Original Article

Increased risk of multiple metastases and worse overall survival of metastatic pancreatic body and tail cancer: a retrospective cohort study

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Background: Pancreatic cancer (PC) is a lethal disease, especially metastatic PC. And it can be divided into two types: head pancreatic cancer (H-PC) and body and tail pancreatic cancer (BT-PC). Prior studies have proved that they have different overall survival (OS) and should be regarded as two different categories of PC. At present, there remains a gap in the field regarding OS across different primary tumor locations and metastatic sites, as well as the metastatic patterns associated with various primary tumor locations in patients with metastatic PC. Thus, our study aims to address this gap by analyzing data from a large population sourced from the Surveillance, Epidemiology, and End Results (SEER) database. The different prognosis of different primary tumor locations and metastatic sites may indicate that different primary locations and metastatic sites may require different therapy and follow-up strategy. It is hoped that these findings will lay the groundwork for future guideline updates and related research.

Methods: Patients with pathologically confirmed stage IV metastatic PC from the National Cancer Institute's SEER program between 2010 and 2015 were included, excluding patients with various tumors, without specifying age, specific sites of metastasis, or OS. Data including age, race, gender, tumor size, T stage, N stage, grade, sites, number of metastatic sites, surgery, radiotherapy, chemotherapy and years of diagnoses were collected from the SEER database. OS was defined as the period from initial diagnosis to the date of death. Specific metastatic sites for the different primary locations of tumor were compared. Survival was analyzed by Cox regression analyses.

Results: Overall, 14,406 patients with metastatic PC were included in this research (7,104 of H-PC and 7,302 of BT-PC). Gender proportion, tumor size, T stage, N stage, number of metastatic sites surgery of the primary lesions and radiotherapy were different between BT-PC and H-PC. The proportion of only 1 metastatic site was 68.3% in H-PC compared with 58.3% in the BT-PC. The BT-PC was an independent risk factor for liver metastases compared with the H-PC [odds ratio (OR) =1.510; 95% confidence interval (CI): 1.320–1.727]. No matter for those with multiple metastases, or for those with solitary liver or lung metastases, patients with metastatic H-PC showed better OS (P<0.001, P=0.001, P=0.04, respectively). In patients with solitary liver metastases, worse OS was observed in the BT-PC than the H-PC [hazard ratio (HR) =1.109; 95% CI: 1.046–1.175].

Conclusions: The metastatic BT-PC had worse OS and increased risk to suffer from liver and multiple metastases. Moreover, in patients with solitary metastases, those with liver metastases presented poorest survival.

Keywords: Pancreatic cancer (PC); metastases; location; risk factors; survival

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Introduction

Pancreatic cancer (PC) is a lethal disease with poor survival, 466,000 patients died out of the total cases 496,000 recorded. It is the seventh leading cause of cancer death (1). Radical resections are considered as the only way to cure this malignant tumor, however, most patients lose the chance of operation at initial diagnosis, only 15–20% of patients are with resectable PC (2). Patients with PC could be divided into two types according to the locations of primary tumor locations: head pancreatic cancer (H-PC) and body and tail pancreatic cancer (BT-PC). Previous studies have shown that the overall survival (OS) of PC varies with the different sites of primary tumor locations. For all patients with PC, most research supports that better survival is witnessed in patients with H-PC compared with BT-PC (3-6). And it may be attributed to the early onset of jaundice of H-PC, while BT-PC is usually detected late due to lack of early specific symptoms. The different prognosis between H-PC and BT-PC indicates that they should be regarded as two different categories of PC. But for patients underwent surgery, BT-PC showed better OS (7). The prognosis of patients with metastatic PC is extremely poor as most of them lose the chance to undergo radical resection. As reported in a recent Dutch population-based study which involved 5,385 patients with metastatic PC, the median OS was 9.6 weeks (8). According to the National Comprehensive Cancer Network (NCCN) guidelines, patients with metastatic PC are recommended to participate in clinical trials or receive systemic therapy, including FOLFIRINOX and gemcitabine plus nab-paclitaxel. Generally, the common metastatic sites of PC are liver, lung, distant lymph nodes, bone and brain (9). Patients with multiple metastatic sites has worse OS than those with solitary metastases. Different metastatic sites also represent various OS. Patients with solitary liver metastases showed decreased OS compared to other metastatic sites (10,11).

Considerable research has investigated the survival of different primary tumor locations and metastatic sites in patients with PC. However, there has been a dearth of studies specifically focusing on metastatic PC. Existing research has primarily examined prognostic factors associated with metastatic PC, with a limited number of studies shedding light on this aspect. For instance, Xiao *et al.* identified elevated serum gamma-glutamyltransferase as a potential predictor of poorer OS (12). And another study showed that increased circulating NPTX2 methylation levels were associated with poor prognosis (13). Despite these findings, there remains a gap in the field regarding OS across different primary tumor locations and metastatic sites, as well as the metastatic patterns associated with various primary tumor locations in patients with metastatic PC. Thus, our study aims to address this gap by analyzing data from a large population sourced from the Surveillance, Epidemiology, and End Results (SEER) database. Currently, the NCCN guidelines have incorporated the impact of primary site on treatment decisions for colon cancer (14). While the NCCN guidelines for pancreatic head and body/tail cancers are currently the same, as mentioned earlier, their prognoses differ significantly. Therefore, the clinical significance of this study lies in exploring the differences in prognosis and patterns of metastasis among metastatic PC originating from different primary sites, as well as investigating the prognostic differences among metastatic PC at different metastatic sites. The different prognosis

Highlight box

Key findings

- Metastatic body and tail pancreatic cancer (BT-PC) had worse overall survival (OS) and increased risk to suffer from liver and multiple metastases.
- Patients with solitary liver metastases had worse OS compared with those with other solitary metastases.

What is known and what is new?

- Patients with liver metastases showed decreased OS has been reported.
- This study finds that metastatic BT-PC has worse OS and metastatic pattern, addressing the gap in this field.

What is the implication, and what should change now?

- The findings support that metastatic pancreatic head cancer and BT-PC may be treated and followed-up in different ways due to the different prognosis.
- More real-world clinical trials are needed to lay the groundwork for updating guidelines for PC, particularly regarding the primary location of metastatic PC.

may indicate that different primary locations and metastatic sites may require different therapy and follow-up strategy. It is hoped that these findings will lay the groundwork for future guideline updates and related research. We present this article in accordance with the STROBE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-465/rc).

Methods

Data source

Data from the National Cancer Institute's SEER program between 2010 and 2015 were collected and analyzed. The program includes the population-based central cancer registries of 18 geographically defined regions. The study did not require an approval or a declaration due to all the data used in the study were from the SEER database of publicly available data. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Patient selection

For this study, patients with PC with pathology codes 8000, 8010, 8140, 8141, 8144, 8211, 8255, 8490, 8500, 8020 and 8021 were enrolled. And then, we selected those who were diagnosed during 2010 to 2015. Then, patients with specific sites of primary tumor were selected and were classified based on the tumor locations: head (C25.0), body (C25.1), tail (C25.2). Besides, pathological confirmations were also required and patients with diagnosed stage IV disease were remained. We excluded all patients without data about specific sites of metastases and OS. Furthermore, patients with multiple tumors and unknown ages were excluded as well.

Information of age at diagnosis, gender, race, tumor size, T stage, N stage, site of metastases, surgery of primary tumors, survival months, chemotherapy, radiotherapy, grade, specific year of diagnoses was collected.

Variables of patients

Data about demographic elements (age, race, gender), tumor-related elements (tumor size, T stage, N stage, grade, sites and number of metastatic sites), therapeutic elements (surgery, radiotherapy and chemotherapy) and years of diagnoses were collected from the SEER database. OS was defined as the period from initial diagnosis to the date of death.

Statistical analysis

We used the χ^2 test to analyze the dichotomous outcomes. Metastatic sites were analyzed for each primary tumor site, including solitary metastatic sites and combined metastatic sites.

For those with the solitary liver or lung metastases, both univariable and multivariable logistic regression analyses were used to assess the interaction between metastatic sites and primary tumor locations. And we used odds ratio (OR) with 95% confidence interval (CI) to represent the results.

Survival was analyzed for each metastatic site and different primary tumor location by Log-rank analyses and Kaplan-Meier method.

Univariate and multivariate Cox regression analyses were performed on all variables to determine independent prognostic factors, hazard ratios (HRs) with 95% CI were used to present the results. Besides primary tumor locations and metastatic sites, the variables used in the multivariable analyses also included gender, age, race, tumor size, T and N stages, surgery of the primary tumor, radiotherapy, chemotherapy, and period of diagnosis. Metastatic sites were categorized as liver only, lung only, distant lymph nodes only, bone and brain only and multiple metastatic sites.

Statistically significance was defined as P values less than 0.05 (bilateral). We used SPSS Statistics for Windows (version 26.0) for all analyses.

Results

Clinicopathological characteristics according to tumor locations

Overall, 14,406 patients, who were diagnosed with metastatic PC during the period of 2010 to 2015, were involved in this research (*Table 1*). There were 7,104 patients with the primary locations of pancreatic head compared to 7,302 with the primary tumors located in the pancreatic body and tail.

Characteristics of patients and tumor are shown in *Table 1*. Both the H-PC and the BT-PC were found on male (52.5% and 55.9%, respectively) more frequently than on female, however, the BT-PC was seen more often on male than the H-PC (P<0.001). When it comes to the age and

Table 1 Patient and tumor characteristics for pancreatic cancer, stratified to primary tumor location

Characteristics	Head (n=7,104)	Body/tail (n=7,302)	P value
Gender			<0.001
Male	3,728 (52.5)	4,082 (55.9)	
Female	3,376 (47.5)	3,220 (44.1)	
Age (years)	66.7±11.3	66.5±11.0	0.08
Race			0.45
White	5,625 (79.2)	5,718 (78.3)	
Black	937 (13.2)	1,004 (13.8)	
Other	525 (7.4)	561 (7.7)	
Unknown	17 (0.2)	19 (0.2)	
Tumor size			<0.001
≤2 cm	472 (6.7)	318 (4.4)	
>2 cm	5,478 (77.1)	6,120 (83.8)	
Unknown	1,154 (16.2)	864 (11.8)	
T stage			<0.001
T1	225 (3.2)	174 (2.4)	
T2	1,714 (24.1)	2,287 (31.3)	
T3	2,578 (36.3)	1,882 (25.8)	
T4	1,243 (17.5)	1,478 (20.2)	
Unknown	1,344 (18.9)	1,481 (20.3)	
N stage			<0.001
N0	3,477 (48.9)	3,859 (52.8)	
N1	2,626 (37.0)	2,269 (31.1)	
Unknown	1,001 (14.1)	1,174 (16.1)	
Grade			0.41
G1	118 (1.6)	91 (1.3)	
G2	622 (8.8)	556 (7.6)	
G3	912 (12.8)	762 (10.4)	
G4	54 (0.8)	35 (0.5)	
Unknown	5,398 (76.0)	5,858 (80.2)	
Number of metastatic sites			<0.001
1	4,853 (68.3)	4,255 (58.3)	
≥2	1,286 (18.1)	1,688 (23.1)	
Unknown	965 (13.6)	1,359 (18.6)	
Surgery of the primary			<0.001
Yes	244 (3.5)	140 (1.9)	
No	6,849 (96.4)	7,154 (98.0)	
Unknown	11 (0.1)	8 (0.1)	
Radiotherapy			0.001
Yes	414 (5.8)	337 (4.6)	
No	6,664 (93.8)	6,952 (95.2)	
Unknown	26 (0.4)	13 (0.2)	
Chemotherapy			0.16
Yes	3,924 (55.2)	4,118 (56.4)	
No	3,180 (44.8)	3,184 (43.6)	
Years of diagnosis			0.32
2010–2012	3,310 (46.6)	3,342 (45.8)	
2013–2015	3,794 (53.4)	3,960 (54.2)	

Data are presented as n (%) or mean ± standard deviation.

race, there was no significant difference between the H-PC and the BT-PC. Besides, the proportion of tumor size ≤2 cm was higher in the H-PC (6.7% *vs.* 4.4%, P<0.001). Nevertheless, the percentages of T2 and T4 stages were lower in the H-PC while the T3 stages was larger. Despite the less likelihood of invasion of artery, the H-PC suffered more from lymph nodes metastases, and N0 stage was less frequently seen in it (48.9% *vs.* 52.8%, P<0.001). The number of metastatic sites also showed a dramatic difference, the proportion of only one metastatic site was 68.3% in H-PC compared with 58.3% in the BT-PC.

Impact of tumor locations on metastatic pattern

The general percentage of different metastatic sites was similar between the H-PC and the BT-PC, with liver metastases ranked first, followed by lung metastases and distant lymph nodes metastases as the second and third place respectively, and the bone and brain metastases accounted for the least cases. Whereas, there were still some significant differences when comparing the two groups (*Figure 1A*). The distant lymph nodes metastases were found

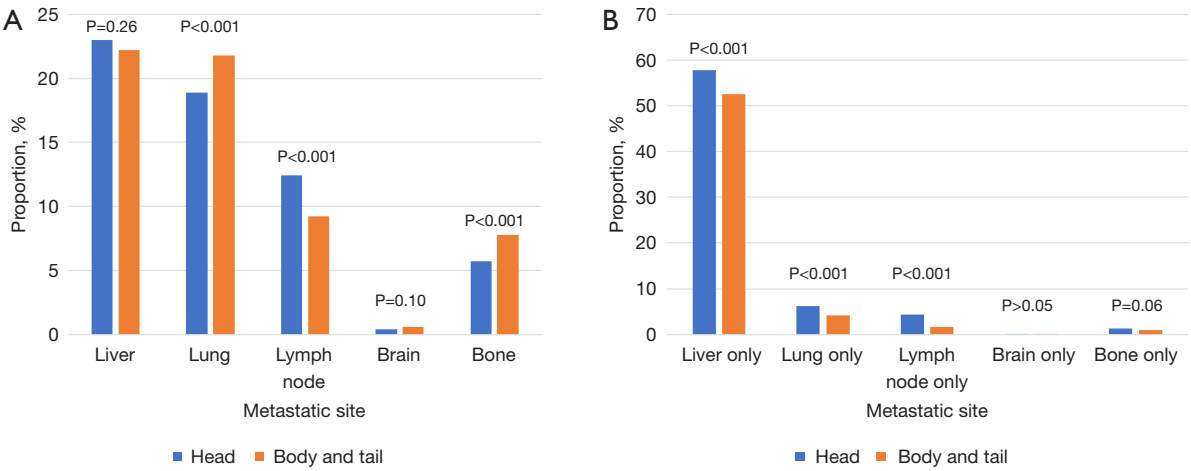

Figure 1 Distribution of different metastatic sites. (A) Distribution of all combinations of metastatic sites. (B) Distribution of solitary metastatic sites. Patients with unknown specification of metastatic organ sites were excluded.

more frequently in the H-PC (12.41%) compared with the BT-PC (9.19%, P<0.001). On the other hand, less patients with the H-PC suffered from the lung metastases (18.14% *vs.* 20.80%, P<0.001).

Patients with solitary metastatic site were also analyzed and there were significant differences on almost each site (*Figure 1B*). The H-PC were more likely to suffer from the solitary liver, lung and distant lymph nodes metastases (P<0.001, respectively). In patients with metastatic PC, the multivariate logistic analysis indicated that the BT-PC was an independent risk factor for liver metastases compared with the H-PC (OR =1.510; 95% CI: 1.320–1.727) (*Table 2*). On the contrary, in patients with lung metastases, multivariate logistic analysis showed that there was not significant difference between the BT-PC and the H-PC (*Table 2*).

Impact of tumor locations on OS in patients with combined metastases

The OS for patients with metastatic PC is shown in *Figure 2*. No matter for those with multiple metastases, or for those with solitary liver or lung metastases, patients with metastatic H-PC showed better OS (P<0.001, P=0.001, P=0.04, respectively).

After the univariate and multivariate analysis of the OS of all patients (*Table 3*), the BT-PC was deemed as an independent prognosis factor compared with the H-PC (HR =1.094; 95% CI: 1.043–1.147). Female and old age (>65 years) were considered as prognostic factors as well (HR =0.933, 95% CI: 0.890–0.978; HR =1.209, 95% CI: 1.152–1.268, respectively). Patients who underwent resections of the primary tumors had a better OS than those who did not (HR =0.400; 95% CI: 0.344–0.466). In addition, patients who underwent radiotherapy or chemotherapy had a better OS than those who did not (HR =0.822, 95% CI: 0.741–0.912; HR =0.321, 95% CI: 0.305–0.337, respectively). Besides, patients with lung only or distant lymph nodes only metastases had a better OS than those with liver only (HR =0.733, 95% CI: 0.663–0.811; HR =0.684, 95% CI: 0.603–0.776, respectively), while those with multiple metastatic sites showed a worse OS (HR =1.300; 95% CI: 1.227–1.378). However, patients with bone or brain only metastases had a similar OS as those with liver only (HR =1.011; 95% CI: 0.822–1.243). Patients who were diagnosed during 2013–2015 seemed to have a better OS than those during 2010–2012.

Impact of tumor locations on OS in patients with solitary metastases

In patients with solitary liver metastases, worse OS was observed in the BT-PC than the H-PC (HR =1.109; 95% CI: 1.046–1.175) (*Table 4*), while no significant difference was seen in patients with solitary lung metastases (*Table 4*). In contrast, better OS was shown in the BT-PC (HR =0.631; 95% CI: 0.466–0.856) in those with solitary distant lymph nodes metastases (*Table 4*). Besides, larger tumor size might mean worse OS in patients with solitary liver metastases. But when it came to the patients with solitary

Table 2 Multivariable logistic analysis for liver metastases or lung metastases of PC, and stratified to metastatic sites

Characteristics	Liver		Lung	
	OR (95% CI)	P value	OR (95% CI)	P value
Primary tumor site				
Head	1		1	
Body/tail	1.510 (1.320–1.727)	0.03	1.027 (0.897–1.176)	0.70
Gender				
Male	1		1	
Female	0.729 (0.640–0.830)	<0.001	1.419 (1.240–1.624)	<0.001
Age				
≤65 years	1		1	
>65 years	0.706 (0.617–0.808)	<0.001	1.523 (1.327–1.749)	<0.001
Tumor size				
≤2 cm	1		1	
>2 cm	1.499 (1.043–2.153)	0.03	1.212 (0.769–1.910)	0.41
N stage				
N0	1		1	
N1	0.623 (0.545–0.712)	<0.001	0.963 (0.838–1.107)	0.60

Variables also included the race, the T stage, surgery of the primary tumor, chemotherapy, radiotherapy, years of diagnosis, and number of metastatic sites. PC, pancreatic cancer; OR, odds ratio; CI, confidence interval.

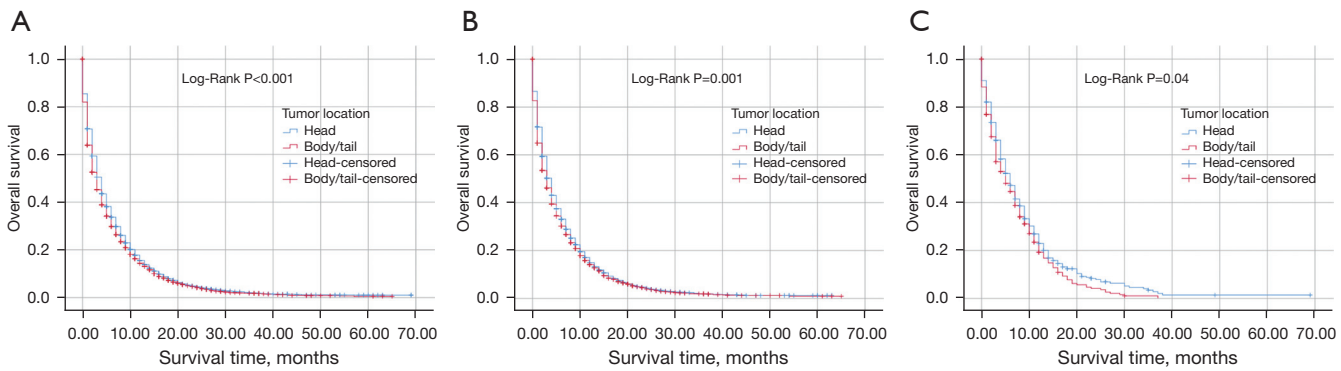

Figure 2 Overall survival for patients with metastatic sites. Survival was analyzed per metastatic site and stratified to primary tumor location. (A) All metastatic patients. (B) Patients with solitary liver metastases. (C) Patients with solitary lung metastases.

lung and distant lymph nodes metastases, tumor size seemed to play a dispensable role in OS.

Discussion

To the best of our knowledge, this is the largest population-based study regarding the prognosis of metastatic PC until now. In this research, primary locations of PC was demonstrated to be an independent factor of survival. Furthermore, the OS varied with different metastatic sites.

The BT-PC are larger in size, as a consequence, there are more regional lymph nodes involved because larger tumor size (within 4 cm) is deemed to be related to more lymph nodes involved according to recent research (15). In

Table 3 Survival analyses of all patients with metastatic pancreatic cancer

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Primary tumor site				
Head	1		1	
Body/tail	1.093 (1.056–1.132)	<0.001	1.094 (1.043–1.147)	<0.001
Gender				
Male	1		1	
Female	0.962 (0.929–0.997)	0.03	0.933 (0.890–0.978)	0.004
Age				
≤65 years	1		1	
>65 years	1.341 (1.295–1.389)	<0.001	1.209 (1.152–1.268)	<0.001
Tumor size				
≤2 cm	1		1	
>2 cm	1.151 (1.065–1.245)	<0.001	1.279 (1.087–1.504)	0.003
Surgery of the primary				
Yes	0.451 (0.401–0.507)	<0.001	0.400 (0.344–0.466)	<0.001
No	1		1	
Radiotherapy				
Yes	0.711 (0.657–0.769)	<0.001	0.822 (0.741–0.912)	<0.001
No	1		1	
Chemotherapy				
Yes	0.334 (0.322–0.347)	<0.001	0.321 (0.305–0.337)	<0.001
No	1		1	
Years of diagnosis				
2010–2012	1		1	
2013–2015	0.944 (0.911–0.977)	0.001	0.953 (0.909–0.999)	0.044
Metastatic organ site				
Liver only	1		1	
Lung only	0.777 (0.715–0.844)	<0.001	0.733 (0.663–0.811)	<0.001
Distant lymph nodes only	0.651 (0.584–0.725)	<0.001	0.684 (0.603–0.776)	<0.001
Bone and brain only	0.923 (0.779–1.094)	0.34	1.011 (0.822–1.243)	0.92
Multiple metastatic sites	1.291 (1.232–1.352)	<0.001	1.300 (1.227–1.378)	<0.001

HR, hazard ratio; CI, confidence interval.

Table 4 Survival analyses of pancreatic cancer patients with solitary liver metastases, solitary lung metastases or solitary distant lymph nodes metastases, and stratified to metastatic sites

Characteristics	Liver		Lung		Distant nodes	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Primary tumor site						
Head	1		1		1	
Body/tail	1.109 (1.046–1.175)	0.001	1.159 (0.947–1.419)	0.15	0.631 (0.466–0.856)	0.003
Age						
≤65 years	1		1		1	
>65 years	1.219 (1.150–1.293)	<0.001	1.305 (1.052–1.618)	0.02	1.413 (1.075–1.859)	0.01
Tumor size						
≤2 cm	1		1		1	
>2 cm	1.338 (1.080–1.658)	0.008	0.700 (0.411–1.193)	0.19	1.419 (0.733–2.605)	0.26
Surgery of the primary						
Yes	0.404 (0.336–0.486)	<0.001	0.553 (0.326–0.939)	0.03	0.342 (0.216–0.540)	<0.001
No	1		1		1	
Radiotherapy						
Yes	0.764 (0.659–0.885)	<0.001	1.128 (0.765–1.662)	0.54	0.514 (0.352–0.749)	0.001
No	1		1		1	
Chemotherapy						
Yes	0.331 (0.311–0.353)	<0.001	0.308 (0.249–0.380)	<0.001	0.308 (0.233–0.406)	<0.001
No	1		1		1	

Variables also included gender, race, T stage, N stage and years of diagnosis. HR, hazard ratio; CI, confidence interval.

spite of larger tumor size, the H-PC have less T4 indicating that it was less involved to artery. It may be explained partly by the better biological behavior of the H-PC.

The solitary metastases occurred in the H-PC more frequently while the BT-PC suffered more from the multiple metastases which represent a worse OS. According to a recent study, the H-PC was associated with the squamous subtype which indicated a wore OS (4). Besides, the BT-PC enriched for gene programs related to tumor invasion and epithelial-to-mesenchymal transition, and exhibited a dampened anti-tumor immune response and increased immune avoidance. As a result, the BT-PC had worse biological behavior and OS.

The BT-PC was regarded as an independent risk factors of liver metastases in this study, as well as the male, the age no more than 65 years, the tumor size more than 2 cm and the N0 stage. It may be caused by the late onset symptoms of BT-PC and it led to liver metastases, which were deemed as the most common metastatic site, and probably had already happened at the time of diagnosis. On the other hand, the risk factors of lung metastases included the female, the age more than 65 years. In a retrospective study, large primary tumor (>8 cm) and poorly differentiated histological tumor grade were also deemed as highly related to the lung metastases (16). Patients with lung metastases benefit from the surgery and chemotherapy, but radiotherapy seems to be meaningless. It may be explained by the low use of radiotherapy in PC and most of the time, radiotherapy is performed to improve the effect of chemotherapy. A study focused on PC with lung metastases showed the corresponding results (17). So, surgery may be alternative after neoadjuvant chemotherapy, at the same time, local radiotherapy may be performed to control local symptom and enhance systematic therapy. However, more research with real-world data and randomized controlled trials should be done to investigate the efficacy of this

therapy.

It is interesting that patients diagnosed during 2013–2015 had a better OS. The main reason may be that the regime of gemcitabine plus nab-paclitaxel for metastatic PC emerged in 2013 (18,19). As an indispensable role in systematic therapy of metastatic PC, the efficient regime undoubtedly improved the OS of patients. Recently, immunotherapy combined with chemotherapy shows inspiring benefit for PC. And there is a recent study focusing on the sensitivity and resistance mechanisms of anti-programmed cell death protein 1 (PD-1) in neoadjuvant therapy (20). In this research, granulocyte-macrophage colony-stimulating factor-secreting allogeneic pancreatic ductal adenocarcinoma (PDAC) vaccine (GVAX)-induced tertiary lymphoid aggregates were found to be immune-regulatory sites in response to GVAX plus anti-PD-1. Besides, T cell activators and tumor-associated neutrophil (TAN) regulators were recommended to be combined for an effective therapy.

Although the guideline does not recommend patients with metastatic PC to undergo a radical operation of the primary tumors, we found that patients who underwent a surgery of primary tumor had a better OS. Recent research is also in favor of that (21), with the development of neoadjuvant chemotherapy, resection of primary tumor is becoming increasingly possible, however, the actual clinical benefits of resection in such cases have not yet been sufficiently investigated. The benefit and disadvantages accompanied with resections should be investigated in more high-quality research with reliable data and scientific design.

There were some limitations in this study. First, the information about tumor grade of many patients was absence. Besides, data about the comorbidity, performance status, and regimens of chemotherapy were not collected, which may cause bias and influence survival outcomes. Some other data relating to metastases such as metastatic load, tumor markers and metabolic status were not available in the database. Furthermore, data on molecular pathology were lacking, although there were significant differences between H-PC and BT-PC on squamous subtype and gene programs.

Conclusions

The metastatic BT-PC had worse OS and increased risk to suffer from liver and multiple metastases. It may be due to the late onset of symptoms, more aggressive biologic behavior, worse pathological subtype and gene programs. Moreover, patients with solitary liver metastases presented worse OS than those with solitary lung or distant lymph nodal metastases. Besides, with effective adjuvant therapy, surgery may be performed and increase the OS of patients even with metastases. Further research should focus on those factors with site-oriented approach and a better design.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-23-465/rc

Peer Review File: Available at https://gs.amegroups.com/article/view/10.21037/gs-23-465/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-23-465/coif). 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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