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WJGS

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# **ABOUT COVER**

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# **AIMS AND SCOPE**

The primary aim of World Journal of Gastrointestinal Surgery (WJGS, World J Gastrointest Surg) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, etc.

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ORIGINAL ARTICLE

# **Retrospective Study** Dissimilar survival and clinicopathological characteristics of mucinous adenocarcinoma located in pancreatic head and body/tail

Zheng Li, Xiao-Jie Zhang, Chong-Yuan Sun, Ze-Feng Li, He Fei, Dong-Bing Zhao

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# Abstract

# BACKGROUND

Growing evidence shows that pancreatic tumors in different anatomical locations have different characteristics, which have a significant impact on prognosis. However, no study has reported the differences between pancreatic mucinous adenocarcinoma (PMAC) in the head vs the body/tail of the pancreas.

# AIM

To investigate the differences in survival and clinicopathological characteristics between PMAC in the head and body/tail of pancreas.

#### **METHODS**

A total of 2058 PMAC patients from the Surveillance, Epidemiology, and End Results database diagnosed between 1992 and 2017 were retrospectively reviewed. We divided the patients who met the inclusion criteria into pancreatic head group (PHG) and pancreatic body/tail group (PBTG). The relationship between two groups and risk of invasive factors was identified using logistic regression analysis. Kaplan-Meier analysis and Cox regression analysis were conducted to compare the overall survival (OS) and cancer-specific survival (CSS) of two patient groups.

# RESULTS

In total, 271 PMAC patients were included in the study. The 1-year, 3-year, and 5year OS rates of these patients were 51.6%, 23.5%, and 13.6%, respectively. The 1year, 3-year, and 5-year CSS rates were 53.2%, 26.2%, and 17.4%, respectively. The median OS of PHG patients was longer than that of PBTG patients (18 vs 7.5 mo, P < 0.001). Compared to PHG patients, PBTG patients had a greater risk of metastases [odds ratio (OR) = 2.747, 95% confidence interval (CI): 1.628-4.636, P <



0.001] and higher staging (OR = 3.204, 95% CI: 1.895-5.415, *P* < 0.001). Survival analysis revealed that age < 65 years, male sex, low grade (G1-G2), low stage, systemic therapy, and PMAC located at the pancreatic head led to longer OS and CSS (all P < 0.05). The location of PMAC was an independent prognostic factor for CSS [hazard ratio (HR) = 0.7, 95%CI: 0.52-0.94, P = 0.017]. Further analysis demonstrated that OS and CSS of PHG were significantly better than PBTG in advanced stage (stage III-IV).

#### **CONCLUSION**

Compared to the pancreatic body/tail, PMAC located in the pancreatic head has better survival and favorable clinicopathological characteristics.

Key Words: Pancreatic mucinous adenocarcinoma; Anatomical location; Pancreatic head; Pancreatic body/tail; Survival

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**Core Tip:** Pancreatic tumors had different clinicopathological characteristics by anatomic location in the pancreas. We first investigated the different outcomes and characteristics between mucinous adenocarcinoma in the pancreatic head and body/tail using a variety of analytical methods. In conclusion, adenocarcinoma located at the pancreatic head tended to be characterized by longer survival and more favorable characteristics.

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# INTRODUCTION

Pancreatic cancer (PC) is a common malignancy with a poor prognosis. The incidence and mortality of PC have dramatically increased in recent decades. It has been estimated that PC will be the third leading cause of cancer-related mortality in the future[1,2]. In the subtype classification of PC, pancreatic mucinous adenocarcinoma (PMAC) is a rare type, a malignancy lined by tall, columnar mucinous epithelium[3]. With main symptoms of abdominal pain, weight loss and diarrhea, PMAC can be detected by endoscopy, computed tomography, and other imaging methods. The diagnosis of PMAC can be confirmed by histopathology, and surgical resection remains the primary treatment strategy<sup>[4]</sup>.

Recently, studies have suggested that there is diversity in the genetic and biological characteristics of pancreatic cancer depending on the localization of the tumor [5,6], which indicates that we can classify pancreatic cancer by anatomical location and develop targeted treatment strategies to achieve better outcomes. There is a burgeoning discussion on how the anatomical location of pancreatic cancer impacts its clinical outcomes and pathological characteristics, such as pancreatic ductal adenocarcinoma<sup>[7-10]</sup> and pancreatic neuroendocrine tumors[11]. However, no study has reported the differences in pancreatic mucinous adenocarcinoma (PMAC) in different pancreatic locations.

Given these considerations, we conducted the present study to compare the survival and clinicopathological features of PMAC in the head vs. the body/tail of the pancreas. A total of 271 PMAC patients from the Surveillance, Epidemiology, and End Results database (1992-2017) were reviewed.

### MATERIALS AND METHODS

#### Data collection and study design

Patients' data in this population-based retrospective study were investigated from the Surveillance, Epidemiology, and End Results (SEER) database (https://seer.cancer.gov/), which is supported by National Cancer Institute. We screened the data "Incidence-SEER Research Plus Data, 13 Registries, Nov 2019 Sub (1992-2017)" using SEER\*Stat 8.4.0.1. Furthermore, "8.6.4 Carcinoma of pancreas", "8480/3: Mucinous adenocarcinoma", and "Positive histology" were selected, and a total of 2058 pathologically confirmed patients with information of age, race, sex, grade, TNM, stage, primary malignancy, systemic therapy, and survival were collected. The exclusion criteria of this study were as follows: (1) Patients



without TNM data (n = 1710); (2) Patients with incomplete information of cancer-specific survival (n = 1710); (2) Patients with incomplete information of cancer-specific survival (n = 1710); (2) Patients with incomplete information of cancer-specific survival (n = 1710); (2) Patients with incomplete information of cancer-specific survival (n = 1710); (2) Patients with incomplete information of cancer-specific survival (n = 1710); (2) Patients with incomplete information of cancer-specific survival (n = 1710); (2) Patients with incomplete information of cancer-specific survival (n = 1710); (2) Patients with incomplete information of cancer-specific survival (n = 1710); (2) Patients with incomplete information (n = 1710); (2) Patients with incomplete informating with (n = 1710); (2) Patients with (n = 12); (3) Patients with carcinoma located at 'OthPancreas' (n = 74); and (4) Patients with unknown race (n= 1). Then, we divided the eligible patients into pancreatic head group (PHG) and pancreatic body/tail group (PBTG) according to the location of PMAC. Additionally, we have to declare that the patients included in this study were not including those with cystic mucinous adenocarcinoma and intraductal papillary mucinous tumor, which could lead to a contaminated result.

#### Statistical analysis

Student's t test, Mann–Whitney U test, chi-square test, and  $X^2$  test were properly utilized to compare the clinicopathological data and survival of the two groups of patients. Logistic regression analysis was applied to identify the relationship between tumor locations and pathological characteristics. The survival analyses were conducted using Kaplan-Meier analysis (log-rank test) and Cox regression analysis. Significance was considered as P < 0.05. All statistical analyses in the study were conducted using R software (version 4.2.0).

#### RESULTS

#### **Baseline characteristics**

Finally, 271 patients met the inclusion criteria and were included in the study. According to the locations of tumor, these patients were divided into pancreatic head group (PHG) (n = 159) and PBTG (n= 112) (Table 1). In general, the median OS of 271 patients was 13 mo. Patients over 65 years old (61.3%)and white (74.5%) accounted the majority. Concerning the clinical characteristics, males in PHG were more than that in PBTG (P = 0.009), and the ratios of male to female of PHG and PBTG were 1.45 vs 0.67, while there was no significant difference of age and race between the two groups. Compared to PHG, PBTG patients were observed to have more metastatic tumors (P < 0.001) staged in advanced stage (P < 0.001) 0.001). The differences in T, N, and primary malignancy of the two groups were not statistically significant. Moreover, patients in PHG were likely to have a longer OS than PBTG (median OS 18 vs 7.5 mo, P < 0.001).

#### The correlation between clinicopathological features and risk of aggressive factors

By comparing the basic characteristics of the two groups, we identified that locations of the tumor were related to the metastasis and higher staging. After eliminating confounding factors, we included sex, age, race, location, and primary malignancy into the logistic regression models (Figure 1). It was shown that patients in PBTG have higher risk of metastasis [OR = 2.747, 95% confidence interval (CI): 1.628-4.636, *P* < 0.001] and high staging (III-IV) (OR=3.204, 95% CI: 1.895-5.415, *P* < 0.001) compared with PHG. Additionally, there was a higher risk of metastasis in patients over 65 years old (OR = 1.877, 95% CI: 1.079-3.264, P=0.026) with PMAC as the primary malignancy (OR = 2.317, 95% CI: 1.196-4.488, P = 0.013).

#### General survival analysis of the two groups

The 1-year, 3-year, and 5-year OS rates of all patients were 51.6%, 23.5%, and 13.6%, respectively. While the 1-year, 3-year, and 5-year CSS rates were 53.2%, 26.2%, and 17.4%, respectively. Univariate and multivariate Cox regression models of OS and CSS were further constructed (Table 2; Table 3), and the results could be drawn that age, grade, stage, and systemic therapy were independent factors for predicting both OS and CSS of these patients (all P < 0.05). Besides, tumor located at pancreatic head was considered as a favorable independent prognostic factor for CSS (HR = 0.7, 95%CI: 0.52-0.94, P = 0.017). Then, we depicted survival curves of the two groups using Kaplan-Meier analysis, which suggested that patients in PHG had longer OS and CSS than those in PBTG (all P < 0.05) (Figure 2A and B). Nevertheless, it is known that cancers of the body and especially of the tail are diagnosed at a more advanced stage or even metastatic than cancers of the head, which manifest themselves by jaundice at an earlier stage, probably being one of the contributors of "better prognosis" of pancreatic head cancer. Additionally, the rate of R1 surgery will be higher in PHG during cephalic resections because of the closer vascular relationships. Given these, we made a selection of PMAC without surgical resection treatment and compared the long-term survival of PHG (n = 81) and PBTG (n = 80), which avoided the imbalance in surgery thoroughness (non-surgery, R0 and R1 resection) of the two groups. The Kaplan-Meier curves elucidated that the long-term outcomes of PHG without surgery were better than PBTG without surgery (all P < 0.05) (Figure 3A and B).

#### Survival analysis of systemic therapy

In this retrospective study, 86 patients (31.7%) received systemic therapy, while the remaining 185 (68.3%) patients did not. Patients who received systemic therapy had longer OS and CSS (all P < 0.05) (Figure 4A and B). Then, we conducted the analysis in PHG and PBTG, respectively. It demonstrated that regardless of which group the patients were in, patients who had received systemic therapy had better prognosis (all P < 0.05) (Figure 4C-F). Furthermore, we divided the patients into systemic therapy



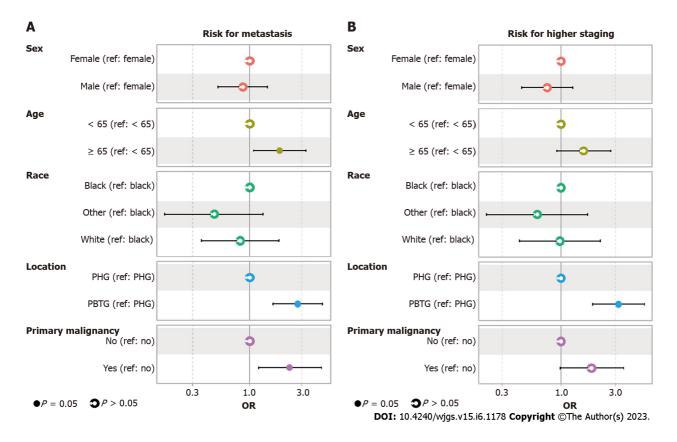


Figure 1 Logistic regression analysis of aggressive factors. A: Risk analysis of metastasis; B: Risk analysis of higher staging. PHG: Pancreatic head group; PBTG: Pancreatic body/tail group; OR: Odds ratio.

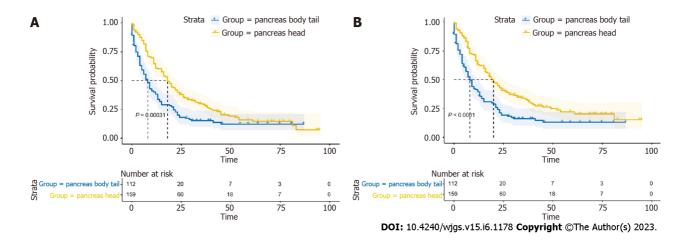


Figure 2 Kaplan-Meier survival analysis of the two groups. A: Analysis for overall survival; B: Analysis for cancer-specific survival.

group and non-systemic therapy group and compared the survival of PHG and PBTG in each group. It showed that patients in PHG had a better survival in non-systemic therapy group (all P < 0.05) (Figure 5A and B), while there were no significant differences of survival in systemic therapy group (Figure 5C and D).

#### Subgroup analysis of stages

The significant differences of survival curves for all patients in stage I-IV were identified (P < 0.05) (Figure 6A and B). In early stage (stage I-II), there were no statistically significant differences between the survival of PHG and PBTG (Figure 6C and D). However, OS and CSS of PHG were significantly better than PBTG in advanced stage (stage III-IV) (Figure 6E and F). Moreover, surgical resection was considered as the best potential curative treatment for PMAC. The ratio of patients with advanced stage who received a surgery of two groups were calculated and depicted to avoid the impact of surgery on the results (Figure 7). From the ratio, we can see that more patients in PBTG received a surgery than PHG (6.8% vs 5.1%).

|                    | PBTG ( <i>n</i> = 112) | PHG ( <i>n</i> = 159) | Overall ( <i>n</i> = 271) | P value |
|--------------------|------------------------|-----------------------|---------------------------|---------|
| Age, yr            | . ,                    |                       | . ,                       |         |
| < 65               | 39 (34.8)              | 66 (41.5)             | 105 (38.7)                | 0.538   |
| ≥ 65               | 73 (65.2)              | 93 (58.5)             | 166 (61.3)                |         |
| Race               |                        |                       |                           |         |
| Black              | 15 (13.4)              | 17 (10.7)             | 32 (11.8)                 | 0.443   |
| Other              | 20 (17.9)              | 17 (10.7)             | 37 (13.7)                 |         |
| White              | 77 (68.8)              | 125 (78.6)            | 202 (74.5)                |         |
| Sex                |                        |                       |                           |         |
| Female             | 67 (59.8)              | 65 (40.9)             | 132 (48.7)                | 0.009   |
| Male               | 45 (40.2)              | 94 (59.1)             | 139 (51.3)                |         |
| Grade              |                        |                       |                           |         |
| G1 + G2            | 35 (31.3)              | 70 (44.0)             | 105 (38.7)                | 0.041   |
| G3 + G4            | 11 (9.8)               | 26 (16.4)             | 37 (13.7)                 |         |
| Unknown            | 66 (58.9)              | 63 (39.6)             | 129 (47.6)                |         |
| Stage              |                        |                       |                           |         |
| Ι                  | 10 (8.9)               | 18 (11.3)             | 28 (10.3)                 | < 0.001 |
| П                  | 28 (25.0)              | 82 (51.6)             | 110 (40.6)                |         |
| III                | 9 (8.0)                | 6 (3.8)               | 15 (5.5)                  |         |
| IV                 | 65 (58.0)              | 53 (33.3)             | 118 (43.5)                |         |
| Г                  |                        |                       |                           |         |
| T1                 | 11 (9.8)               | 15 (9.4)              | 26 (9.6)                  | 0.209   |
| T2                 | 26 (23.2)              | 34 (21.4)             | 60 (22.1)                 |         |
| T3                 | 49 (43.8)              | 93 (58.5)             | 142 (52.4)                |         |
| T4                 | 26 (23.2)              | 16 (10.1)             | 42 (15.5)                 |         |
| Τ0                 | 0 (0)                  | 1 (0.6)               | 1 (0.4)                   |         |
| N                  |                        |                       |                           |         |
| N0                 | 67 (59.8)              | 83 (52.2)             | 150 (55.4)                | 0.462   |
| N1                 | 45 (40.2)              | 76 (47.8)             | 121 (44.6)                |         |
| М                  |                        |                       |                           |         |
| M0                 | 47 (42.0)              | 106 (66.7)            | 153 (56.5)                | < 0.001 |
| M1                 | 65 (58.0)              | 53 (33.3)             | 118 (43.5)                |         |
| Primary malignancy |                        |                       |                           |         |
| No                 | 23 (20.5)              | 36 (22.6)             | 59 (21.8)                 | 0.918   |
| Yes                | 89 (79.5)              | 123 (77.4)            | 212 (78.2)                |         |
| OS, mo             |                        |                       |                           |         |
| mean (SD)          | 14.6 (18.5)            | 24.1 (21.2)           | 20.2 (20.6)               | < 0.001 |
| Median [Min, Max]  | 7.50 [0, 87.0]         | 18.0 [0, 95.0]        | 13.0 [0, 95.0]            |         |

PBTG: Pancreatic body/tail group; PHG: Pancreatic head group.

# DISCUSSION

For pancreatic cancer (PC), there are various studies focusing on the characteristics of tumors occurring



| Table 2 Cox regression analysis of overall survival in patients with pancreatic mucinous adenocarcinoma |            |            |         |           |              |         |  |
|---|------------|------------|---------|-----------|--------------|---------|--|
| Characteristics   | Univariate |            |         | Multivar  | Multivariate |         |  |
| Characteristics   | HR         | 95%CI      | P value | HR        | 95%CI        | P value |  |
| Age, yr   |            |            |         |           |              |         |  |
| < 65  | Reference  |            |         | Reference |              |         |  |
| ≥ 65  | 1.62       | 1.23-2.14  | 0.001   | 1.42      | 1.06-1.89    | 0.017   |  |
| Race  |            |            |         |           |              |         |  |
| Black   | Reference  |            |         |           |              |         |  |
| Other   | 0.91       | 0.54-1.53  | 0.725   |           |              |         |  |
| White   | 0.94       | 0.62-1.41  | 0.751   |           |              |         |  |
| Sex   |            |            |         |           |              |         |  |
| Female  | Reference  |            |         | Reference | 2            |         |  |
| Male  | 0.68       | 0.52-0.89  | 0.004   | 0.81      | 0.61-1.07    | 0.134   |  |
| Location  |            |            |         |           |              |         |  |
| Pancreas body/tail  | Reference  |            |         | Reference |              |         |  |
| Pancreas head   | 0.61       | 0.47-0.8   | < 0.001 | 0.76      | 0.57-1.01    | 0.057   |  |
| Grade   |            |            |         |           |              |         |  |
| G1 + G2   | Reference  |            |         | Reference | 2            |         |  |
| G3 + G4   | 1.82       | 1.21-2.73  | 0.004   | 2.17      | 1.43-3.31    | < 0.001 |  |
| Unknown   | 2.21       | 1.64-2.97  | < 0.001 | 1.23      | 0.89-1.69    | 0.216   |  |
| Stage   |            |            |         |           |              |         |  |
| Ι   | Reference  |            |         | Reference | Reference    |         |  |
| П   | 2.39       | 1.3-4.37   | 0.005   | 3.2       | 1.73-5.92    | < 0.001 |  |
| III   | 6.2        | 2.81-13.68 | < 0.001 | 6.5       | 2.89-14.61   | < 0.001 |  |
| IV  | 6.73       | 3.67-12.37 | < 0.001 | 6.2       | 3.34-11.5    | < 0.001 |  |
| Systemic therapy  |            |            |         |           |              |         |  |
| No  | Reference  |            |         | Reference | 2            |         |  |
| Yes   | 0.32       | 0.24-0.44  | < 0.001 | 0.39      | 0.27-0.56    | < 0.001 |  |

HR: Hazard ratio; CI: Confidence interval.

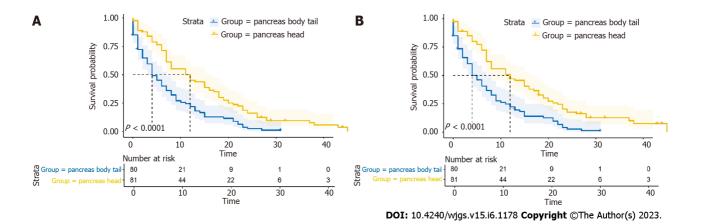


Figure 3 Kaplan-Meier survival analysis of the two groups without surgical resection. A: Analysis for overall survival; B: Analysis for cancer-specific survival.

#### Li Z et al. Survival and clinicopathological characteristics of PMAC

#### Table 3 Cox regression analysis of cancer-specific survival in patients with pancreatic mucinous adenocarcinoma

| Characteristics    | Univariate | )          |         | Multivari | ate        |                |  |  |
|--------------------|------------|------------|---------|-----------|------------|----------------|--|--|
| Characteristics    | HR         | 95%CI      | P value | HR        | 95%CI      | <i>P</i> value |  |  |
| Age, yr            |            |            |         |           |            |                |  |  |
| < 65               | Reference  |            |         | Reference |            |                |  |  |
| ≥65                | 1.56       | 1.17-2.08  | 0.002   | 1.37      | 1.02-1.84  | 0.038          |  |  |
| Race               |            |            |         |           |            |                |  |  |
| Black              | Reference  |            |         |           |            |                |  |  |
| Other              | 0.91       | 0.54-1.55  | 0.739   |           |            |                |  |  |
| White              | 0.89       | 0.58-1.34  | 0.568   |           |            |                |  |  |
| Sex                |            |            |         |           |            |                |  |  |
| Female             | Reference  |            |         | Reference |            |                |  |  |
| Male               | 0.64       | 0.48-0.84  | 0.001   | 0.77      | 0.58-1.03  | 0.082          |  |  |
| Location           |            |            |         |           |            |                |  |  |
| Pancreas body/tail | Reference  |            |         | Reference |            |                |  |  |
| Pancreas head      | 0.56       | 0.43-0.74  | < 0.001 | 0.7       | 0.52-0.94  | 0.017          |  |  |
| Grade              |            |            |         |           |            |                |  |  |
| G1 + G2            | Reference  |            |         | Reference |            |                |  |  |
| G3 + G4            | 1.75       | 1.14-2.67  | 0.01    | 2.2       | 1.42-3.4   | < 0.001        |  |  |
| Unknown            | 2.12       | 1.56-2.88  | < 0.001 | 1.1       | 0.79-1.54  | 0.559          |  |  |
| Stage              |            |            |         |           |            |                |  |  |
| Ι                  | Reference  | Reference  |         |           | Reference  |                |  |  |
| П                  | 3.7        | 1.71-8.03  | 0.001   | 5.02      | 2.29-11    | < 0.001        |  |  |
| III                | 10.3       | 4.09-25.95 | < 0.001 | 10.75     | 4.19-27.61 | < 0.001        |  |  |
| IV                 | 10.47      | 4.83-22.73 | < 0.001 | 9.81      | 4.47-21.51 | < 0.001        |  |  |
| Systemic therapy   |            |            |         |           |            |                |  |  |
| No                 | Reference  |            |         | Reference |            |                |  |  |
| Yes                | 0.3        | 0.22-0.42  | < 0.001 | 0.35      | 0.24-0.51  | < 0.001        |  |  |

HR: Hazard ratio; CI: Confidence interval.

in different anatomical locations[6,8]. However, pancreatic mucinous adenocarcinoma (PMAC) is a rare type of PC. To the best of our knowledge, there is no study reported to discuss the characteristics of PMAC in different locations. Based on these viewpoints, this retrospective study was conducted to compare the survival and clinicopathological features of PMAC in pancreatic head and that in pancreatic body/tail. The new findings may provide novel insights for clinical workers to select appropriate strategies for pancreatic ductal adenocarcinoma (PDAC) management in the future.

Several previous studies had revealed that compared to pancreatic body/tail, patients with PC occurring in pancreatic head owned a better survival, especially for PDAC and pancreatic neuroendocrine tumors (PNETs)[6-8,12,13]. Not only that, anatomical locations of multiple cancer types produced a significant impact on cancer prognosis, such as gastric cancer[14-16], breast cancer[17], lung cancer[18], colorectal cancer[19-22]. These previous evidences provided support for our study through a broader cancer spectrum. However, there was also a study revealed that PDAC of pancreatic head had similar oncological outcomes with PDAC of pancreatic body/tail[10]. The divergence may be caused by different inclusion criteria of patients and various types of biases. In the present study, we firstly identified the better survival of PMAC located at pancreatic head compared to pancreatic body/tail, which was consistent with previous studies. Concerning the potential mechanisms underlying this situation, we believe that it is related to genetics and tumor biological diversity<sup>[5]</sup>. Pancreatic cancer cells in different anatomical positions have various embryonic origins and biological progresses[6], thereby leading to different clinical and pathological characteristics.

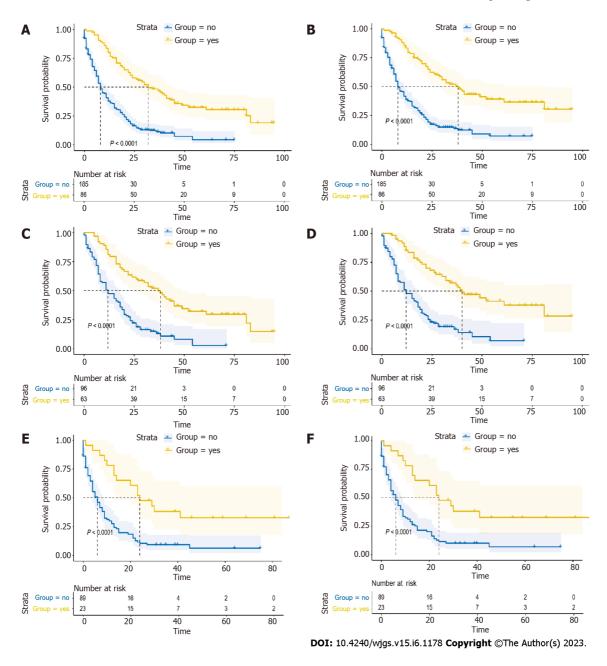


Figure 4 Analysis of systemic therapy. Survival of patients receiving and not receiving systemic therapy (A: Overall survival; B: Cancer-specific survival). Survival of pancreatic head group patients with and without systemic therapy (C: Overall survival; D: Cancer-specific survival). Survival of pancreatic body/tail group patients with and without systemic therapy (E: Overall survival; F: Cancer-specific survival).

In the risk analysis for aggressive pathological factors, it was also shown that patients with PMAC of pancreatic body/tail had a greater risk for metastasis and higher staging compared to PMAC of pancreatic head. Such results were not contradictory to previous studies, which demonstrated that the pancreatic body/tail PDAC was larger, more frequently metastasized, and less likely to be resected compared to pancreatic head PDAC[8]. We thought the possible mechanisms were as follows: Firstly, the stemness of pancreatic tumor stem cells varies widely according to various embryonic origins and is related to the resistance to radiotherapy, chemotherapy, and tumor metastasis[23]. In this study, pancreatic body/tail PMAC was easy to metastasize, which may be caused by the high stemness of tumor cells in the body/tail of the pancreas. Secondly, the tumor microenvironment (TME) of different tumor sites is variable. TME is considered to play an important role in the process of pancreatic tumor metastasis, which can promote metastasis by stimulating angiogenesis/Lymphangiogenesis, epithelialmesenchymal transition and so on[24]. Among these, pancreatic stellate cells (PSCs) were found to regulate angiogenesis and immune evasion, thereby promoting the resistance of therapy and tumor metastasis[25]. Thirdly, due to genetic and biological diversity, different tumor sites are characterized by variable gene communities. Alterations in these genes and characteristic signaling pathways are associated with tumor invasion and metastasis[26-29].

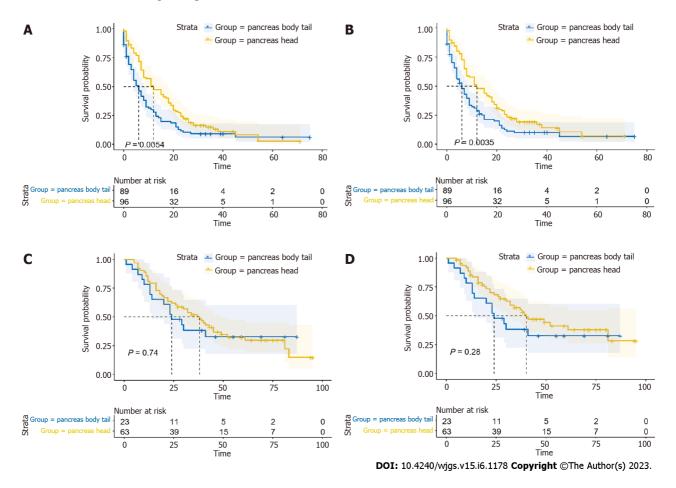


Figure 5 Survival analysis of pancreatic head group and pancreatic body/tail group patients without systemic therapy. (A: Overall survival; B: Cancer-specific survival). Survival analysis of pancreatic head group and pancreatic body/tail group patients with systemic therapy (C: Overall survival; D: Cancer-specific survival).

Systemic therapy is a combination of chemotherapy, radiotherapy, immunotherapy, targeted therapy and so on. Cancer patients rarely receive radical treatment, and more patients are treated with systemic therapy to control disease progression and prolong survival time[30]. In the survival analysis of this study, we revealed that patients treated with systemic therapy were prone to longer OS and CSS, regardless of the PMAC locations. In further investigation, non-systemic therapy patients with pancreatic head PMAC were observed to have a significant better survival compared to those with pancreatic body/tail PMAC. However, the survival of the two groups had no statistically significant difference after treated with systemic therapy. Although this was an observational analysis, without intervention experiments. Such results can also suggest that systemic therapy played an important role in prolonging the prognosis of patients. Meanwhile, systemic therapy has been paid attention to and applied to various cancer types, including cervical cancer[31], breast cancer[32], lung cancer[33], and even genitourinary malignancies of patients infected with COVID-19[34]. These consistent evidences from previous studies make our results easier to understand and more reliable.

There were also several limitations in this study that should be taken into account. Firstly, this was a retrospective study containing a relatively small simple size. Therefore, various biases existed in the study that may affect the results. Secondly, this study was unable to determine the exact mechanisms underlying the results, and further experiments are preferred to confirm our results. Thirdly, due to the limitations of SEER database, data of aggressive factors were incomplete including tumor size, tumor metastasis site and so on. In addition, typically pancreatic head cancer shows symptom in earlier stage than pancreatic body/tail ones and receives a surgical resection. That may be one of the contributors of "better prognosis" of pancreatic head cancer. Furthermore, in the group of patients who received curative surgery, the rate of R1 surgery will be higher during cephalic resections because of the closer vascular relationships, and such imbalance in surgery (R0 and R1) will lead to a compromised result. To solve there problems, we selected the PMAC located in pancreatic head (PHG) and body/tail (PBTG) without surgical resection treatment and compared the long-term outcomes of PHG and PBTG, which made the two groups comparable and drew more rigorous conclusions.

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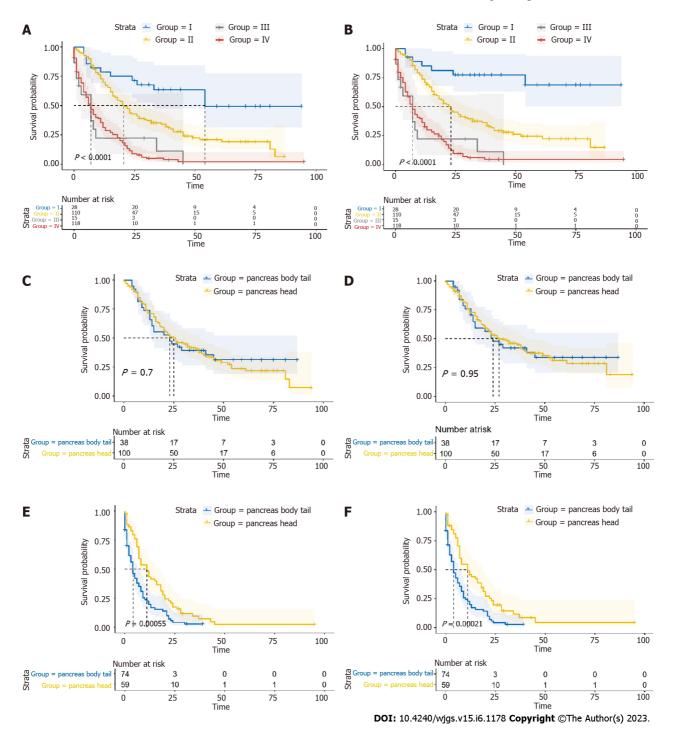


Figure 6 Survival analysis of stages between the two groups. Survival curves of all patients in stage I-IV (A: Overall survival; B: Cancer-specific survival). Different survival of pancreatic head group (PHG) and pancreatic body/tail group (PBTG) patients in early stage (stage I-II) (C: Overall survival; D: Cancer-specific survival). Different survival of PHG and PBTG patients in advanced stage (stage III-IV) (E: Overall survival; F: Cancer-specific survival).

# CONCLUSION

In summary, mucinous adenocarcinoma of pancreatic head has better survival and favorable clinicopathological characteristics compared to that of pancreatic body/tail. Moreover, systemic therapy was observed to effectively prolong the long-term survival of patients including OS and CSS.

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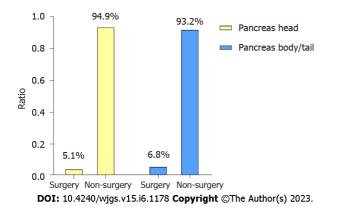


Figure 7 Ratio of surgery in pancreatic head group and pancreatic body/tail group.

# **ARTICLE HIGHLIGHTS**

#### Research background

Growing evidence shows that pancreatic tumors varied according to different anatomical locations, which produce a significant impact on the prognosis. However, there was no study reported to determine the differences between pancreatic mucinous adenocarcinoma (PMAC) in the head and body/tail of pancreas.

#### **Research motivation**

We aimed to investigate the differences in long-term outcomes (overall survival and cancer-specific survival) and clinicopathological characteristics between PMAC in the head and body/tail of pancreas.

#### **Research objectives**

A total of 2058 PMAC patients from the Surveillance, Epidemiology, and End Results database diagnosed between 1992 and 2017 were retrospectively reviewed.

#### **Research methods**

We divided the patients who met the inclusion criteria into pancreatic head group (PHG) and pancreatic body/tail group (PBTG). The relationship between two groups and risk of invasive factors was identified using logistic regression analysis. Kaplan-Meier analysis and Cox regression analysis were conducted to compare the overall survival (OS) and cancer-specific survival (CSS) of two patient groups.

#### **Research results**

After selection, 271 PMAC patients were included in the study. The 1-year, 3-year, and 5-year OS rates of these patients were 51.6%, 23.5%, and 13.6%, respectively. While the 1-year, 3-year, and 5-year CSS rates were 53.2%, 26.2%, and 17.4%, respectively. The median OS of PHG was longer than that of PBTG (18 *vs* 7.5 mo, P < 0.001). Compared to PHG, patients in PBTG had a greater risk of metastases [odds ratio (OR) = 2.747, 95% confidence interval (CI): 1.628-4.636, P < 0.001] and higher staging (OR = 3.204, 95% CI: 1.895-5.415, P < 0.001). Survival analysis revealed that age < 65 years, male, low-grade (G1-G2), low-stage, systemic therapy, and PMAC located at pancreatic head led to longer OS and CSS (all P < 0.05). The location of PMAC was an independent prognostic factor for CSS [hazard ratio (HR)=0.7, 95% CI: 0.52-0.94, P = 0.017]. Further analysis demonstrated that OS and CSS of PHG were significantly better than PBTG in advanced stage (stage III-IV).

#### **Research conclusions**

Compared to pancreatic body/tail, the PMAC located in pancreatic head have a better long-term outcomes and favorable clinicopathological characteristics.

#### **Research perspectives**

The new findings may provide novel insights for clinical workers to select appropriate strategies for pancreatic ductal adenocarcinoma management in the future.

# FOOTNOTES

Author contributions: Li Z, Zhang XJ and Zhao DB designed research; Sun CY, Fei H and Li Z collected data; Li Z analyzed data; Li Z, Zhang XJ, Fei H, Li Z and Zhao DB wrote the paper; Zhao DB guaranteed integrity of study.

Institutional review board statement: This study was reviewed and approved by the institutional review board of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College.

Informed consent statement: This was a retrospective, observational cohort study based on publicly accessible database-SEER, therefore informed consent was waived.

Conflict-of-interest statement: The authors have declared that no competing interest exists.

Data sharing statement: The data used is from a publicly accessible database-SEER (www.seer.cancer.gov).

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