Original Article

Comparative study of sarcomatoid carcinoma and carcinosarcoma of the pancreas: a population-based study

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Background: Sarcomatoid carcinoma (SCP) and carcinosarcoma (CSP) of the pancreas are extremely rare entities and little is known about their characteristics. Using a population-based cancer registry, we aimed at improving our understanding of these entities with a focus on the comparison between these two entities.

Methods: Patients with SCP or CSP were identified through the Surveillance Epidemiology and End Results (SEER) database. Demographic and clinical characteristics were collected and compared. Survival was compared using the Kaplan-Meier method and analyzed using the log-rank test and Cox proportional hazards models.

Results: A total of 85 patients with SCP and 32 patients with CSP were included in the study. There was no difference in the patient age, race distribution, year of diagnosis, primary site, tumor size, tumor stage, receipt of chemotherapy and receipt of radiotherapy between the two groups. However, more patients with CSP received surgical treatment (P<0.001) when compared to patients with SCP. Overall survival was comparable between the two groups (P=0.562) with a 1-year survival rate of 20.8% and 22.2% for SCP and CSP, respectively. Multivariate analysis showed that surgical resection was independent prognostic factor of both SCP (HR: 0.34, P=0.017) and CSP (HR: 0.17, P=0.017). Chemotherapy was a prognostic factor of CSP in univariate analysis, but not of SCP.

Conclusions: SCP and CSP are rare malignant tumors of the pancreas with a dismal prognosis. Surgical resection was the common prognostic factor and was recommended when possible.

Keywords: Sarcomatoid carcinoma; carcinosarcoma; pancreas; Surveillance, Epidemiology, and End Results (SEER)

Submitted Feb 19, 2022. Accepted for publication May 17, 2022.
doi: 10.21037/tcr-22-410
View this article at: https://dx.doi.org/10.21037/tcr-22-410

Introduction

With approximately 62,210 new cases and 49,830 deaths in 2022, pancreatic cancer was projected to be the third leading cause of cancer-related death in the United States (1). Both sarcomatoid carcinoma (SCP) and carcinosarcoma (CSP) of the pancreas are rare histological subtypes of pancreatic cancer. Histologically, SCP is an epithelial carcinoma with a sarcoma-like appearance (2), characterized by a predominant composition of spindle cells having morphologic features with epithelial derivation, such as epithelial markers and epithelial ultrastructural features (3-5). In contrast, CSP consists of two pathologically-distinct epithelial and mesenchymal components, which were distinguished by the mutually exclusive expression of cytokeratin and vimentin (6,7). Together, SCP and CSP were classified under the

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category of undifferentiated carcinoma of the pancreas by the World Health Organization (WHO) classification (8).

However, little of pathogenesis and response to different types of therapy was known about both of these two entities. Due to the rarity, previous studies in the literature were limited to case reports and small case series and sometimes were inappropriately used interchangeably [2–5]. Li *et al.* recently reported the so far largest case series of CSP from a single center with a total of nine cases (9), while the so far largest single-center case series of SCP by Blair *et al.* had a total of eight cases (3). While some authors suggest that out of practical purposes, CSP and SCP can be used interchangeably (5,10), the other authors argue that these two entities are different subtypes of pancreatic cancer and should not be confused with each other (11). Recently, using the Surveillance, Epidemiology, and End Results (SEER) database, Alhatem *et al.* reported 39 cases of CSP, which is the largest case series so far (12). However, there are no reports on SCP using the SEER database. No direct comparison between these two entities was performed before.

In the present study, to better understand SCP, using data from the SEER database, we evaluated the demographics, treatment methods, and survival outcomes of SCP and CSP and performed a direct comparison of these two diseases. We present the following article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-410/rc).

Methods

Data source

This is a retrospective study using the population-based National Cancer Institute's SEER database. The SEER database collects cancer incidence and survival data from population-based cancer registries that cover approximately 34.6% of the U.S. population. In the present study, the ASCII text version of the data: SEER 18, 1975–2016 was downloaded and used for data mining.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Because data from SEER were de-identified and publicly available for research purposes, ethical approval from the Institutional Review Board was exempted, and no informed consent was signed for this study.

Cohort selection

As treatment strategy, as well as the inspection and diagnosis method, have changed a lot after 2000, only cases diagnosed after 2000 were included in the present study. The codes of the International Classification of Oncology, third edition (ICD-O-3/WHO 2008) were used to identify eligible cases. Topographic codes C25.0-C25.4 and C25.7-C25.9 were used to identify primary pancreatic cancer cases. Topographic codes 8033 and 8980 were used to identify sarcomatoid carcinoma (a synonym of pseudosarcomatous carcinoma) and carcinosarcoma of the pancreas, respectively. Patients with a histologically confirmed diagnosis were included in the study, while patients with a diagnosis reported by autopsy only/death certificate only were excluded from the analysis.

Demographic data including age at diagnosis, year of diagnosis, sex, race, tumor location within the pancreas and tumor stage were collected. Since TNM staging information was only available for patients who were diagnosed in 2004 and afterward, SEER historic stage was adopted for tumor stage, which was reported from 1975 to 2015. According to the SEER historical staging classification, tumor stage was divided into three groups: localized, regional, and distant stage (13,14).

Treatment data included receipt of cancer-directed surgery (CDS), use of adjuvant chemotherapy and use of adjuvant radiation was collected. Survival data included vital status, cause of death, and survival time in months were collected. CDS was defined by any surgery performed on the primary tumor as a part of curative or radical treatment (15).

Statistical analysis

All data analyses were performed using Stata/MP 13.1 for Windows (StataCorp LP, College Station, TX, USA). Continuous variables were displayed as mean ± standard deviation or median (interquartile range) and were compared using student *t*-test or rank-sum test. Categorical variables were displayed as frequency and proportion and were compared using chi-square test. Overall survival rate and median overall survival were calculated using the Kaplan-Meier method and compared using log-rank test. Cox proportional hazard regression was used multivariate analysis to determine independent predictors of overall

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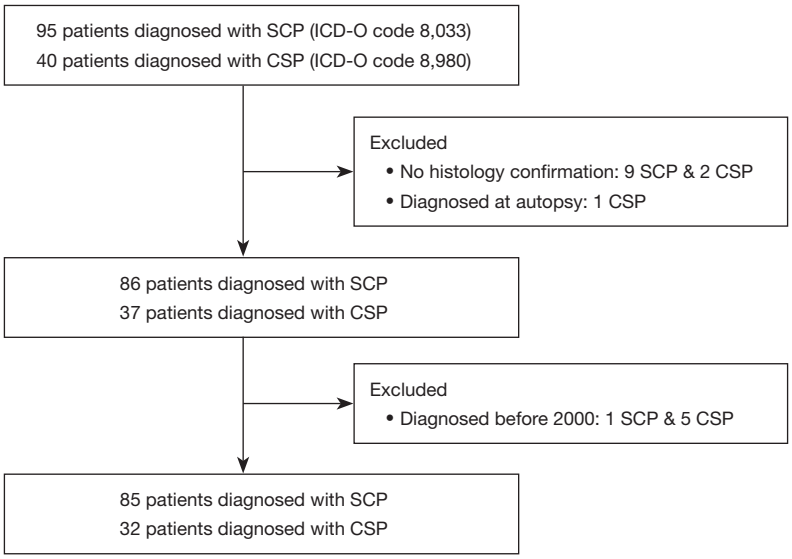

Figure 1 Patient selection flowchart. SCP, sarcomatoid carcinoma of the pancreas; CSP, carcinosarcoma of the pancreas; ICD-O, International Classification of Diseases of Oncology.

survival. Variables with a P<0.10 in univariate analysis were selected for multivariate analysis. A two-sided P<0.05 was considered to be statistically significant.

Results

Clinicopathological characteristics of patients

Between 2000 and 2016, a total of 85 patients who were histologically diagnosed with SCP were identified from the SEER database, and 32 patients with SCP were identified during the same period (*Figure 1*). The demographic and clinicopathological characteristics of the two entities are shown in *Table 1*.

Between the two subtypes of cancer (SCP versus CSP), patients have similarly distributions in age at diagnosis (69.5±11.9 versus 68.1±11.1 years, P=0.552), sex (50.6% female versus 50.0% female, P=0.955), race (82.4% White people versus 84.4% White people, P=0.833), tumor location in the pancreas (45.9% versus 40.6% at head, P=0.581) and tumor size (6.4±3.7 versus 6.4±3.7 cm, P=0.989). In addition, there was also no significant difference in terms of the year of diagnosis (P=0.581) or the tumor stage (P=0.158).

Regarding the treatment modality, patients with SCP were significantly less likely to undergo CDS (32.9% versus 78.1%, P<0.001), but with a similar chance to receive chemotherapy (P=0.892) and radiation therapy (P=0.877).

Survival outcomes

The observed overall survival was similar in patients with SCP compared with those with CSP in the overall cohort (P=0.562) (*Figure 2A*). The survival analysis revealed that the median overall survival was 3 months (95% CI: 2–5 months) and 8 months (95% CI: 4–9 months) for SCP and CSP, respectively. The overall survival rates in patients with SCP were 20.8% (95% CI: 11.9–31.5%) at 1 year and 15.9% (95% CI: 8.1–25.9%) at 3 years; in patients with CSP were 22.2% (95% CI: 9.1–38.8%) at 1 year and 11.1% (95% CI: 2.8–28.8%) at 3-year. Median overall survival comparisons for different subgroups of all factors between SCP and CSP were shown in *Table 2*. Survival comparisons for patients who underwent CDS (*Figure 2B*), patient with (*Figure 2C*) or without (*Figure 2D*) chemotherapy did not show significant difference.

Prognostic factors

In patients with SCP, univariate analysis showed that tumor stage and surgery were prognostic factors of overall survival. Subsequent multivariate analysis indicated that surgery was the only independent prognostic factor of overall survival (HR: 0.34; 95% CI: 0.14–0.83; P=0.017; *Table 3*). In patients with CSP, univariate analysis showed that not only tumor stage and surgery but also chemotherapy and race were prognostic factors of overall survival. Subsequent

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Table 1 Patient demographics and tumor characteristics

Variables	SCP (n=85), n (%)	CSP (n=32), n (%)	P
Age[‡], years	69.5±11.9	68.1±11.1	0.552
Sex			0.955
Female	43 (50.6)	16 (50.0)	
Male	42 (49.4)	16 (50.0)	
Race			0.833
White	70 (82.4)	27 (84.4)	
Black	11 (12.9)	3 (9.4)	
Asian/Pacific Islander	4 (4.7)	2 (6.2)	
Year of diagnosis			0.368
2000–2009	27 (31.8)	13 (40.6)	
2010–2016	58 (68.2)	19 (59.4)	
Primary site			0.581
Head	39 (45.9)	13 (40.6)	
Body/tail	26 (30.6)	13 (40.6)	
Other[¶]	20 (23.5)	6 (18.8)	
Tumor size, cm*	6.4±3.7	6.4±3.7	0.989
SEER stage[#]			0.158
Localized	7 (9.0)	3 (9.7)	
Regional	24 (30.8)	14 (45.2)	
Distant	47 (60.3)	13 (41.9)	
Unknown	0 (0.0)	1 (3.2)	
CDS			<0.001
Yes	28 (32.9)	25 (78.1)	
No	57 (67.1)	7 (21. 9)	
Chemotherapy			0.892
Yes	36 (42.3)	14 (43.7)	
No/unknown	49 (57.7)	18 (56.3)	
Radiation			0.877
Yes	6 (7.1)	2 (6.3)	
No/unknown	79 (92.9)	30 (93.7)	

[‡], data are shown as mean ± standard deviation; [¶], including other specified parts of pancreas (Code of the International Classification of Oncology, third edition: C257), Overlapping lesion of pancreas (C258), and Pancreas, NOS (C259); *, exact data available for 74 cases of SCP and 28 cases of CSP; [#], data not available for 8 cases who were diagnosed in 2016. SCP, sarcomatoid carcinoma of the pancreas; CSP, carcinosarcoma of the pancreas; SEER, Surveillance Epidemiology and End Results; CDS, cancer-directed surgery.

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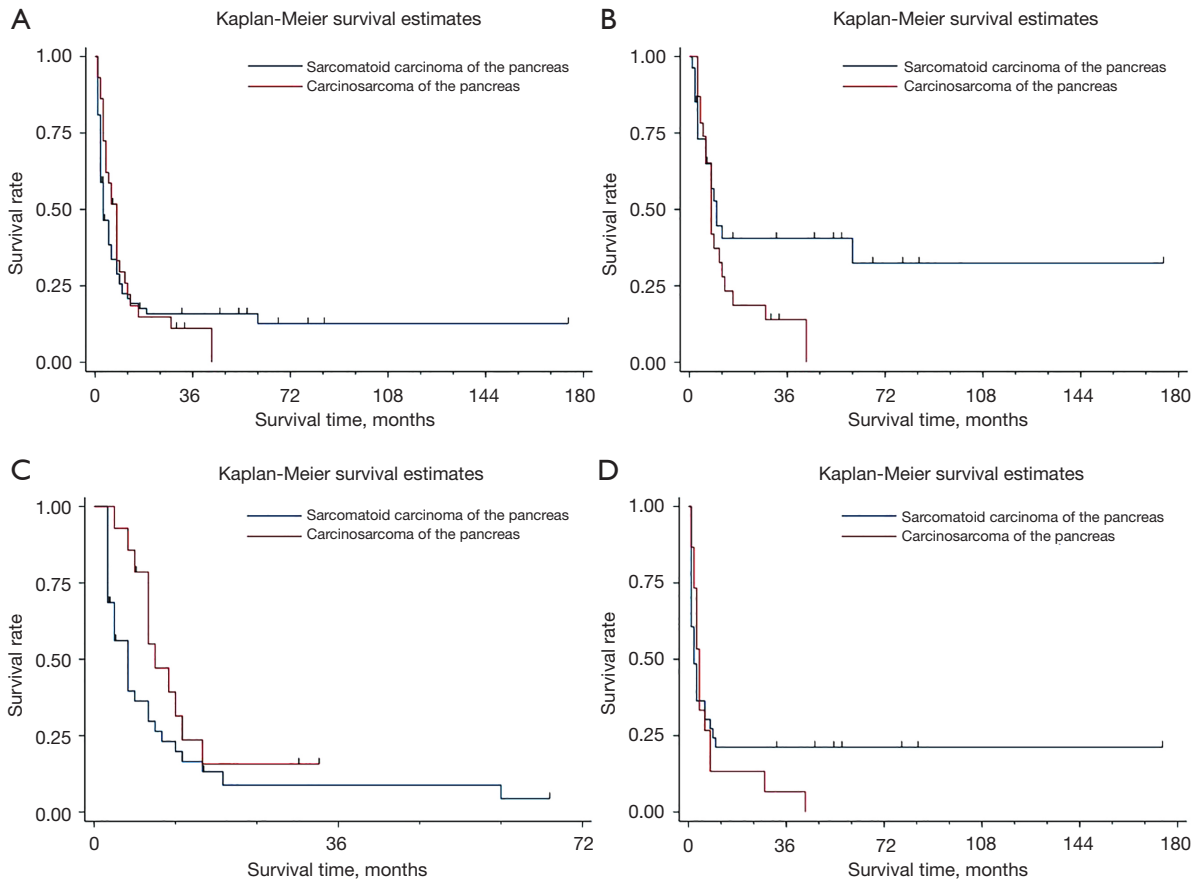

Figure 2 Survival comparison between patients with sarcomatoid carcinoma and carcinosarcoma of the pancreas. (A) Comparison between entire cohorts (P=0.562); (B) comparison between subgroups with cancer-direct surgery (P=0.115); (C) comparison between subgroups with chemotherapy (P=0.102); (D) comparison between subgroups without chemotherapy (P=0.586).

multivariate analysis indicated that CDS (HR: 0.17; 95% CI: 0.04–0.72; P=0.017) was the only independent prognostic factors of CSP, but race, tumor stage, and chemotherapy were not any more.

Discussion

SCP and CSP are extremely rare histological subtypes of pancreatic cancer. Using data from the population-based SEER database, this study is the first to be able to perform direct comparisons of clinicopathological characteristics, treatment modalities and survival outcomes between these two entities. Both SCP and CSP are likely to occur in the late 60s of the patients with a nearly even distribution in sex. There are no significant differences in race, the year of diagnosis, primary tumor location, tumor size, SEER stage, receipt of chemotherapy and receipt of radiation between the two entities. Overall survival was also comparable between the two entities. However, when compared to patients with SCP, patients with CSP were more likely to undergo CDS.

SCP is characterized by a predominance of spindle cells and sarcomatous morphologic features with epithelial derivation. CSP is characterized by epithelial (carcinomatous) and mesenchymal (sarcomatous) components. The pathogeneses of both SCP and CSP remain to be elucidated. SCP is believed to have an entirely epithelial origin (11,16). By using genomic and molecular analysis, recent studies suggested that the two components of CSP have a monoclonal origin since they have the same KRAS and TP53 mutations (6,9). Other proposed pathogenesis theories of CSP include combination theory, which denotes that a combination of epithelial and mesenchymal cells underwent early differentiation from a

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Table 2 Median overall survival for different subgroups

Subgroups	SCP, months (95% CI)	CSP, months (95% CI)	P
Entire cohort	3 (2, 5)	8 (4, 9)	0.562
Age, years			
<70	3 (3, 5)	8 (2, 16)	0.244
≥70	5 (2, 8)	5 (3, 8)	0.617
Sex			
Female	3 (2, 6)	6 (3, 12)	0.840
Male	3 (2, 8)	8 (4, 11)	0.500
Race			
White	3 (2, 8)	8 (4, 11)	0.784
Black	2 (1, 5)	2 (2, –)	0.979
Asian/Pacific Islander	5 (1, –)	4 (4, –)	0.501
Year of diagnosis			
2000–2009	3 (2, 10)	6 (3, 11)	0.858
2010–2016	3 (2, 6)	8 (4, 16)	0.413
Primary site			
Head	3 (2, 6)	8 (3, 28)	0.624
Body/tail	5 (2, 6)	5 (3, 11)	0.985
Other[¶]	3 (2, 10)	6 (1, –)	0.761
Tumor size*			
<6 cm	3 (2, 8)	6 (4, 8)	0.885
≥6 cm	3 (2, 5)	8 (2, 13)	0.305
SEER stage[#]			
Localized	16 (2, –)	11 (3, –)	0.844
Regional	9 (2, 60)	9 (6, 16)	0.501
Distant	2 (2, 3)	3 (1, 5)	0.936
CDS			
Yes	10 (6, –)	8 (6, 12)	0.115
No	2 (2, 3)	2 (1, –)	0.254
Chemotherapy			
Yes	5 (3, 8)	9 (6, 13)	0.102
No/unknown	2 (1, 6)	4 (2, 6)	0.586
Radiation			
Yes	5 (2, –)	6 (6, –)	0.622
No/unknown	3 (2, 6)	8 (3, 9)	0.628

[¶], including other specified parts of pancreas (Code of the International Classification of Oncology, third edition: C257), Overlapping lesion of pancreas (C258), and Pancreas, NOS (C259). *, exact data available for 74 cases of SCP and 28 cases of CSP; [#], data not available for 8 cases who were diagnosed in 2016. SCP, sarcomatoid carcinoma of the pancreas; CSP, carcinosarcoma of the pancreas; CI, confidence interval; SEER, Surveillance Epidemiology and End Results; CDS, cancer-directed surgery.

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Table 3 Uni- and multivariate survival analysis

Variables	SCP			CSP		
	Univariate*	Multivariate		Univariate*	Multivariate	
	P	HR (95% CI)	P	P	HR (95% CI)	P
Age[#]	0.402			0.314		
Sex[‡]	0.983			0.907		
Race	0.306			0.045		
White					Reference	
Black					2.73 (0.48, 15.48)	0.257
Asian/Pacific Islander					2.12 (0.21, 21.63)	0.525
YOD[&]	0.909			0.256		
Primary site[//]	0.875			0.465		
Tumor size[§]	0.556			0.234		
SEER stage[#]	<0.001[a]			<0.001		
Localized		0.62 (0.20, 1.94)	0.413		0.94 (0.20, 4.46)	0.936
Regional		Reference			Reference	
Distant		1.33 (0.53, 3.35)	0.545		3.13 (0.94, 10.47)	0.064
Unknown		–			NA	
CDS	<0.001[a]			<0.001		
No/unknown		Reference			Reference	
Yes		0.34 (0.14, 0.83)	0.017		0.17 (0.04, 0.72)	0.017
Chemotherapy	0.778			0.032		
Yes					Reference	
No/unknown					0.71 (0.29, 1.78)	0.469
Radiation[¶]	0.792			0.719		

*, calculated using the log-rank test; [#], <70 versus ≥70 years; [‡], female versus male; [&], 2000–2009 versus 2010–2016; [//], head of the pancreas versus body/tail versus other sites; [§], <6 versus ≥6 cm; [¶], yes versus no/unknown. SCP, sarcomatoid carcinoma of the pancreas; CSP, carcinosarcoma of the pancreas; HR, hazard ratio; CI, confidence interval; YOD, year of diagnosis; SEER, Surveillance Epidemiology and End Results; CDS, cancer-directed surgery.

common stem cell (17,18); collision theory, which denotes that two independently growing carcinomas and sarcomas collide together (19); and transformation theory, which denotes that a section of the carcinoma transforms into a sarcomatous component (20,21). Mesenchymal tumor differentiation exists both in CSP and SCP (5,6). Therefore, the epithelial-mesenchymal transition may play a role in the formation of CSP and SCP (3).

In the present study, we found more patients with CSP received surgical treatment. This might be because that less patients with CSP were diagnosed with distant stage when compared with patients with SCP, although statistically insignificant. We also found that chemotherapy was a prognostic factor of CSP but not of SCP in the univariate analysis. This suggests that these two entities may have different tumor biology and responded differently to chemotherapy. Therefore, we believe SCP and CSP should be regarded as different subtypes of pancreatic cancer and these two terms should not be used interchangeably, although they were classified as the same entity, namely undifferentiated carcinoma of the pancreas by WHO (8). Multivariate analysis showed that CDS was the

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only independent prognostic factor of both CSP and SCP, which indicating both diseases were surgical disease. This was in line with the findings that patients could achieved long-term survival after margin-negative surgery with or without adjuvant chemotherapy (22-24). However, further results from larger prospective studies are needed.

The findings derived from this study should be interpreted with caution since there were several limitations to this study, which were inherent to the use of the SEER database (25). First, even though this study was the so far largest series comparing SCP and CSP, the sample size was still relatively small due to the rarity of the two entities. Second, a centralized histopathologic review of the diagnosis along with lab examinations and imaging was not possible (26). However, it is reasonable to believe that to make a pathological diagnosis of rare cancer, one or several senior pathologists would be consulted. Therefore, we assumed that the diagnosis was correct in most cases. This assumption probably is the common prerequisite for all SEER-based paper that focus on rare cancers. Third, the data of the variables provided by SEER database is not perfect, especially for radiation therapy and chemotherapy, which is reported that overall sensitivity was 68% for SEER chemotherapy data and 80% for SEER radiation therapy data (27). Fourth, this study had a retrospective design in nature. Therefore, it has a predisposition to potential bias, including the biases associated with unmeasured reasons for receiving or not receiving chemotherapy/radiation therapy. Nevertheless, SEER is still a useful resource that allows for a meaningful study of rare subtypes of pancreatic cancer and this study provided the first comparative investigation that would be difficult to perform otherwise (28,29).

Conclusions

In conclusion, using data from the SEER database, this study was the first to compare the clinicopathological characteristics between SCP and CSP. The analysis found that SCP and CSP are rare malignant tumors of the pancreas with a similar dismal prognosis. SCP and CSP might respond differently to chemotherapy. Surgical resection was the prognostic factor and was recommended when possible. Further prospective large studies were needed.

Acknowledgments

We thank The Surveillance, Epidemiology, and End Results (SEER) Program for providing the information.

Funding: This work was supported by Hangzhou Health Science and Technology Program (A20210271 to Xinchun Liu).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-410/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-410/coif). XL received funding from Hangzhou Health Science and Technology Program (A20210271). The other 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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Cite this article as: Liu X, Wang H, Ying R. Comparative study of sarcomatoid carcinoma and carcinosarcoma of the pancreas: a population-based study. Transl Cancer Res 2022;11(7):2061-2069. doi: 10.21037/tcr-22-410

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