



Primary squamous cell carcinoma of pancreas: a population-based study

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Background: Primary squamous cell carcinoma of pancreas (SCCP) is an extremely rare pathological subtype of pancreatic cancer of ductal origin. Due to its rarity, most previous studies on SCCP focused on case reports or series and the clinio-pathological characteristics of SCCP patients remain unclear.

Methods: A retrospective analysis of SCCP patients registered in the Surveillance, Epidemiology and End Results (SEER) database from 1988 to 2016 were performed, and clinical characteristics and prognosis of these patients were also further determined.

Results: A total of 373 patients diagnosed with SCCP were identified. Most SCCP patients 154/243 (63.4%) SCCP patients had distant metastases. The prognosis of SCCP patients was poor with a median overall survival (mOS) of only 3.0 months (95% CI, 2.0–5.0). The 6-month, 1-year and 2-years survival rate were 25.6%, 13.2% and 5.7%, respectively. The prognosis of SCCP patients became much worse with the increasing age ($P=0.01$) and distant metastases ($P<0.01$). Cancer-directed surgery, chemotherapy and radiotherapy could significantly prolong the survival time for SCCP patients ($P<0.01$ for all). Multivariate Cox analysis showed that only distant metastases were independent prognostic factors of worse survival in SCCP patients (HR =1.58, 95% CI, 1.18–2.12). Conversely, both cancer-directed surgery and chemotherapy were an independent protective factor that decreased the risk of death by 66% (HR =0.18, 95% CI, 0.11–0.29) and 46% (HR =0.54, 95% CI, 0.43–0.68) for SCCP patients.

Conclusions: SCCP is a rare type of pancreatic malignancies with poor prognosis. The present study could provide some useful information for future management and prospective studies for SCCP patients.

Keywords: Pancreatic cancer; squamous cell carcinoma; Surveillance, Epidemiology and End Results (SEER) database; prognosis

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Introduction

Primary squamous cell carcinoma of pancreas (SCCP) is an extremely rare pathological subtype of pancreatic cancer of ductal origin, accounting for approximately 1% of all pancreatic malignancies, with a reported incidence range of 0.5% to 5% (1,2). Because of its rarity, SCCP is typically diagnosed only after excluding other primary sources of cancer and should be further confirmed a lack of glandular component. The pathological mechanism of SCCP was not totally clear. Theoretically, the pancreas is totally devoid of squamous cells, the previous studies have suggested SCCP may arise from ductules that have undergone squamous metaplasia secondary to chronic pancreatitis (3,4). Due to the finding that most SCCP are not related with chronic inflammation, SCCP has been thought to result from malignant transformation of squamous metaplastic zones in the pancreatic ductal epithelium (5). Other possibility for SCCP development included malignant change in a primitive cell and an aberrant squamous cells in pancreas (6).

Specific risk factors for SCCP have not been fully defined. The same risk factors for adenocarcinoma appear to also be related with SCCP. The symptoms of SCCP is similar to pancreatic adenocarcinoma, including abdominal pain, back pain, jaundice, anorexia (7). Previous study reported the enhancement of the tumor with contrast computed tomography and blush patterns with angiography could be used to differentiate SCCP from pancreatic adenocarcinoma (2,8). Analysis of the biologic behavior of SCCP from previous studies observed its propensity to affect older patients, presence of metastasis at diagnosis, low response to chemotherapy and radiotherapy, and poor prognosis (9).

Due to its rarity, most previous studies on SCCP focused on case reports or series (5,7-9). To identify its clinicopathological characteristics and prognosis, we performed a retrospective analysis of SCCP patients registered in the Surveillance, Epidemiology and End Results (SEER) database from 1988 to 2016, and we determine the clinical characteristics and prognosis of these patients. We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/gs-20-317>).

Methods

Participants

The data of SCCP patients for this analysis were obtained

from the Surveillance, Epidemiology, and End Results (SEER) database, which is a publicly available cancer registry maintained by the National Cancer Institute of United States and collects information including cancer incidence and survival of approximately 28% of the US population. All patients diagnosed with SCCP (ICD-0-3: 8070/8071/8072/8073/8074/8075) from SEER databased between 1988 and 2016 were identified. Demographic information and clinical-pathological characteristics for each SCCP patient were isolated using SEER*stat 8.3.6 software. Besides, the overall survival time of each SCCP patient was also extracted from SEER database. Because the SEER data are de-identified before release, institutional review board approval and informed consent are not required for this study. All authors have signed the research agreement form and received permission to access to SEER database. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Statistical analysis

The clinical-pathological characteristics of all SCCP patients were described with count and percentage. The clinical Survival analysis stratified by each feature were performed using Kaplan-Meier curves and Log-Rank test. Univariate and multivariate Cox regression analysis were used to determine potential prognostic factors correlated with survival. All statistical analyses were performed using MedCalc software (Mariakerke, Belgium).

Results

Patients characteristics

A total of 373 patients diagnosed with SCCP were identified from SEER database between 1988 and 2016 (*Table 1*). 137,232 patients with pancreatic ductal adenocarcinoma (PDAC) were identified in the same period. The incidence ratio of SCCP to PDAC is 1:368. The average age at diagnose was 69.4±11.8 years old. Most of lesion were located in head of pancreas. Patients had a poorly pathological differentiation. Among all patients with known stage status, 65.3% (154/237) of SCCP patients were diagnosed with IV stage, 236/349 patients were diagnosed with distant stage according to SEER historic stage classification. 154/243 (63.4%) SCCP patients had distant metastases and 100 out of 224 patients had lymph node metastases. As for treatment, a majority (341/372) of

Table 1 Clinico-pathological characteristics of the 373 patients with SCCP

Characteristics	Total
Age (year)	69.4±11.8
Gender	
Female	175
Male	198
Ethnicity	
White	283
Black	52
Other	36
Unknown	2
Pathological differentiation	
Well	10
Moderate	24
Poor	119
Undifferentiated	6
Unknown	214
Summary stage	
Distant	236
Regional	93
Localized	20
Unstaged	24
Primary site	
Head of pancreas	160
Body of pancreas	50
Tail of pancreas	67
Overlapping lesion of pancreas	30
Unknown	66
TNM stage	
I	11
II	43
III	29
IV	154
Unknown	136

Table 1 (continued)

Table 1 (continued)

Characteristics	Total
Tumor size	
T1	0
T2	50
T3	88
T4	60
Unknown	172
Lymph node metastases	
N0	114
N1	100
Unknown	159
Distant Metastases	
M0	89
M1	154
Unknown	130
Surgery	
Yes	31
No	341
Unknown	1
Radiation	
Yes	54
No	319
Chemotherapy	
Yes	159
No/unknown	214

SCCP, squamous cell carcinoma of pancreas.

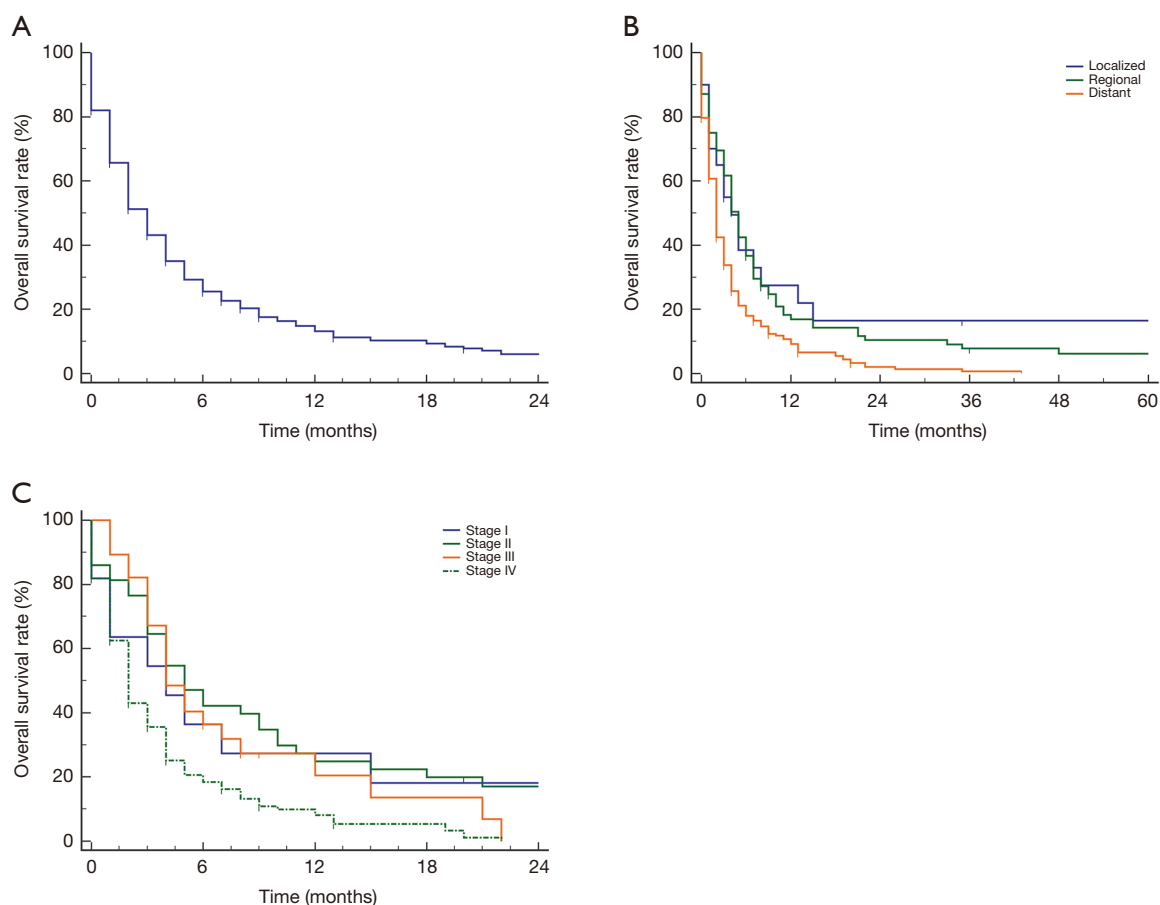


Figure 1 the overall survival of 373 SCCP patients. (A) overall survival; (B) stratified by SEER stage; (C) stratified by TNM stage. SCCP, squamous cell carcinoma of pancreas.

SCCP patients did not receive surgery and 159 out of 373 patients had a history of receiving chemotherapy.

Patients survival

The prognosis of SCCP patients was poor with a mOS of only 3.0 months (95% CI, 2.0–5.0 months). The 6-month, 1-year and 2-years survival rate were 25.6%, 13.2% and 5.7%, respectively (Figure 1A). SCCP patient with advanced stage had significantly shorter survival time than other patients. SCCP patients with distant stages had significantly poorer prognosis than those with localized or regional stage ($P < 0.01$ for both), but no significantly difference in survival time between patients with localized and regional stage ($P = 0.65$) (Figure 1B). SCCP patients with distant stages only had a mOS of 2.0 months with 6-months, 1-years survival rate of 17.9%, 9.2%. Similar results could be observed in

patients with different TNM stages. SCCP patients with IV stage had the shortest survival time than other stages, and no SCCP patients with IV stage could survival more than 21 months with only a 18.4% 6-month OS rate (Figure 1C).

Features influencing prognosis

The prognosis of SCCP patients became much worse with the increasing age ($P = 0.01$) (Figure 2A), older patients have significantly much shorter mOS than younger patients (3.0 vs. 2.0 months). The SCCP patients with distant metastases also had significantly shorter mOS than those without distant metastases (mOS: 2.0 vs. 5.0 months, $P < 0.01$) (Figure 2B). In addition, no significant associations between race ($P = 0.14$), gender ($P = 0.82$), pathological grade ($P = 0.75$), lesion site ($P = 0.40$), T stage ($P = 0.98$), N stage ($P = 0.47$) and prognosis were observed (Figure S1).

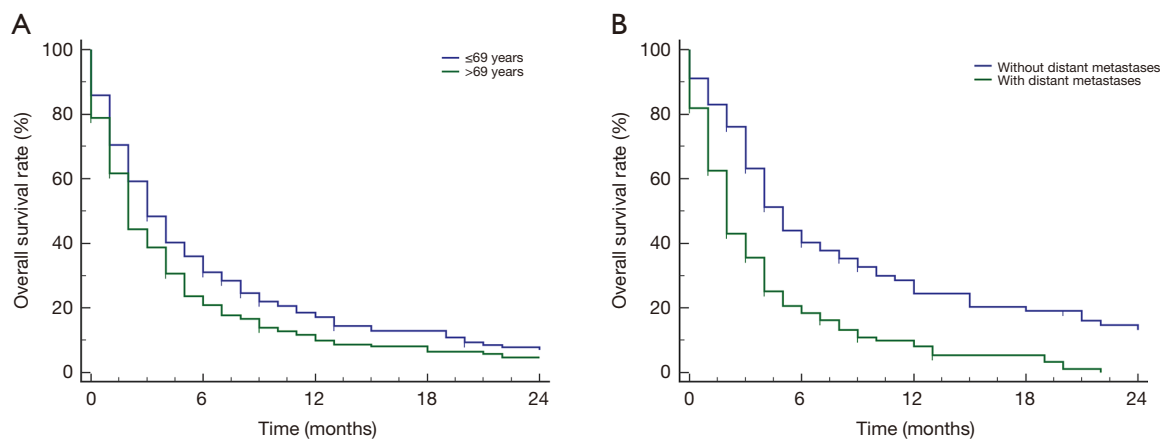


Figure 2 the effect of clinio-pathological features on prognosis in SCCP patients. (A) age; (B) distant metastases. SCCP, squamous cell carcinoma of pancreas.

Effect of treatment on prognosis

Figure 3A shows that cancer-directed surgery significantly could prolong the survival time for SCCP patients ($P < 0.01$, mOS: 10.0m vs. 2.0m). Among the SCCP patients who received surgery, the 1-, 2-, and 3-year survival rate was 44.6%, 34.3%, 22.8%. The mOS of SCCP patients receiving chemotherapy was 5.0 months (95% CI, 4.0–6.0), while patients without chemotherapy only had 1.0 months of OS (95% CI, 1.0–2.0) (Figure 3B). Similarly, the survival analysis also showed that SCCP patients who received radiotherapy had significant longer overall survival time than those patients without radiotherapy (5.0 vs. 2.0 months; $P < 0.01$; Figure 3C).

Univariate and multivariate Cox proportional hazard analyses

Further, the characteristics potentially influencing prognosis were determined using univariate and multivariate Cox proportional hazards analysis, and Table 2 shows that older age and distant metastases were significantly associated with poor prognosis ($P < 0.05$ for all, Table 2). The use of surgery, radiotherapy as well as chemotherapy was significantly associated with prolonged overall survival ($P < 0.01$ for all). Multivariate Cox analysis showed that only distant metastases were independent prognostic factors of worse survival in SCCP patients. Conversely, both cancer-directed surgery and chemotherapy were an independent protective factor that decreased the risk of death by 66% (HR = 0.18, 95% CI, 0.11–0.29) and 46% (HR = 0.54, 95% CI, 0.43–

0.68) for SCCP patients.

Discussion

The most common malignancy located in the pancreas are of ductal cell origin, including PDCA and SCCP, with the vast majority being PDCA. Although overestimation of incidence of SCCP due to erroneous categorization of adenosquamous carcinoma as SCCP, SCCP have a low incidence reported less than 5% of all pancreatic cancers. Due to its rarity, the clinio-pathological characteristics of SCCP patients remain unclear. In the present study, we have performed a population-based study from SEER database to define the clinical characteristics and prognosis for these patients.

Previous studies reported that SCCP patients tend to occur in older people. One study including 25 SCCP suggested that mean age at diagnosis of SCCP was 62 years ranged from 33–80 years (2). Another analysis of 6 SCCP patients yielded a mean age of 65 years (10). Some previous studies revealed that 92% of SCCP occur in individuals over 50 years old (11–13). Makarova-Rusher *et al.* conducted a population-based study using the data of 214 SCCP patients and found higher SCCP incidence rates in older age groups (14). The data of the present study were in consistent with previous data. In the present study, the average age of all 373 SCCP patients were 69 years ranged from 39 years to 93 years and 78.0% of cases were more than 60 years old. Besides, the previous analysis of 25 SCCP cases did not show a significant sex preference, and SCCP seems to

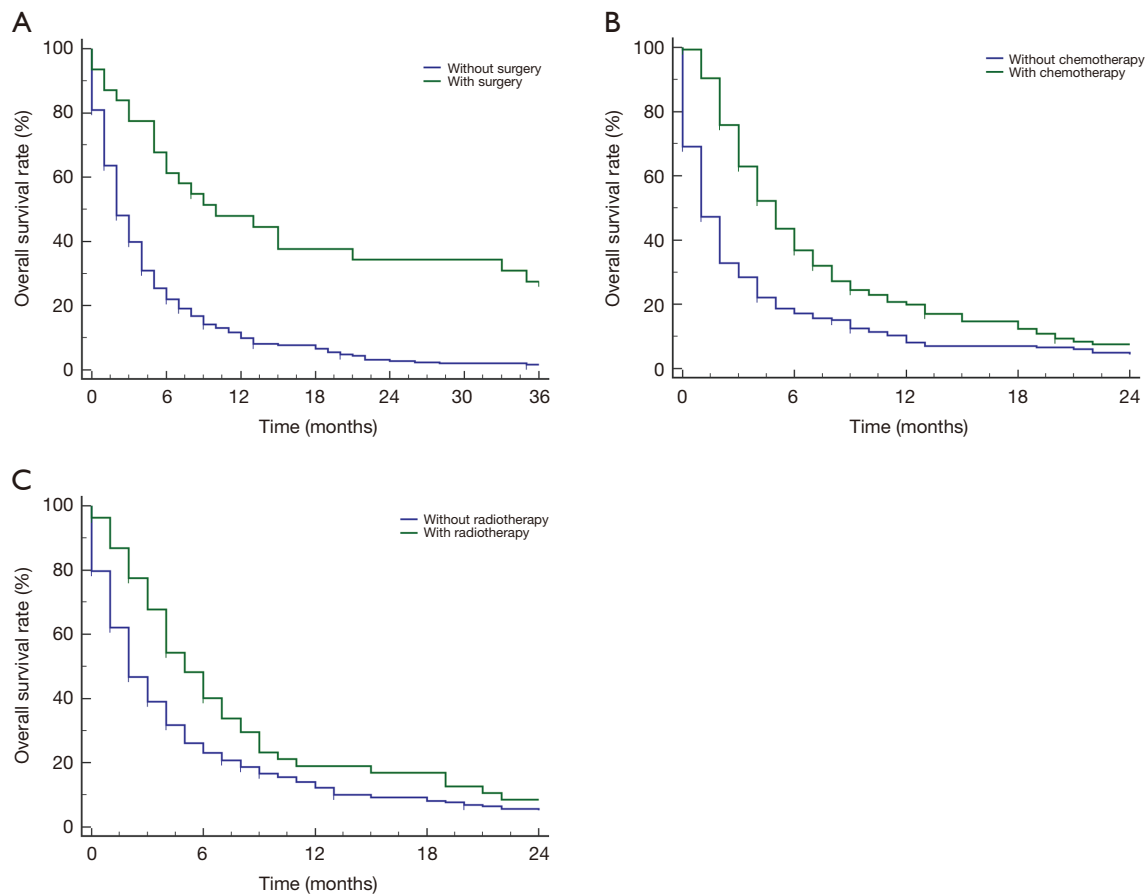


Figure 3 the effect of treatment method on prognosis in SCCP patients. (A) surgery; (B) chemotherapy; (C) radiotherapy. SCCP, squamous cell carcinoma of pancreas.

affect both sexes equally (2). In the present study, also no sex preference could be observed in the present cohort of 373 SCCP patients (175 men and 198 women). Previous studies showed that the anatomic head, tail and body of the pancreas were affected equally by SCCP (2,10,15). In the present study, 42.9% of cases was located in the head of pancreas 13.4% in the body as well as 17.9% in the tail. And 8% of cases had overlapping lesion of the pancreas due to tumor may span more than one portion of the organ. The survival analysis showed that no difference in overall survival among different site of pancreas. Previous study reported that the biological behavior of SCCP present to be similar to PDCA. Approximately 95% of patients show evidence of disseminated or locally metastatic disease at the time of initial evaluation or laparotomy, with the regional lymph nodes, liver, lung, and bones being most commonly affected (10,11,13). In consistent with this data, our study showed that 94.2% of patients were diagnosed with regional

stage and distant stage. Among all patients with metastases information, 100/214 patients had lymph node metastases and 154/243 patients had distant metastases.

The treatment regimen for SCCP is limited, but surgical resection, chemotherapy and radiotherapy could improve prognosis for SCCP patients. For example, Brown HA's study reported a median survival of 7.0 months for patients who received surgery and only 3 months for those who did not receive surgery (2). Gruhl *et al.* reported that SCCP patients undergoing surgical resection had significantly longer median OS than those without surgery (21.3 *vs.* 6.8 months) (16). Tella *et al.*'s study observed that median OS for SCCP patients was 4 months and was significantly higher in patients who underwent surgical resection (17.0 *vs.* 4.0 months) (17). Combined with the previous studies, SCCP patients had 1-year and 5-year survival rates of 4.8% and 1% respectively (3). In consistent with this data, our study also reported the median survival of 10.0 months

Table 2 Univariate and multivariate Cox proportional hazard analyses of the clinical characteristics for prognosis in SCCP patients

Factor	Category	Univariate		Multivariate	
		HR (95% CI)	P value	HR (95% CI)	P value
Age, years	>69/≤69	1.27 (1.03–1.57)	0.02	1.01 (0.8–1.26)	0.90
Gender	Male/female	1.08 (0.81–1.44)	0.61		
Race	White	Reference			
	Black	1.30 (0.96–1.79)	0.09		
	Other	0.93 (0.65–1.33)	0.67		
Pathological differentiation	Well	Reference			
	Moderate	1.35 (0.62–2.93)	0.45		
	Poor	1.48 (0.75–2.93)	0.26		
	Undifferentiated	1.59 (0.53–4.77)	0.40		
Summary stage	Localized	Reference			
	Regional	1.27(0.74–2.17)	0.39		
	Distant	2.04 (1.21–3.41)	<0.01		
Primary site	Head of pancreas	Reference			
	Body of pancreas	0.98 (0.71–1.37)	0.93		
	Tail of pancreas	0.99 (0.73–1.34)	0.94		
	Overlapping lesion of pancreas	1.35 (0.89–2.04)	0.15		
T stage	T1	Reference			
	T2	1.21 (0.16–8.69)	0.85		
	T3	1.16 (0.16–8.24)	0.88		
	T4	1.22 (0.17–8.75)	0.84		
Lymph node metastases	Yes/no	0.91 (0.68–1.21)	0.51		
Distant metastases	Yes/no	1.92 (1.44–2.56)	<0.01	1.58 (1.18–2.12)	<0.01
Surgery	Yes/no	0.33 (0.21–0.51)	<0.01	0.34 (0.22–0.53)	<0.01
Radiation	Yes/no	0.68 (0.51–0.93)	0.01	0.77 (0.57–1.06)	0.11
Chemotherapy	Yes/no + unknown	0.56 (0.45–0.70)	<0.01	0.54 (0.43–0.68)	<0.01

SCCP, squamous cell carcinoma of pancreas.

and 2.0 months for patients who receive cancer-directed surgery or not, respectively. Similarly, the SCCP patients from our study had 1-year and 5-years survival rate were 13.2% and 1.8%, respectively (18-20). However, SCCP is often metastatic or locally advanced at time of diagnosis, making resection impossible in most SCCP patients. Katz *et al.* reported the use of chemo-radiation could improve significantly prognosis in the palliative setting, but not adjuvant therapy (21). Tella *et al.*'s study demonstrated that stage IV patients treated with chemotherapy had

a better OS than those without chemotherapy (5.0 *vs.* 2.0 months) (17). In the present study, both patients with radiotherapy and chemotherapy had a significant longer mOS than those without radiotherapy or chemotherapy. Meanwhile, previous study demonstrated different chemotherapeutic agents had different influence on prognosis. For example, previous reports suggested regimens including bleomycin, or gemcitabine could have an improved response (8,22). To date, no standard chemotherapy regimen has been established for SCCP and

further investigation is required. Besides, previous reported have suggested that SCCPAg could be used as an important biomarker for diagnosis and monitor of tumor recurrence in SCCP patients (23), but we could not evaluate these due to inadequate information from SEER database.

Similar to other studies using SEER as a data source, there are several limitations. First, there are inadequate information about TNM stage and chemotherapy in the present cohort. For example, 136 out of 373 patients lacked TNM stage information. Two hundred and fourteen patients out of 373 patients have no accurate information about chemotherapy. Second, the data about other potential variables are lack, such as performance status, tumor size and gene alterations which limit the accurate interpretation of these results. Third, surgery methods and chemotherapy regimens were unknown, and the effect of potential advances in chemotherapy could not be evaluated, thus limiting our ability to describe treatment patterns for SCCP patients.

In conclusion, we performed a population-based study to yield a crude stratification of prognoses for SCCP patients based on the data from SEER database. The results showed that the prognosis of SCCP patients was poor with a mOS of only 3.0m, and distant metastases were independent prognostic factors of worse survival in SCCP patients, surgery and chemotherapy were independent protective factors. The present study was the largest series investigating the clinical characteristics and outcomes of SCCP patients to date and provide some useful information for future management and prospective studies for SCCP patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <http://dx.doi.org/10.21037/gs-20-317>

Conflicts of Interest: All authors declare that there is no conflict of interest (available at <http://dx.doi.org/10.21037/gs-20-317>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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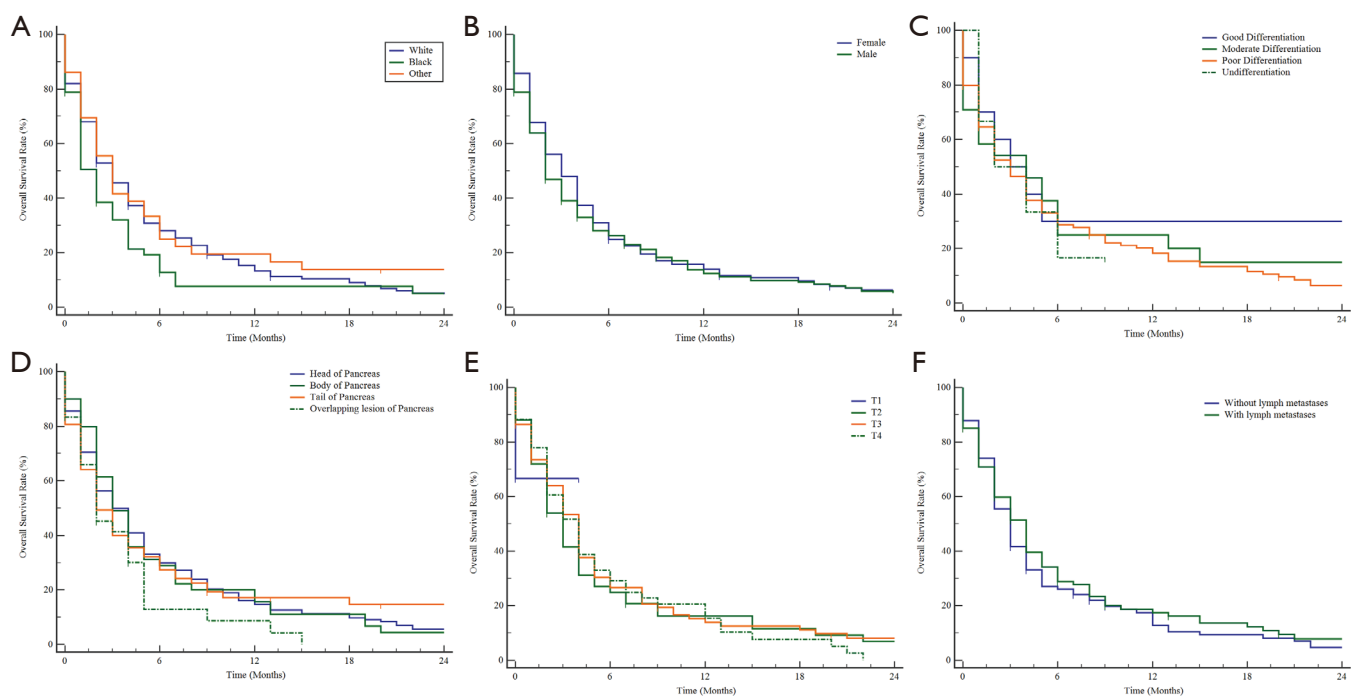


Figure S1 the effect of clinio-pathological features on prognosis in SCCP patients. (A) race; (B) gender; (C) pathological grade; (D) lesion site; (E) T stage; (F) N stage. SCCP, squamous cell carcinoma of pancreas.