Technology in Cancer Research & Treatment
Volume 21: 1-13

DOI: 10.1177/15330338221106533
journals.sagepub.com/home/tct
SAGE

Epidemiology, Treatment, and Outcome of Pancreatic Squamous Cell Carcinoma and Pancreatic Adenocarcinoma: A Propensity Score-Matching Analysis Based on SEER-Database

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Abstract

Background: Pancreatic squamous cell carcinoma (PSCC) is a rare pancreatic malignancy compared to most common pancreatic adenocarcinoma (PAC). **Aims:** To analyze the prognostics factors of PSCC and compare PAC with PSCC in demographic patterns, clinicopathologic characteristics and treatment modalities. **Methods:** Data of PSCC and PAC patients from January 1, 2004 to December 31, 2015 were extracted from Surveillance, Epidemiology and End Results (SEER) database for case-control study. Kaplan-Meier method and Cox proportional hazards analysis were used in survival analysis. A 1:3 propensity-score matching (PSM) was performed to compare the overall survival (OS) and cancer specific survival (CSS) between PAC and PSCC in each variable. **Results:** PAC patients (n = 38 968) and PSCC patients (n = 124) were analyzed. After PSM, 372 PAC patients and 124 PSCC patients were obtained. PSCC tends to happen to elders, white and female with a predilection site of pancreatic head, followed by tail, then body. PSCC have a higher proportion to be poorly differentiated and metastatic when diagnosed. The prognosis of PSCC patients was significantly worse than PAC patients in both univariate and multivariate analyses. Surgery and chemotherapy were independent prognostic factors for PSCC. **Conclusions:** PSCC patients were identified associated with a worse prognosis than PAC patients. PSCC tend to be poorly differentiated and more easily to be metastatic. Surgery and chemotherapy may be effective therapies to improve the OS of PSCC significantly.

Keywords

pancreatic squamous cell carcinoma, pancreatic adenocarcinoma, propensity-score matching, prognosis, survival

Abbreviations

AC, Adenocarcinoma; AJCC, American Joint Committee on Cancer; CI, confidence interval; CSS, cancer specific survival; HR, hazard ratio; ICD-O-3, International Classification of Diseases for Oncology, third edition; M, metastasis; N, node; NCDB, National Cancer Database; OS, overall survival; PAC, pancreatic adenocarcinoma; PSCC, pancreatic squamous cell carcinoma; PSM, propensity-score matching; RECORD, REporting of studies Conducted using Observational Routinely-collected Data; SCC, squamous cell carcinoma; SEER, Surveillance, Epidemiology and End Results; T, tumor

Received: December 15, 2021; Revised: April 20, 2022; Accepted: May 25, 2022.

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Introduction

Pancreatic squamous cell carcinoma (PSCC) is a rare exocrine pancreatic malignancy, accounting for 0.5% to 3.5% of all pancreatic neoplasms.[1,2] Chronic inflammation (ex. chronic pancreatitis) causes malignant metaplasia of ductal columnar cells to squamous cells, which is the leading cause of PSCC.[3] Besides, malignant differentiation of a progenitor cell into squamous cell carcinoma (SCC) and cancerization of an aberrant squamous cell are possible theories inducing PSCC.[4] Due to the rarity of PSCC, other common histologic types should always be excluded before the identified diagnosis of it.[5] Pancreatic adenocarcinoma (PAC) is the most frequent pancreatic malignancy which consists of 90% primary pancreatic cancers.[6] Based on the data available, male, black, and elders have a higher incidence suffering from pancreatic cancers, which suits PAC as well.[7,8] Patients in developed countries acquire higher mortality and incidence rate than developing countries.[9]

Nowadays, the epidemiology and clinicopathologic characters of PAC have been widely explored while studies focusing on PSCC are documented in case reports and retrospective studies with small sample size.[2,5,10] Given the uncommon disease characters and a lack of clinical experience, information on treatment patterns and survival outcomes remains limited. Treatment modalities of PSCC are similar to that of PAC and there is no standard of care for it.[11] Surgery is still the mainstay treatment when tumors are operable.[12] Chemotherapy is always applied as neoadjuvant therapy or to PSCC patients without indications of operation.[13] However, the therapeutic effects to PSCC have not been systemically reviewed. Therefore, in our case-control study, we analyze the survival and potential risk factors of PSCC, comparing the differences between PSCC and PAC based on Surveillance, Epidemiology and End Results (SEER) database, in search for better treatment modalities for it.

Materials and Methods

Patients and Data Collection

Patients diagnosed with PSCC and PAC between January 1, 2004 and December 31, 2015 in SEER Research Plus Data, 18 registries were enrolled for our case-control study. PSCC and PAC were defined according to the International Classification of Diseases for Oncology, third edition (ICD-O-3). Morphology codes used in SCC were 8070/3-8076/3 and in adenocarcinoma (AC) were 8140/3, 8141/3, 8211/3, 8480/3, 8481/3.[14,15] Topographical codes were C25.0 (Head), C25.1 (Body), C25.2 (Tail), C25.3 (Duct), C25.7 (Other specified parts), C25.8 (Overlapping lesions), C25.9 (NOS). TNM stage was recorded according to the 6th edition of American Joint Committee on Cancer (AJCC). Patients met all the following criteria were eligible: (1) age ≥ 18; (2) diagnosed with primary PAC or PSCC; (2) survival time ≥ 1 month; (3) complete information on demographics, clinicopathologic characteristics, treatment, and survival. Patients with unknown race, SEER stage, TNM stage, survival time < 1, age < 18, diagnosis without positive exfoliative cytology, microscopic or histological confirmation were excluded (Figure 1).

Variables

Age was defined as categorical variables divided as following intervals: ≤ 40; 40-60; >60. Besides, categorical variables abstracted from SEER also include sex, race, primary location, marital status, SEER stage (reginal, localized, distant disease), grade, TNM stage, treatment modalities (surgery, chemotherapy, radiation therapy).

Data Analysis

Categorical variables were expressed as counts and percentages. Unordered categorical variables of demographics and clinicopathological characteristics were compared by chi-square test while ordered categorical variables were compared by rank sum test. OS and CSS are outcome variables. OS represents the lifetime which is ceased because of any reasons while CSS documents death caused by cancer. Propensity-score matching (PSM) was performed to eliminate the influence of confounding factors using logistic regression. A 1:3 matching between patients with PAC and PSCC were accomplished using the nearest neighbor matching method with a caliper width equal to 0.20 standard deviation of logit of propensity score. Matched variables contain all the categorical variables which are statistically significant in multivariate analyses of PSCC and PAC cohorts before PSM (Tables 1 and 2; Supplementary Table 1). Kaplan-Meier analyses were performed to analyze OS and CSS. Survival curves of treatment modalities were compared by log-rank test. Univariate and multivariate cox proportional hazards analyses were used in multiple variables for suspicion of risk factors. PSM was performed by R version 3.6.2 (http://www.R-project.org). Statistical analysis was conducted by SPSS version 25 (IBM). $P < .05$ indicated statistical significance. The reporting of this study conforms to RECORD guidelines.[16]

Results

Demographic Patterns and Clinicopathologic Characteristics of Study Cohort

A total number of 39 092 patients who met the inclusive criteria were eligible in this study, consisting of 99.7% PAC patients (n = 38 968) and 0.3% PSCC patients (n = 124). After 1:3 PSM, 124 PSCC patients and 372 PAC patients were obtained (Figure 1). Baseline characters of eligible patients were enumerated in Table 3. More than half of patients with PSCC were female while male accounts for a larger proportion in patients with PAC. PSCC was most likely to invade the head of pancreas (46.0%), followed by body (23.4%), then tail (19.4%). In

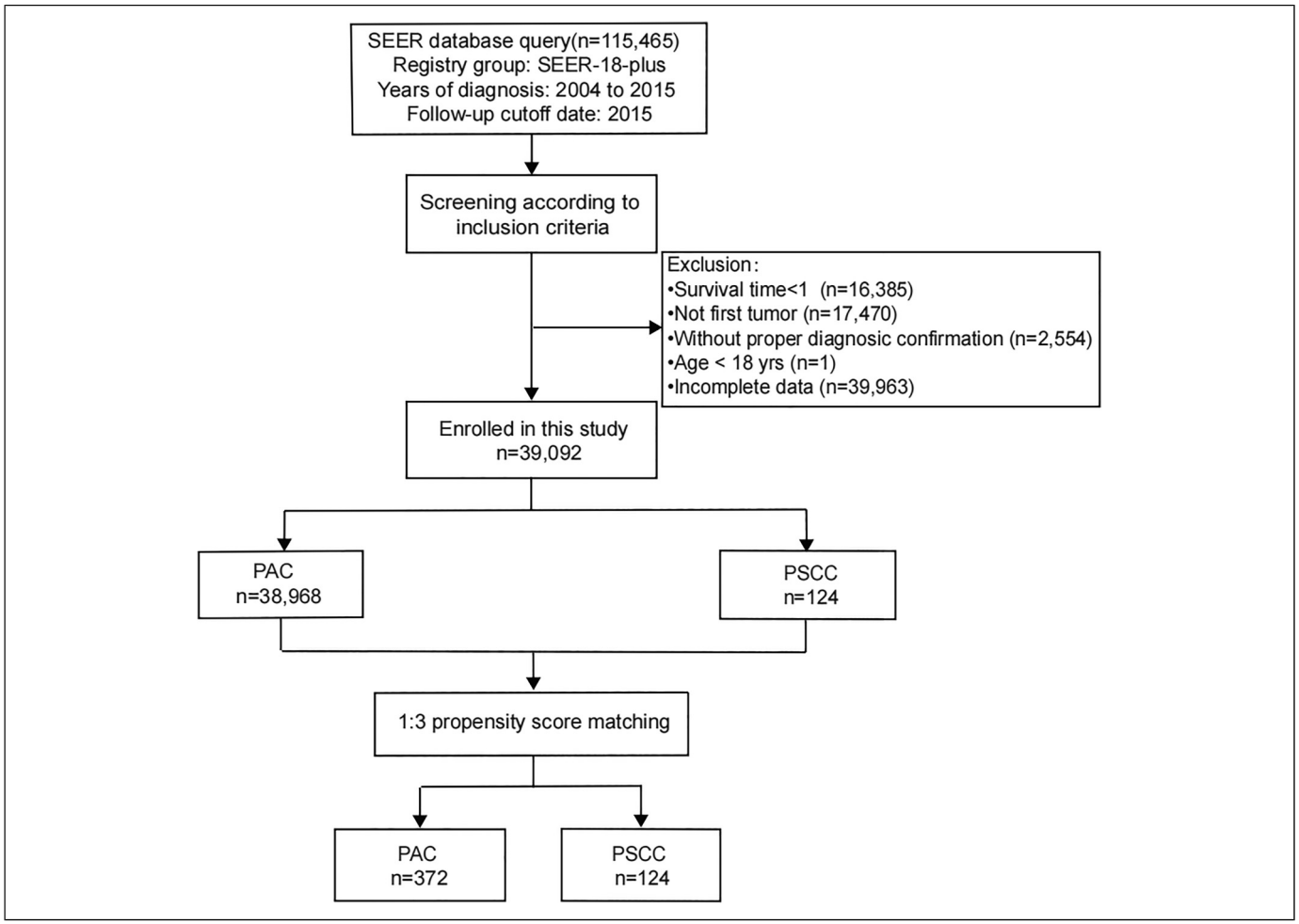

Figure 1. Flow diagram showing process of selecting patients.
Abbreviations: SEER, surveillance, epidemiology, and end results; T, tumor; N, lymph node; M, metastasis.

addition, PSCC had a higher tendency to be poorly differentiated than PAC. Compared with PAC, liver metastasis occurred more frequently in patients with PSCC. In PSCC patients, liver was the most common site in single-organ metastasis (86.5%) (Figure 2a). Similar trend was observed in PAC patients with a proportion of 71.2% to liver and 9.0% to lung (Figure 2b). Double-organ metastases mostly occurred in liver and lung both in PAC and PSCC patients. Patients with 4-organ metastases occupied 0.1% in PAC patients while there were no 4-site metastases in PSCC patients.

Similarly, PSCC had a higher potential to metastasize distantly. No statistically significant differences were detected in sex, race, SEER stage, TNM stage, metastasis to bone, brain and lung between PAC and PSCC patients. Chemotherapy was the most common treatment modality applied in both groups. Besides, radiation therapy and surgery were conducted less in patients with PSCC than PAC. After the PSM of age, race, primary location, marital status, SEER stage, TNM stage, grade, metastasis to bone, brain and liver, surgery, radiation therapy and chemotherapy, there was no statistically significant difference between PSCC and PAC.

Survival Analysis of PSCC

In univariate analysis of PSCC patients, distant metastasis in SEER stage (HR = 2.603; 95%CI, 1.736-3.904; $P < .001$) and metastasis in TNM stage (HR = 2.071; 95%CI, 1.460-2.938; $P < .001$) were prognostic factors which increased the risk of death (Table 1). Conduction of surgery (4 months vs 21 months, HR = 0.260; $P < .0001$) was associated with improved OS (Figure 3a and d). Similar trend was also observed in CSS (4 months vs 25 months, HR = 0.244; $P < .0001$). Higher mOS (2 months vs 5 months; HR = 0.806; $P = .25$) and CSS (2 months vs 6 months; HR = 0.771; $P = .17$) was achieved with the application of chemotherapy in PSCC patient (Figure 3c and f). Patients with tumors located in overlapping anatomical region of pancreas and tumors metastasizing distantly were associated with a significant worse prognosis. As for organs of metastasis, liver indicated a strong correlation to worse prognosis. After adjusting the confounding factors of each variable, in multivariate analysis, surgery (HR = 0.156; 95%CI, 0.071-0.346; $P < .001$) and chemotherapy (HR = 0.481; 95%CI, 0.294-0.787; $P = .004$) were independent predictive factors for better prognosis.

Table 1. Univariate and Multivariate Cox Analyses of Patients With PSCC Before PSM.

Characteristics	Univariable Hazard ratio	95.0% CI	*P* value	Multivariable Hazard ratio	95.0% CI	*P* value
Age						
Age (≤40)	Reference			Reference		
Age (40-60)	1.393	0.494-3.927	.531	0.790	0.259-2.406	.678
Age (>60)	1.852	0.674-5.087	.232	1.447	0.492-4.257	.502
Sex						
Male	Reference					
Female	0.945	0.655-1.363	.761			
Race						
White	Reference			Reference		
Black	1.575	0.954-2.603	.076	2.111	1.198-3.721	**.010**
Other	0.921	0.502-1.690	.791	0.849	0.436-1.651	.629
Primary location						
Head	Reference			Reference		
Body	0.983	0.618-1.564	.942	0.791	0.470-1.331	.378
Tail	1.217	0.734-2.020	.447	0.923	0.512-1.664	.790
Overlapping	2.665	1.376-5.161	**.004**	1.756	0.771-3.997	.180
NOS	1.244	0.388-3.995	.713	0.568	0.149-2.160	.407
Marital status						
Married	Reference					
Unmarried	0.938	0.585-1.502	.790			
Unknown	0.567	0.139-2.309	.428			
SEER stage						
Regional	Reference					
Localized	0.993	0.356-2.772	.99			
Distant	2.603	1.736-3.904	**<.001**			
Grade						
Well differentiated	Reference					
Moderately differentiated	0.675	0.179-2.549	.562			
Poorly differentiated	1.134	0.345-3.723	.836			
Undifferentiated	0.586	0.098-3.507	.558			
Unknown	2.001	0.623-6.429	.244			
T						
1	Reference			Reference		
2	1.069	0.145-7.879	.948	0.737	0.084-6.469	.783
3	0.669	0.092-4.875	.692	0.693	0.079-6.089	.741
4	0.974	0.133-7.164	.980	0.669	0.078-5.746	.714
N						
0	Reference			Reference		
1	0.811	0.561-1.171	.264	1.178	0.780-1.901	.385
M						
0	Reference			Reference		
1	2.384	1.619-3.512	**<.001**	1.320	0.660-2.640	.433
Bone metastasis						
No	Reference					
Yes	0.683	0.214-2.181	.520			
Unknown	0.757	0.517-1.108-	.152			
Brain metastasis						
No	Reference					
Unknown	0.879	0.728-1.061	.179			
Liver metastasis						
No	Reference			Reference		
Yes	2.652	1.641-4.283	**<.001**	1.921	0.828-4.457	.128
Unknown	1.129	0.722-1.767	.595	1.153	0.633-2.099	.642
Lung metastasis						
No	Reference					
Yes	1.183	0.430-3.254	.744			
Unknown	0.779	0.532-1.141	.200			

(continued)

Table 1. (continued)

Characteristics	Univariable Hazard ratio	95.0% CI	*P* value	Multivariable Hazard ratio	95.0% CI	*P* value
Surgery (%)						
No	Reference			Reference		
Yes	0.193	0.101-0.367	**<.001**	0.156	0.071-0.346	**<.001**
Radiotherapy (%)						
No/Unknown	Reference			Reference		
Yes	1.012	0.624-1.641	.963	0.922	0.500-1.698	.794
Chemotherapy (%)						
No/Unknown	Reference			Reference		
Yes	0.775	0.518-1.158	.213	0.481	0.294-0.787	**.004**

Bold values indicates the difference is statistically significance as the *P* value is less than 0.05.
Abbreviations: PSCC, pancreatic squamous cell carcinoma; PAC, pancreatic adenocarcinoma; SEER, surveillance, epidemiology, and end results; NOS, no other specific; T, tumor; N, node; M, metastasis; OS, overall survival; HR, hazard ratio; CI, confidence interval.
Note: Other include American Indian/Alaska Native, and Asian or Pacific Islander.

Table 2. Univariate and Multivariate Cox Analyses of Patients With PAC Before PSM.

Characteristics	Univariable Hazard ratio	95.0% CI	*P* value	Multivariable Hazard ratio	95.0% CI	*P* value
Age						
Age (≤40)	Reference			Reference		
Age (40-60)	1.183	1.070-1.308	**<.001**	1.194	1.080-1.319	**<.001**
Age (>60)	1.421	1.287-1.569	**<.001**	1.438	1.302-1.589	**<.001**
Sex						
Male	Reference					
Female	0.980	0.960-1.000	.053			
Race						
White	Reference			Reference		
Black	1.116	1.082-1.150	**<.001**	1.099	1.066-1.134	**<.001**
Other	0.997	0.959-1.036	.871	0.974	0.937-1.013	.191
Primary location						
Head	Reference			Reference		
Body	1.212	1.175-1.249	**<.001**	0.966	0.937-0.997	**.031**
Tail	1.390	1.346-1.435	**<.001**	1.093	1.057-1.131	**<.001**
Overlapping	1.319	1.269-1.370	**<.001**	1.055	1.014-1.097	**.008**
duct	0.834	0.721-0.966	**.016**	0.967	0.835-1.121	.659
NOS	1.271	1.222-1.321	**<.001**	1.035	0.995-1.076	.091
Marital status						
Married	Reference					
Unmarried	1.079	1.047-1.112	**<.001**	1.056	1.024-1.089	**<.001**
Unknown	0.978	0.926-1.034	.435	0.949	0.899-1.003	.064
SEER stage						
Regional	Reference			Reference		
Localized	0.885	0.849-0.921	**<.001**	0.747	0.710-0.786	**<.001**
Distant	2.051	2.007-2.096	**<.001**	1.118	1.061-1.179	**<.001**
Grade						
Well differentiated	Reference			Reference		
Moderately differentiated	1.153	1.089-1.220	**<.001**	1.287	1.216-1.363	**<.001**
Poorly differentiated	1.585	1.497-1.678	**<.001**	1.676	1.582-1.775	**<.001**
Undifferentiated	1.699	1.468-1.965	**<.001**	1.436	1.241-1.662	**<.001**
Unknown	2.102	1.995-2.216	**<.001**	1.354	1.283-1.429	**<.001**
T						
1	Reference			Reference		
2	1.877	1.770-1.991	**<.001**	1.387	1.306-1.473	**<.001**

(continued)

Table 2. (continued)

Characteristics	Univariable Hazard ratio	95.0% CI	*P* value	Multivariable Hazard ratio	95.0% CI	*P* value
3	1.383	1.307-1.464	**<.001**	1.278	1.202-1.360	**<.001**
4	1.768	1.667-1.874	**<.001**	1.271	1.193-1.355	**<.001**
N						
0	Reference			Reference		
1	0.934	0.915-0.953	**<.001**	1.103	1.079-1.127	**<.001**
M						
0	Reference			Reference		
1	2.177	2.132-2.223	**<.001**	1.295	1.224-1.369	**<.001**
Bone metastasis						
No	Reference					
Yes	1.954	1.807-2.113	**<.001**	1.310	1.209-1.419	**<.001**
Unknown	1.094	1.072-1.118	**<.001**	1.387	1.100-1.748	**.006**
Brain metastasis						
No	Reference					
Yes	3.052	2.312-4.028	**<.001**	1.949	1.474-2.577	**<.001**
Unknown	1.080	1.058-1.103	**<.001**	0.841	0.679-1.042	.114
Liver metastasis						
No	Reference			Reference		
Yes	2.112	2.053-2.173	**<.001**	1.200	1.159-1.242	**<.001**
Unknown	1.329	1.299-1.360	**<.001**	1.103	0.925-1.316	.274
Lung metastasis						
No	Reference					
Yes	1.717	1.641-1.796	**<.001**	1.021	0.974-1.071	.382
Unknown	1.126	1.102-1.150	**<.001**	0.916	0.795-1.056	.228
Surgery (%)						
No/Unknown	Reference			Reference		
Yes	0.332	0.323-0.342	**<.001**	0.382	0.369-0.395	**<.001**
Radiotherapy (%)						
No/Unknown	Reference			Reference		
Yes	0.588	0.574-0.603	**<.001**	0.930	0.905-0.956	**<.001**
Chemotherapy (%)						
No/Unknown	Reference			Reference		
Yes	0.538	0.526-0.549	**<.001**	0.487	0.475-0.498	**<.001**

Bold values indicates the difference is statistically significance as the *P* value is less than 0.05.
Abbreviations: PSCC, pancreatic squamous cell carcinoma; PAC, pancreatic adenocarcinoma; SEER, surveillance, epidemiology, and end results; NOS, no other specific; T, tumor; N, node; M, metastasis; OS, overall survival; HR, hazard ratio; CI, confidence interval.
Note: Other include American Indian/Alaska Native, and Asian or Pacific Islander.

Prognosis of PSCC patients was significantly worse than PAC patients, reflected in OS (4 months vs 8 months; HR = 1.287; 95%CI, 1.046-1.584; $P = .0046$) and CSS (4 months vs 8 months; HR = 1.318; 95%CI, 1.064-1.632; $P = .0024$) (Figure 4b and a). 1-year, 2-year OS rates were 32.5%, 14.0% in PAC patients and 19.8%, 8.9% in PSCC patients. 1-year, 2-year CSS rates were 34.3%, 15.4% in PAC patients and those in PSCC patients were 21.5%, 9.7%, respectively.

After PSM, PSCC was associated with a worse prognosis than PAC in both OS (4 months vs 7 months; HR = 1.176; 95% CI, 0.944-1.465; $P = .11$) and CSS (4 months vs 7 months; HR = 1.193; 95%CI, 0.953-1.494; $P = .088$) (Figure 5b and b). Based on survival curves of Kaplan-Meier analyses, the 1-year, 2-year OS rates were 19.8%, 8.9% in PSCC patients and 29.9%, 10.1% in PAC patients. CSS rates were 21.5%, 9.7% in patients with PSCC, 32.1%, 11.4% in patients with PAC, respectively.

Stratified Analysis

After the stratification of each variable, the prognosis of patients with PSCC was significantly more dismal than patients with PAC in married patients. Prognosis of PSCC patients at distant SEER stage, M1 with primarily invaded pancreatic overlapping region, with liver metastasis was also significantly worse than PAC patients (Table 4). In patients treated with chemotherapy (HR = 1.357; 95%CI, 1.053-1.748; $P < .001$), radiotherapy (HR = 2.025; 95%CI, 1.194-3.433; $P = .009$), prognosis of PSCC group was worse than PAC group. Patients without surgery in PSCC group had an unfavorable prognosis compared with PAC (HR = 1.530; 95%CI, 1.219-1.920; $P < .001$). Comparable prognosis was observed in PAC and PSCC patients treated with surgery.

Table 3. Demographics and Clinicopathological Characteristics of Patients.

Variables	Data before PSM PSCC N = 124	PAC N = 38 968	*P*-value	Data after PSM PSCC N = 124	PAC N = 372	*P*-value
Age			**.045**			.628
Age(≤40)	4 (3.2)	444 (1.1)		4 (3.2)	7 (1.9)	
Age (40-60)	41 (33.1)	11 214 (28.8)		41 (33.1)	132 (35.5)	
Age (>60)	79 (63.7)	27 310 (70.1)		79 (63.7)	233 (62.6)	
Sex			.453			.717
Male	59 (47.6)	19 856 (51.0)		59 (47.6)	184 (49.5)	
Female	65 (52.4)	19 112 (49.0)		65 (52.4)	188 (50.5)	
Race (%)			.154			.504
White	90 (72.6)	31 016 (79.6)		90 (72.6)	289 (77.7)	
Black	21 (16.9)	4935 (12.7)		21 (16.9)	50 (13.4)	
Other	13 (10.5)	3017 (7.7)		13 (10.5)	33 (8.9)	
Primary location			**.001**			.145
Head	57 (46.0)	22 573 (57.9)		57 (46.0)	190 (51.1)	
Body	29 (23.4)	5405 (13.9)		29 (23.4)	54 (14.5)	
Tail	24 (19.4)	4677 (12.0)		24 (19.4)	68 (18.3)	
Overlapping	11 (8.9)	3096 (7.9)		11 (8.9)	35 (9.4)	
Duct	0 (0.0)	198 (0.5)		0 (0)	1 (0.3)	
NOS	3 (2.4)	3019 (7.7)		3 (2.4)	24 (6.5)	
Marital status (%)			**.041**			.681
Married	97 (78.2)	32 405 (83.2)		97 (78.2)	292 (78.5)	
Unmarried	25 (20.2)	5127 (13.2)		25 (20.2)	69 (18.5)	
Unknown	2 (1.6)	1436 (3.7)		2 (1.6)	11 (3.0)	
SEER stage (%)			.150			.636
Regional	50 (40.3)	16 751 (43.0)		50 (40.3)	134 (36.0)	
Localized	5 (4.0)	3132(8.0)		5 (4.0)	13 (3.5)	
Distant	69 (55.6)	19 085 (49.0)		69 (55.6)	225 (60.5)	
Grade (%)			**<.001**			.185
I/II	14 (11.3)	8273 (21.2)		14 (11.3)	62 (16.7)	
III/IV	39 (31.5)	6289 (16.1)		39 (31.5)	92 (24.7)	
Unknown	71 (57.3)	24 406 (62.6)		71 (57.3)	218 (58.6)	
T			.866			.894
1	1 (0.8)	1508 (3.9)		1 (0.8)	5 (1.3)	
2	33 (26.6)	8955 (23.0)		33 (26.6)	103 (27.7)	
3	58 (46.8)	18 659 (47.9)		58 (46.8)	165 (44.4)	
4	32 (25.8)	9846 (25.3)		32 (25.8)	99 (26.6)	
N			.088			.468
0	63 (50.8)	22 747 (58.4)		63 (50.8)	175 (47.0)	
1	61 (49.2)	16 221 (41.6)		61 (49.2)	197 (53.0)	
M			.081			.567
0	59 (47.6)	21 577 (55.4)		59 (47.6)	166 (44.6)	
1	65 (52.4)	17 391 (44.6)		65 (52.4)	206 (55.4)	
Bone metastasis (%)			.625			**.022**
No	73 (58.9)	21 826 (56.0)		73 (58.9)	216 (58.1)	
Yes	3 (2.4)	660 (1.7)		3 (2.4)	0 (0.0)	
Unknown	48 (38.7)	16 482 (42.3)		48 (38.7)	156 (41.9)	
Brain metastasis (%)			.501			.527
No	76 (61.3)	22 416 (57.5)		76 (61.3)	216 (58.1)	
Yes	0 (0.0)	50 (0.1)		0 (0.0)	0 (0.0)	
Unknown	48 (38.7)	16 502 (42.3)		48 (38.7)	156 (41.9)	
Liver metastasis (%)			**.026**			.506
No	39 (31.5)	14 704 (37.7)		39 (31.5)	97 (26.1)	
Yes	37 (29.8)	7879 (20.2)		37 (29.8)	118 (31.7)	
Unknown	48 (38.7)	16 385 (42.0)		48 (38.7)	157 (42.2)	
Lung metastasis (%)			.309			.249
No	72 (58.1)	20 319 (52.1)		72 (58.1)	191 (51.3)	
Yes	4 (3.2)	2123 (5.4)		4 (3.2)	24 (6.5)	
Unknown	48 (38.7)	16 526 (42.4)		48 (38.7)	157 (42.2)	

(continued)

Table 3. (continued)

Variables	Data before PSM PSCC N = 124	PAC N = 38 968	*P*-value	Data after PSM PSCC N = 124	PAC N = 372	*P*-value
Surgery (%)			.144			.726
No/Unknown	105 (84.7)	30 927 (79.4)		105 (84.7)	310 (83.3)	
Yes	19 (15.3)	8041 (20.6)		19 (15.3)	62 (16.7)	
Radiotherapy (%)			.103			.616
No/Unknown	103 (83.1)	29 959 (76.9)		103 (83.1)	316 (84.9)	
Yes	21 (16.9)	9009 (23.1)		21 (16.9)	56 (15.1)	
Chemotherapy (%)			.478			.692
No/Unknown	39 (31.5)	13 437 (34.5)		39 (31.5)	110 (29.6)	
Yes	85 (68.5)	25 531 (65.5)		85 (68.5)	262 (70.4)	

Bold values indicates the difference is statistically significance as the *P* value is less than 0.05.
Abbreviations: PSCC, pancreatic squamous cell carcinoma; PAC, pancreatic adenocarcinoma; SEER, surveillance, epidemiology, and end results; NOS, no other specific; T, tumor; N, node; M, metastasis; OS, overall survival; HR, hazard ratio; CI, confidence interval.
Note: Other include American Indian/Alaska Native, and Asian or Pacific Islander.

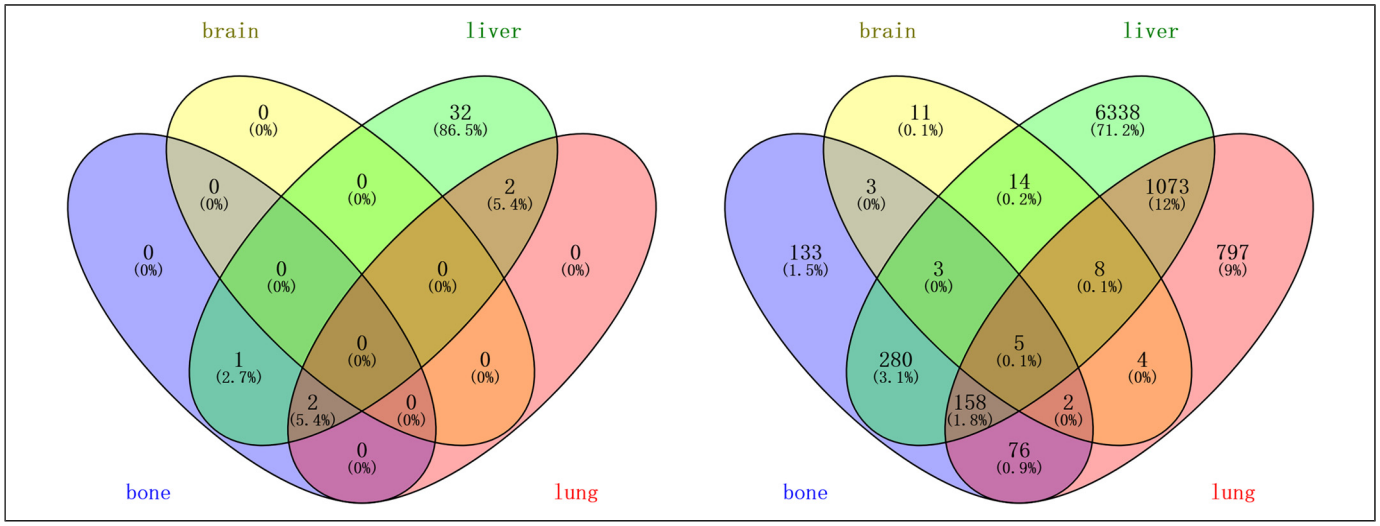

Figure 2. Venn diagram showing distribution of metastasis in (a) PSCC cohort and (b) PAC cohort.
Abbreviations: PSCC, pancreatic squamous cell carcinoma; PAC, pancreatic adenocarcinoma.

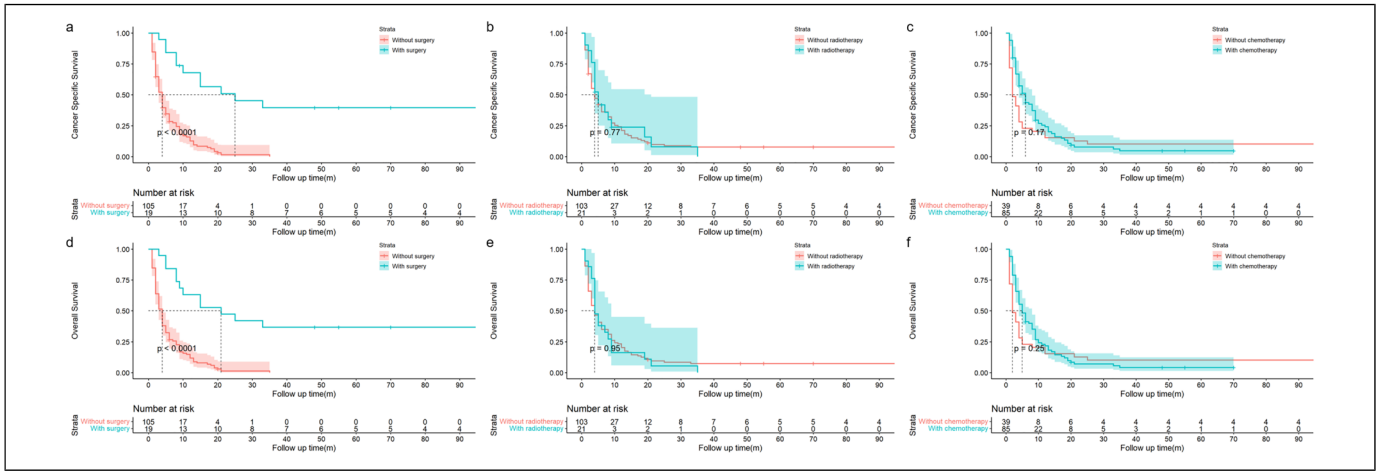

Figure 3. Kaplan-Meier curves of CSS and OS in PSCC patients according to surgery (a and d), radiation (b and e), and chemotherapy (c and f).
Abbreviations: PSCC, pancreatic squamous cell carcinoma; CSS, cancer specific survival; OS, overall survival.

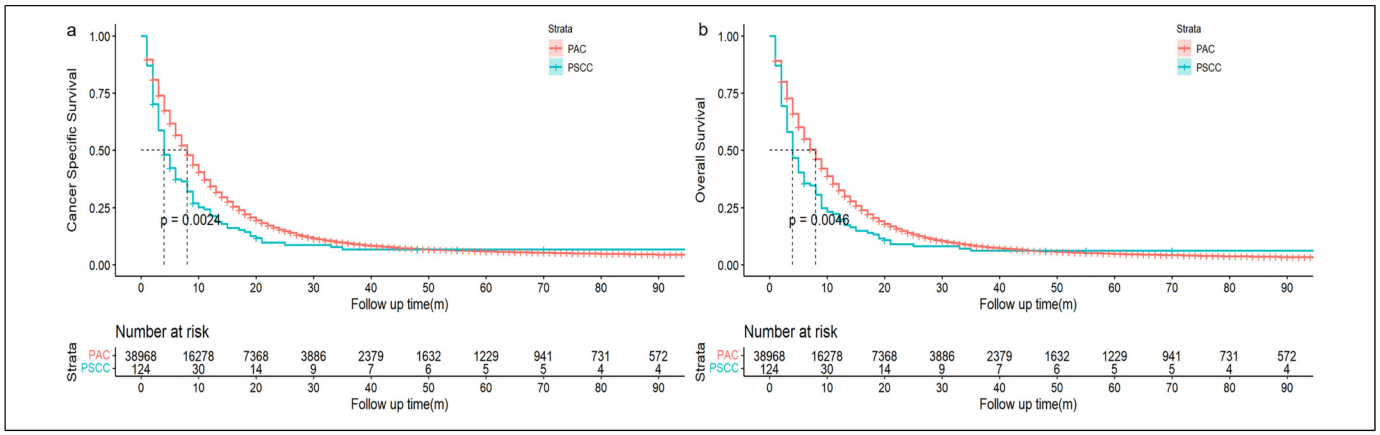

Figure 4. Kaplan-Meier plot and log-rank test of (a) CSS and (b) OS before PSM.
Abbreviations: PSCC, pancreatic squamous cell carcinoma; PAC, pancreatic adenocarcinoma; CSS, cancer specific survival; OS, overall survival; PSM, propensity-score matching.

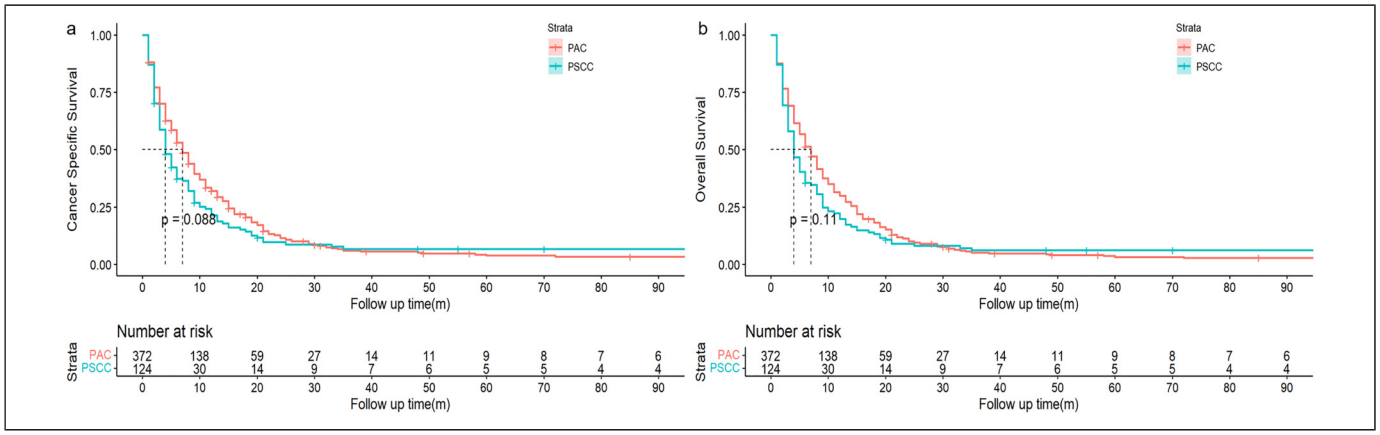

Figure 5. Kaplan-Meier plot and log-rank test of (a) CSS and (b) OS after PSM.
Abbreviations: PSCC, pancreatic squamous cell carcinoma; PAC, pancreatic adenocarcinoma; CSS, cancer specific survival; OS, overall survival; PSM, propensity-score matching.

Discussion

Current studies focusing on the survival and prognostic factors of PSCC are limited. There is also no comprehensive understanding in PSCC due to lack of comparisons between the most common PAC and extremely rare PSCC. Therefore, our study concentrated on the characteristics of PSCC and discrepancies between PSCC and PAC. We discovered that the majority of PSCC patients were elders, white and female. In addition, PSCC presented to be poorly differentiated and metastatic when diagnosed, with a more dismal prognosis than PAC. T stage could not be regarded as a predictive factor as there was only 1 PSCC patient at T1 stage. Liver and lymph nodes were the most common metastatic sites. As for treatment, PSCC patients received more favorable prognosis from surgery and chemotherapy. The therapeutic effects of radiotherapy to PSCC patients is worth discussing and it indicated better efficacy in PAC than PSCC. Conduction of surgery led to comparable prognosis in PAC and PSCC patients.

Another SEER-based study and a retrospective analysis using National Cancer Database (NCDB) of PSCC reached analogous conclusions with our study. Common conclusions showed the vulnerable population were elders and the most predilection site of pancreatic was head. PSCC patients had a higher proportion of poor differentiation and inferior survival. On the contrary, NCDB-based study indicated a higher frequency of PSCC occurred in male, which was in accordance with PAC. While the proportional differences in sex distribution between PSCC and PAC were not statistically significant in NCDB-based study and our study. Corresponding to previous retrospective studies and case reports,[15,17,18] surgery was identified as an independent positive prognostic factor both in univariate and multivariate analysis.

In our study, 1-year OS rate in PSCC patients was 19.8%, which was close to another SEER-based analysis with 1-year OS rate of 14.0%.[15] Statistically significant worse mOS in PSCC group compared with PAC group (4 months vs 8

Table 4. Stratified Analyses of the 1:3 Matched Cohort (OS).

	PAC (n = 372) versus PSCC (n = 124)		
Characteristics	Hazard ratio	95.0% CI	*P* value
Age			
Age≤60	1.240	0.868-1.770	.237
Age>60	1.154	0.888-1.500	.284
Sex			
Male	1.125	0.831-1.523	.447
Female	1.278	0.953-1.715	.102
Race (%)			
White	1.201	0.940-1.535	.144
Black	1.551	0.905-2.658	.110
Other	0.890	0.452-1.753	.736
Primary location			
Head	1.245	0.916-1.693	.162
Body	1.018	0.638-1.625	.940
Tail	0.961	0.586-1.577	.876
Overlapping	3.491	1.665-7.322	**<.001**
NOS	1.339	0.395-4.543	.639
Marital status (%)			
Married	1.325	1.044-1.682	**.021**
Unmarried	0.854	0.524-1.394	.529
SEER stage (%)			
Regional	0.991	0.698-1.408	.962
Localized	1.059	0.335-3.354	.922
Distant	1.655	1.255-2.182	**<.001**
Grade (%)			
I/II	0.802	0.416-1.545	.509
III/IV	0.931	0.626-1.385	.725
T			
1/2	1.364	0.915-2.034	.127
3/4	1.151	0.897-1.476	.268
N			
0	1.311	0.976-1.761	.072
1	1.085	0.801-1.471	.597
M			
0	1.073	0.779-1.479	.666
1	1.512	1.138-2.009	**.004**
Bone metastasis (%)			
No	1.316	0.999-1.733	.051
Brain metastasis (%)			
No	1.294	0.987-1.696	.063
Liver metastasis (%)			
No	1.167	0.786-1.732	.443
Yes	0.468	1.220-2.617	**.003**
Lung metastasis (%)			
No	1.322	0.998-1.752	.052
Yes	1.487	0.504-4.387	.473
Surgery (%)			
No/Unknown	1.530	1.219-1.920	**<.001**
Yes	0.609	0.324-1.145	.124
Radiotherapy (%)			
No/Unknown	1.092	0.867-1.376	.456
Yes	2.025	1.194-3.433	**.009**
Chemotherapy (%)			
No/Unknown	0.995	0.677-1.463	.980
Yes	1.357	1.053-1.748	**.018**

Bold values indicates the difference is statistically significance as the *P* value is less than 0.05.

Abbreviations: PSCC, pancreatic squamous cell carcinoma; PAC, pancreatic adenocarcinoma; SEER, surveillance, epidemiology, and end results; NOS, no other specific; T, tumor; N, node; M, metastasis; OS, overall survival; HR, hazard ratio; CI, confidence interval.

Note: Other include American Indian/Alaska Native, and Asian or Pacific Islander.

months) was detected in our analysis before PSM. After PSM, there was no significant difference between PSCC and PAC in mOS in our study (4 months vs 7 months), similar trend was observed in NCDB-based study (4 months vs 4.8 months). In NCDB-based analysis, matched variables contained age, sex, race, insurance, Charlson-Deyo score, year of diagnosis, facility type, tumor grade, stage, surgery, radiation, and chemotherapy. In our study, in addition to variables related to demographics, variables closely connected to prognosis, including primary location, SEER stage, grade, TNM stage, and 3 sites of metastasis (bone, brain, liver) were matched. Meanwhile, metastatic tumor and tumor without positive cytological, microscopic, or histological confirmation were excluded, together with patients with unknown information in race, SEER stage, TNM stage. Although the sample size of the retrospective analysis extracted from NCDB was larger, inclusion of metastatic tumor and tumor without diagnostic confirmation with golden standard increased the influence of confounding factors. Therefore, discrepancies between PAC and PSCC could not be accurately obtained. Variables covered in multivariate analysis were limited in NCDB-based study, containing age, sex, race, Charlson-Deyo score, insurance status, grade, and therapy received. In another SEER-based study, there were no disparities in primary tumor location, extent of disease between PAC and PSCC, which were not corresponding to our results. Distinctions in results are possibly derived from the different inclusive year and the historically diagnostic standard. In addition, propensity score matching was not conducted to balance the confounders.[15] Information of 4-organ metastasis were analyzed in our study which was not mentioned in that previously published SEER-based study. Liver metastasis was identified as a predictive factor with worse prognosis in PSCC. Therefore, conclusions reached in our study give a more comprehensive and precise description to PSCC, as well as a clear understanding on differences between PAC and PSCC.

Previous study has proved that the primary location of pancreatic cancer is a prognostic factor for survival, reflected in decreased lifetime in patients with body and tail lesions than head lesions. Pancreatic cancer with primary location on body and tail lesions seems to late manifestations in those patients.[19,20] In our study, worse prognosis of PSCC patients may be associated with higher proportion of tail and body lesions discovered in PSCC (42.8%) than PAC (25.9%). Interestingly, overlapping lesions indicated strongest correlation with worse prognosis in PSCC cohorts rather than PAC cohorts, which may be a noteworthy character related to histology type. We also identified that PSCC was always prone to be poorly differentiated and the lower differentiation may be related to worse prognosis in univariate analysis, although the difference was not statistically significant. Significant better relapse-free survival in low/moderate grade PSCC tumors than high grade tumors (3 months vs 16.2 months) was identified in another study.[18] Distant metastasis was regarded as a risk factor in our analysis, with a lower possibility of surgery and short survival time observed in case reports.[5,21] Based on the analytical results and case reports, nearly 70% of PSCC patients are diagnosed at advanced stage, indicating a possibility of curative resection less than 30%.[18] But for patients who present with operable PSCC, a pooled survival analysis indicated a significantly 6-month longer OS.[18] Similarly, a prominent better OS of 21 months in PSCC patients with resection at stage I/II was observed in a population-based study.[17] In agreement with our study, surgery was regarded as an independent prognostic factor with remarkably improved OS. For patients with palliative treatment, combined chemotherapy has been proved effective while the prolongation to OS is not notable in every patient.[13]

In addition to pancreas, AC and SCC have been compared in lung, esophagus, cervix, rectum, and anus. According to population-based analysis of AC and SCC in different anatomical regions, better OS in SCC was observed in rectum,[22] anus,[23] and cervix.[24,25] Patients with AC obtain better clinical outcomes in esophagus.[26] In lung cancer, studies reach different conclusions in survival advantages between AC and SCC, and it is difficult to tell whether prognosis is related to pathologic patterns.[27] Regardless of pathologic patterns, the root cause of different prognosis in tumor is the influence of prognostic factors. It has been demonstrated that epidemiology (age, sex, race), clinicopathologic characteristics (tumor location, histologic grade, tumor stage, TNM stage), and treatment modalities (surgery, chemotherapy, radiotherapy) have synergistic effects on tumors prognosis. However, due to the heterogenicity of tumors, prognostic factors should be analyzed in each pathological type of tumor to establish a comprehensive understanding for it.

There are several limitations in our study. Firstly, data we extracted was completely based on the SEER database and it is a retrospective, nonrandomized study. Significant information including the biology of tumor, type of surgical procedure, therapeutic regimen of chemotherapy, dose of radiotherapy, information of neoplasm recurrence, environmental risk factors were not taken into consideration due to their absence in SEER database. Some specific information correlated with the therapeutic decisions like ECOG score standard were not included as variables in SEER database which could be confounding factors to survival. There was no information on stage when patients underwent operations, and it was difficult to tell whether better prognosis was derived from the conduction of surgery or an early stage of tumor. Secondly, the sample size of PSCC in SEER database without missing information was relatively small. Thirdly, the individual difference in gene expression was not analyzed with relevance to prognosis and response to treatment as this information was not applicable in SEER database. In this condition, prospective studies need to be conducted to verify the results we obtained.

Conclusion

Our results indicate that the prognosis of PSCC patients was worse than PAC patients in survival analyses. PSCC occurs mainly in elders, white and female. It is mostly located on pancreatic head, followed by body, then tail. PSCC invading

overlapping regions are associated with worse prognosis. Compared with PAC, PSCC could have a higher proportion to be poorly differentiated and distantly metastatic when diagnosed. Liver and lymph nodes are most common metastatic sites in PSCC. We identify that surgery and chemotherapy are independent prognostic factors which improve the OS in PSCC patients. These findings help to establish a comprehensive understanding on PSCC and give a comparison between PAC and PSCC, which may provide basic information for prospective study and clinical instructions.

Author Contributions

YWang and YZhou collected data, reviewed the literature, analyzed all data, and wrote the manuscript. YChen collected data, wrote, and revised the manuscript. RXia collected data and rechecked the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are available from SEER 18 database. If you need, the data used and analyzed in our study can be downloaded from SEER (https://seer.cancer.gov/). Another way is contact with our corresponding author.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the Sichuan Science and Technology Department Key Research and Development Project (2019YFS0539), 1.3.5 Project for Disciplines of Excellence, West China Hospital, Sichuan University (ZYJC18022).

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Supplemental Material

Supplemental material for this article is available online.

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