White	8 (50.0)	40 (47.6)	
Hispanic	4 (25.0)	18 (21.4)	
Asian	0 (0)	12 (14.3)	
Black	4 (25)	13 (15.5)	
Other/Unknown	0 (0)	1 (1.2)	
Surgery			0.161
No surgery	3 (30.0)	12 (17.8)	
Enucleation	2 (12.5)	4 (4.8)	
Partial pancreatectomy	3 (25.0)	37 (46.7)	
Pancreaticoduodenectomy	3 (15.0)	21 (24.4)	
Total pancreatectomy	5 (30.0)	8 (8.9)	
Other	0 (0)	2 (2.2)	
Lymph node examination[a]			0.307
0 lymph nodes examined	5 (38.5)	17 (23.6)	
≥ 1 lymph node examined	8 (61.5)	55 (76.4)	
Radiation			0.484
None	16 (100)	78 (92.9)	
External beam radiation	0 (0)	4 (4.8)	
Unknown	0 (0)	2 (2.2)	
Overall survival			0.007
1 year	73.7	94.9	
5 year	66.3	90.0	
Disease-specific survival			0.026
1 year	74.1	97.1	
5 year	74.1	91.7	

Values represent frequency and percentages of given sample sizes respectively unless otherwise designated. Unknowns were excluded from statistical analysis. SPC solid pseudopapillary carcinoma; SEER Surveillance, Epidemiology, and End Results database; SEM standard error of the mean

[a]Represents percentage of patients who underwent surgery

Table 2. Pathologic Characteristics of SPCs in men *vs.* women, SEER 2000-2010.

	Male (n=20)	Female (n=90)	P value
Location			0.708
Head	5 (31.3)	25 (29.8)	
Body	2 (12.5)	5 (6.0)	
Tail	8 (50.0)	42 (50.0)	
Other	1 (6.3)	12 (14.3)	
Size			0.282
Mean (cm) (SEM)	7.3 (1.0)	6.2 (0.4)	
0-2.0 cm	1 (6.3)	8 (9.5)	
2.1-5.0 cm	5 (31.3)	30 (35.7)	
5.1-10.0 cm	5 (31.3)	24 (28.6)	
> 10 cm	5 (31.3)	13 (15.5)	
Unknown	0 (0)	9 (10.7)	
Extension			0.601
Intrapancreatic	9 (56.3)	55 (66.3)	
Extrapancreatic	6 (37.5)	21 (25.3)	
Unknown	1 (6.3)	7 (8.4)	
Nodal metastasis[a]			0.076
0 positive lymph nodes	6 (75.0)	53 (96.4)	
≥ 1 positive lymph node	2 (25.0)	2 (3.6)	
Distant metastasis			0.557
None	12 (75.0)	70 (83.3)	
Distant metastasis	3 (18.8)	8 (9.5)	
Unknown	1 (6.3)	6 (7.1)	

Values represent frequency and percentages of given sample sizes respectively unless otherwise designated. Unknowns were excluded from statistical analysis. SPC solid pseudopapillary carcinoma; SEER Surveillance, Epidemiology, and End Results database; SEM standard error of the mean

[a]Represents percentage of patients who underwent nodal examination

Table 3. Multivariate analysis of DSS in SPCs, SEER 2000-2010.

	Hazard Ratio	95% CI	P value
Nodal metastasis			
Lymph nodes not examined	11.2	1.3-96.2	.028
0 positive lymph nodes	1.0	-	-
≥1 positive lymph node	41.4	2.3-753.1	.012
Distant metastasis			
No	1.0	-	-
Yes	9.0	1.8-45.4	.008

noted that the diagnosis of SPNs has increased, with the majority of patients having been diagnosed within the last decade [13, 20]. This has been attributed to increasing awareness of SPNs after classification by the WHO in 1996. Our data from the SEER 18 registries shows an increasing number patients in the United States classified as having SPCs annually. Whether this is reflects a true increase in incidence, increased awareness of these neoplasms, or more frequent use of axial imaging is unclear.

Clinical and radiologic predictors of aggressive behavior in SPNs remain elusive, although large tumor size and male gender have been observed with greater frequency in tumors with aggressive behavior [5, 7, 21]. In our cohort of patients classified as having SPC, 81.1% of patients were women with approximately 50% of tumors located in the tail of the pancreas. These figures are comparable with published series of SPNs, which suggests that gender and tumor location are not predictive of aggressive behavior [7, 8]. However, male gender did appear to be associated with a trend towards increased rates of distant metastasis as well as nodal metastasis in our study [9]. Although not statistically significant, mean tumor size in men was larger than that of women in our study. Additionally, a mean tumor size of 6.4 cm is larger than the mean of 5 cm reported in the literature, and therefore large tumor size may be a predictor of malignancy as previously reported [2, 5, 7, 8, 22]. Race was not shown to be a predictor of malignancy in an Australian series, and in the two largest American series, race was not analyzed [7, 8, 11]. In our study, less than half of patients were white, suggesting that minority race may warrant further study as a predictor of aggressive behavior in an American population. No significant predictors of extrapancreatic extension, nodal metastasis, or distant metastasis were identified in our study on logistic regression, which was likely limited by sample size and the lack of inclusion of "benign" SPNs in SEER during the study period.

The study of clinical outcomes in SPNs has been limited by sample size, and while multiple studies have analyzed predictors of aggressive behavior, none have formally evaluated predictors of survival.[2,5,7] 5-year survival in SPNs has been estimated to be 95%. Furthermore, even among patients with aggressive tumor behavior and distant metastasis, mortality is rare [5, 7, 9]. In our cohort of patients classified as having SPC and therefore aggressive tumor behavior, women had excellent outcomes with 5-year DSS of 91.7%. Survival in men, however, was poorer, with a 5-year DSS of 74.1% (P=0.026). However, while male gender was an independent predictor of OS, it was not an independent predictor of DSS after controlling for nodal and distant metastasis. This suggests that differences in survival may be attributable to higher observed rates of nodal and distant metastasis in men, and that stage for stage, outcomes between men and women are equivalent. While a subset analysis of patients with distant disease revealed a trend towards compromised DSS in men, this difference in survival did not reach statistical significance.

Surgery is the mainstay of treatment for SPNs, and resection using laparoscopic and robotic techniques has been described with success [12-14]. In our study, surgery was clearly associated with improved outcomes, and although our study was retrospective, aggressive resection of disease appears warranted. More radical resection has been proposed in men with SPNs due to higher likelihood of harboring aggressive disease [2]. While limited by a small sample size, our study shows in the US that men may have higher rates of extrapancreatic extension, nodal metastasis, and distant metastasis, and therefore may more frequently require more radical resection. Notably, only 1 of 3 men with distant metastasis underwent surgery while 5 of 8 women with distant metastasis underwent surgery. In the setting of reported long term survival after resection of distant metastasis, this may account for the trend towards compromised DSS in men with distant disease [9].

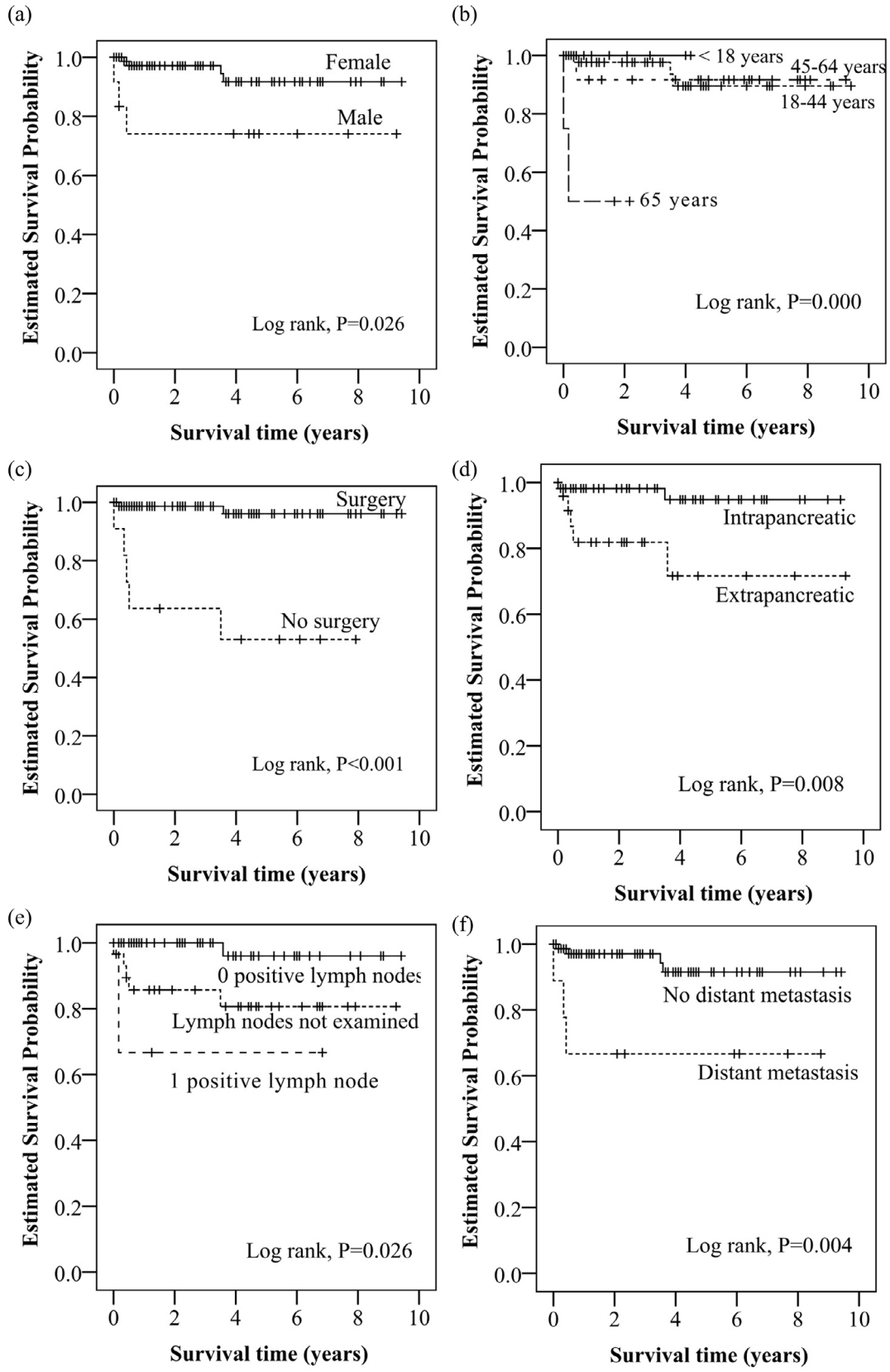

Figure 2. Disease-specific survival of SPCs by **(a.).** gender, **(b.).** age, **(c.).** surgery, **(d.).** extrapancreatic extension, **(e.).** nodal status, and **(f.).** distant metastasis; SPC, solid pseudopapillary carcinoma

The limitations of this study include those inherent to the SEER database, such as coding errors, limited data for certain variables, and lack of data on variables not collected by SEER. As discussed, SPCs as reported by SEER do not encompass the entire spectrum of disease, and represent a subpopulation of patients with aggressive tumor behavior. This situation is similar to that of pancreatic neuroendocrine tumors, and standard approaches of recording these tumors to capture the full spectrum of disease in SEER would benefit future analyses of the SEER

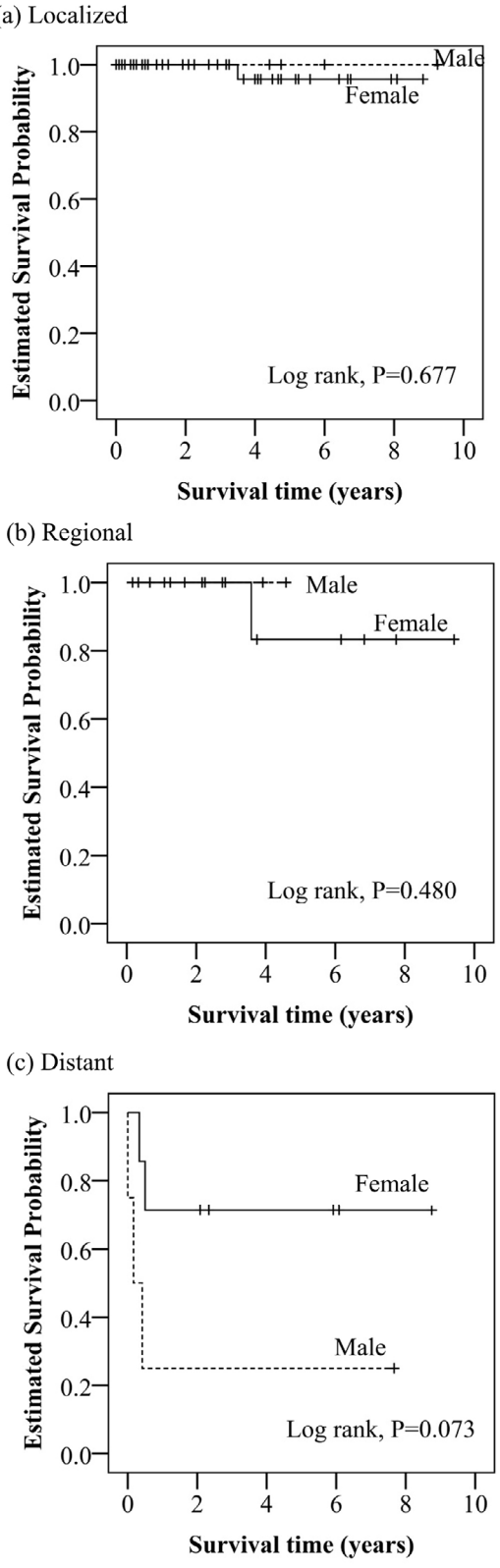

Figure 3. Disease-specific survival of SPCs by gender in the setting of (a.). localized, (b.). regional, or (c.). distant disease; SPC solid pseudopapillary carcinoma

database [23]. Furthermore, because only a fraction of SPNs are recorded in SEER, the resulting small sample size limits our statistical power, and therefore, our study was insufficiently powered to definitively detect higher rates of aggressive features in men and the impact of gender on DSS. Nevertheless, we believe the trends in aggressive behavior and compromised survival observed in men are clinically significant and worthy of future study. The strengths of this study include its use of population-level data and the largest sample of SPCs to date.

Overall, our study confirms on a population-level that the number of patients classified as having SPCs is increasing, and that while prognosis is excellent in women, men in the US exhibit compromised disease specific survival, likely attributable to higher rates of aggressive tumor behavior. More aggressive resection and follow-up in men may be appropriate. Additional detailed studies are necessary to determine whether gender should alter the aggressiveness of resection and closeness of follow-up. Currently, SPNs are regarded as malignant and all should be captured by SEER. Follow-up of SPNs in SEER is recommended as we develop more experience with this rare disease.

Conflict of interest

The authors have no conflict of interest to declare.

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