Pancreatic head versus pancreatic body/tail cancer: are they different?

Kai Sun[1], Charisma Mylavarapu[2], Aubrey Crenshaw[2], Yuqi Zhang[2], Enshuo Hsu[3], Jiaqiong Xu[3], Marilyn Niravath[3], Stephen Jones[3], Adriana Ordonez[3], Maen Abdelrahim[1,4]

[1]Houston Methodist Cancer Center, 6445 Main Street, Houston, Texas 77030

[2]Department of Internal Medicine, Houston Methodist Hospital, 6550 Fannin Street, Houston, Texas 77030

[3]Center for Outcomes Research, Methodist Research Institute, 7550 Greenbriar Drive, Houston, TX 77030

[4]Cockrell Center of Advanced Therapeutics Phase I Program, Houston Methodist Research Institute and Weill Cornell Medical College, 6445 Main Street, Houston, Texas 77030

Abstract

Background: Pancreatic head and body/tail have different embryological origins. The impact of pancreatic tumor location on patient overall survival (OS) has been shown in large national data-based analyses.

Methods: To investigate if there is a difference in overall survival, molecular signature and response to chemotherapy between pancreatic head (PHC) and body/tail cancer (PBTC), we retrospectively queried patient records from July 2016 to June 2020 in our institution. Patient demographics, cancer stage on diagnosis, tumor location, somatic mutations, treatment, survival are recorded and analyzed. A test is considered statistically significant if the p-value was<0.05.

Results: A total of 101 patients with complete records were reviewed. 67 (66.34%) are PHC and 34 (33.66%) are PBTC. More PHC are diagnosed at younger age [61.49 (13.96) vs. 68.97 (9.12), p= 0.010], earlier stages (p=0.006) and underwent surgical resection (p=0.025). There are more TP53 mutations in PBTC (37.0% in PHC vs 70.0% in PBTC %, p=0.03). There are no significant differences in KRAS, SMAD4, CDKN2a/b mutations or mutations involving MAPK, cell cycle or DNA repair pathways. OS was not statistically different between PHC and PBTC (p=0.636) in the overall population and in the surgically resected, advanced stage (Stage III and IV) and Stage IV subgroups. There is not enough information to conclude in the sub-groups of resectable (Stage I and II) and Stage III subgroups due to low event numbers. Chemotherapy FOLFIRINOX-based versus gemcitabine-based chemotherapy didn't impact disease free interval in PHC (p=0.546) or PBTC (p=0.654) who underwent surgical resection, or duration of response to first line palliative treatment in PHC (p=0.915) or PBTC (p=0.524) patients with advanced disease.

Conclusions: PHC and PBTC have different presentations and molecular profiles but similar OS and response to chemotherapy. More studies are needed to better characterize the difference.

Key words: pancreatic cancer, tumor location, molecular profiling, survival

Introduction

Pancreatic cancer is the fourth-leading cause of cancer deaths in the United States. Even though the survival rates have improved slightly over the past four decades, the outcome of pancreatic cancer is still dismal. Anatomically pancreatic cancer can be divided into PHC and PBTC. The lower part of head and uncinate process of pancreas has different embryological origins from the rest of the pancreas (1). This embryological difference leads to significant differences in cell composition, blood supply, lymphatic and venous drainage and innervations between the head and body/tail of pancreas.

The impact of pancreatic tumor location on patient presentation and survival has been shown in large national data-based analyses, even though with conflicting results. 49-77.5% pancreatic cancers are PHC (2–4), which tend to present at earlier stages than PBTC. Historically, survival of PBTC cancer is believed to be worse than PHC; and PBTC is considered as an independent poor prognostic risk factor. However, PBTC was found to have much better survival over PHC (20% vs 9%) when the tumor is localized(2).

Genetic analyses of pancreatic cancer have suggested that PHC and PBTC are different tumors. Advanced technology including whole genome sequencing and RNA sequencing further classified pancreatic cancer into four subtypes: classical, squamous, ADEX and immunogenic(5). The squamous subtype is characterized by genes highly expressed in the C2-squamous-like class of tumors of lung and head and neck cancer defined in the Cancer Genome Atlas pan-cancer studies(6). PBTC is found to have more squamous subtypes(7,8).

Pancreatic squamous subtype shares similar molecular abnormalities with lung squamous subtype, which include loss of TP53, RB1, CDKN2A and PIK3CA, NOTCH1, NFE2L2, KDM6A and EP300 mutations. Squamous cell lung cancer was found to be more sensitive to platinum and gemcitabine combination therapy (9). When the combination therapy was tested in advanced pancreatic cancer, there was an improvement in overall survival, disease free survival and response rate, even though not statistically significant(10). Given that PBTC had more squamous subtype, it is possible that PBTC is more responsive to gemcitabine-based treatment.

We hypothesize that PHC and PBTC are distinct diseases based on their embryological origins and current genetic profiling evidence. To further explore the impact of tumor location on molecular profiling, survival, and response to

chemotherapy, we retrospectively reviewed patients with pancreatic cancer in our institution.

Methods and statistical analysis

The study was approved by the institutional review boards. Informed consent was waived given the retrospective nature of the study. The patient data was queried from Epic electronic medical record system of Houston Methodist Hospital. ~~Eligible patients included these who~~ Patients who had a diagnosis of pancreatic cancer from July 2016 through June 2020 were included~~.~~ Data of patient demographics, tumor location, pathology, staging, molecular profiles, treatment history and survival were collected retrospectively~~.~~ Molecular profiles were performed through a multiplatform approach including next gene sequencing (NGS) and RNA sequencing by commercially available testing from Caris Life Sciences (Phoenix, AZ), FoundationOne (Cambridge, MA), Guardant360 (Redwood City, CA), Tempus (Chicago, IL) and NeoGenomics (Fort Meyers, FL), and in house 50 gene or 70 gene panel that was developed and validated in our institution. Panels of gene mutations are available on each company's website. Duration of response is defined as the duration of having complete response, partial response or stable disease on one. Overall survival is defined as the time from pancreatic cancer diagnosis to the date of death or date of last follow-up. Disease free interval is defined as the time from definitive treatment to the date of disease recurrence. Patients who had response and survival data were included in the survival and response analysis. Patients who had molecular profiling data were included in the tumor location analysis. Those who didn't have either records were excluded from the study.

Mean and standard deviation was calculated for the continuous variables and frequency and percentage (n (%)) was calculated for those categorical variables. T-test was used to compare the mean of a continuous variables between the 2 groups of pancreatic cancer and the Fisher's exact test was used to find the association between a patient's characteristic and the pancreatic cancer's groups. Kaplan Meier curves and Log-rank test were used to compare the survival time between the two location groups of pancreatic cancer. Stata/MP 16.1 for Windows was used to analyze the data. A test was considered statistically significant if the p-value was <0.05.

Results

批注 **[SK1]:** Response to reviewer # 2 comment 3:
Clinical parameters like family history, smoking status, molecular typing and CA199 were not included due to retrospective nature of the study (many patients don't have these recorded) and the relevance of these parameters to our clinical question.

批注 **[SK2]:** Response to Reviewer # 2 comment 4.
CR+ PR+SD are regarded as recorded as response.

批注 **[SK3]:** Response to reviewer 2 comment 2 and reviewer 1 comment 2:
All patients who were diagnosed with pancreatic cancer were screened and those with complete medical records were included in the analysis.

Patients

From July, 2016 to June, 2020, a total of 500 records was retrieved and 101 patients with complete medical records were included in the analysis. 67 patients had pancreatic head cancer and 34 patients had pancreatic body or tail cancer. Compared to patients with PHC, patients with PBTC are older at diagnosis (68.97 vs. 61.49, p= 0.01), diagnosed at more advanced stage (p=0.006) and are less likely to undergo surgical resection (p=0.025) (Table 1). There is no significant difference in gender, ethnicity between patients with PHC and patients with PBTC (p= 0.10 and 0.53 respectively).

Survival and tumor location

In the total population, the OS between PHC and PBTC was not statistically different (p= 0.64, Figure 1A). Patients who underwent surgical resection had better OS than patients who did not (p<0.001, Figure 1B), with a median OS of 2.05 years (interquartile range, 1.21 to 2.86) and 1.00 year (interquartile range, 0.77 to 1.70) respectively. There were no differences in survival between PHC and PBTC in those who underwent surgical resection, those who didn't undergo surgical resection, or those who had Stage IV disease on presentation. In the subgroup of patients who had stage I and II disease, there were 3 patients with PBTC and those were long-term survivors. However, due to small number of patients, no definite conclusion can be made.

Molecular profiling and tumor location

A total of 66 patients (46 PHC and 20 PBTC) who had complete medical records and molecular profiling were reviewed. 20/66 (30.3%) had molecular testing performed on biopsy specimen, 24/66 (36.4%) on peripheral blood, 14/66 (21.2%) on surgical resection specimen and the remaining on samples with unknown sources. Rates of pathogenic mutations were recorded and compared between PHC and PBTC (Figure2). PHC and PBTC have similar tumor mutation numbers (p=0.79). The most common mutations were KRAS mutations (63.6% in total, 65.2% in PHC vs 60.6% in PBTC, p= 0.78), TP53 mutations (47.0% in total, 37.0% in PHC vs 70.0% in PBTC, p= 0.03), SMAD mutations (12.1% in total, 15.2% in PHC vs 5.0% in PBTC, p=0.42) and CDKN2a/b mutations (19.7% in total, 19.6% in PHC vs 20.2% in PBTC, p=1.00). Only TP53 mutations were significantly different. 12.1%% of the mutations were involved in cell cycle pathway (15.2% in PHC vs 5%% in

批注 **[SK4]:** Response to reviewer # 1 comment 1 and reviewer # 2 comment 1 about cohort size:
Only 101 out of 500 patients had molecular testing done. This reflects real world experience that many patients don't get molecular testing/genetic testing done due to various reasons including poor performance status, not a candidate of chemotherapy/surgery, low awareness among oncologists, etc.
Please see related ASCO abstract: https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.e22526

批注 **[SK5]:** response to reviewer # 1 minor comment 2: the survival between PHC and PBTC in stage I/II, III were also compared but due to the small number of patients with PBTC and overlapping K-M curves, no conclusion was made.

批注 **[SK6]:** Response to reviewer # 1 comment 1:
All tests are next generation sequencing testing performed by different companies. Each company has different panels that cover different numbers of genes and the depth of NGS also varies. The panels of genes were not mentioned in the manuscript as they are readily available on each company's website and too extensive to list in the manuscript.

PBTC, p= 0.47), 34.9% in MAPK pathway (34.8% in PHC vs 35.0% in PBTC, p= 0.99) and 15.1% in DNA repair pathway (17.4% in PHC vs 10.0% in PBTC, p= 0.71). There were no differences in the mutations involved in those pathways.

Response to chemotherapy and tumor location

In patients who underwent resection, there were no statistical differences in disease free interval between patients with PHC or PBTC who received FOLFIRINOX based chemotherapy and those who received gemcitabine-based chemotherapy (p values are 0.55 and 0.65 respectively, Figure 3A and 3B). In patients with metastatic disease, there were no statistical differences in duration of response to first line palliative chemo between patients with PHC or PBTC who received FOLFIRINOX-based chemotherapy and those who received gemcitabine-based chemotherapy (p values are 0.91 and 0.52 respectively, Figure 3C and 3D).

Discussion

In this retrospective study, patients with PHC and PBTC were retrieved and the relationships of tumor locations with molecular profiling, overall survival, or response to chemotherapy were explored. Our study showed that patients with PBTC tend to present at later stages and are less likely to undergo resection, consistent with previous studies(11–13). PBTC are older at diagnosis in our study, which could have explained the lower resection rate.

The impact of tumor location on survival has been a controversy. Several population-based studies(2,3,11,14,15) reported contradictory survival of PBTC and PHC in the overall population; however, better survival in PBTC is seen in early stage patients, especially stage I and II. Winer et al(14) examined the relationship of survival and tumor location in patients who had tumor resection and found that even though PHC were more of early stage at presentation and more likely to be resected, they tended to have higher grade, more positive lymph nodes and worse overall survival. The survival advantage of PBTC from this study was further supported by a single center study(16) which examined survival in matched stage II PBTC and PHC. Only one single center study(12) reported worse outcome for PBTC patients who had resection and among those patients with Stage I disease, the survival seemed to be better in PBTC however not

statistically significant. Even though our study didn't show a survival difference in PHC and PBTC, long-term survival was seen in three patients with Stage I/II PBTC who underwent resection. The findings from previous studies and our study suggest that resected early stage PBTC have better survival than those with PHC.

The four most common mutations in our study were KRAS, TP53, SMAD and CDKN2a/b mutations, which is consistent with previous reports(13,17). Among these most common mutations, only TP53 mutations were found to be significantly higher in PBTC in our study. Even thou the frequency of SMAD mutations was higher in PHC (15.5%) compared to PBTC (5%), this result was not statistically significant because the total number of SMAD mutations observed was only 12.12% in our study. The lower frequencies of those mutations detected in our study could be explained by NGS being performed on insufficient tissues, as majority of samples were biopsy specimens or peripheral blood (66.7%). ~~Among these most common mutations, only TP53 mutations were found to be significantly higher in PBTC in our study.~~ TP53 mutation is enriched in pancreatic squamous cell type(5) that is similar to lung squamous subtype, and might be similarly more sensitive to gemcitabine therapy. TP53 was also found to predict sensitivity to gemcitabine-based adjuvant therapy in a survival and mutational analysis from CONKOO-001 study(17). Based on these, our finding of more TP53 mutations in PBTC suggest gemcitabine-based adjuvant therapy to be considered in PBTC, especially in those who can't tolerate FOLFIRINOX therapy.

批注 **[KS7]:** Response to reviewer #3

批注 **[SK8]:** Response to reviewer # 3:
Lung squamous cancer and pancreatic squamous cell type are sensitive to gemcitabine, and TP53 is enriched in squamous cell type.
In addition, CONKOO-001 study showed TP53 predicts sensitivity to gemcitabine based therapy.

To our knowledge, our study is the first study that looked at the impact of tumor location on response to different chemotherapy regimens. Neither PHC or PBTC responded differently to FOLFIRINOX based or gemcitabine-based chemotherapies, suggesting a universal poor prognosis of pancreatic cancer regardless of tumor location when compared based on chemotherapy response. However, differential response to targeted therapy or immunotherapy is yet to be explored given the different distribution of pancreatic cancer subtype like immunogenic.

Limitations

Our study was a retrospective study in a single institution and a relatively small number of patients was retrieved. Due to the retrospective nature, the NGS platforms utilized, and the depths of sequencing were not uniformed. This added another layer of bias in data interpretation. However, this reflects the real-world experience in many community and academic cancer centers that often rely heavily on commercial NGS platforms. Even though there is a trend to suggest better survival in early stage PBTC patients after resection, there were few patients and events in this subgroup and no definitive conclusion can be made.

Conclusion

There is no difference in OS between PHC and PBTC but the long-term survival observed in early stage PBTC after resection suggests better survival in this subgroup of patients. PBTC has significantly more mutations involved in TP53 mutations and its predictive role in gemcitabine sensitivity should be explored in future studies.

Table 1 Patient characteristics by location

	Total N=101	**Head N=67**	**Body/tail N=34**	**p-value**
Age at diagnosis	63.90 (13.03)	61.49 (13.96)	68.97 (9.12)	**0.010**
Gender				0.095
Female	51 (50.50%)	38 (56.72%)	13 (38.24%)	
Male	50 (49.50%)	29 (43.28%)	21 (61.76%)	
Ethnicity				0.53
Caucasian	76 (75.25%)	48 (71.64%)	28 (82.35%)	
Black	11 (10.89%)	8 (11.94%)	3 (8.82%)	
Other	14 (13.86%)	11 (16.42%)	3 (8.82%)	
Pathologic initial stage				**0.006**
I	5 (4.95%)	3 (4.48%)	2 (5.88%)	
II	19 (18.81%)	18 (26.87%)	1 (2.94%)	
III	17 (16.83%)	13 (19.40%)	4 (11.76%)	
IV	51 (50.50%)	28 (41.79%)	23 (67.65%)	
Missing	9 (8.91%)	5 (7.46%)	4 (11.76%)	
Surgical resection				**0.025**
Yes	34 (33.66%)	28 (41.79%)	6 (17.65%)	
No	67 (66.34%)	39 (58.21%)	28 (82.35%)	

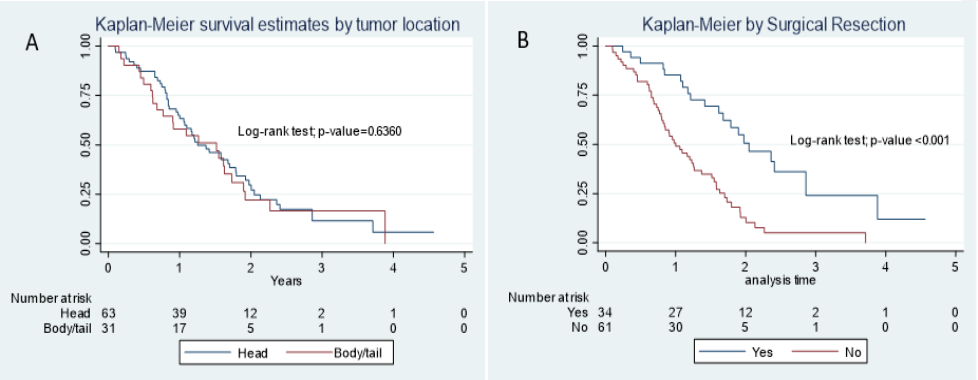

Figure 1. Survival and tumor location. A, Kaplan-Meier curve of overall survival in pancreatic head cancer and pancreatic body/tail cancer in the total population; B, Kaplan-Meier curve of overall survival in patients who underwent surgical resection versus those who did not.

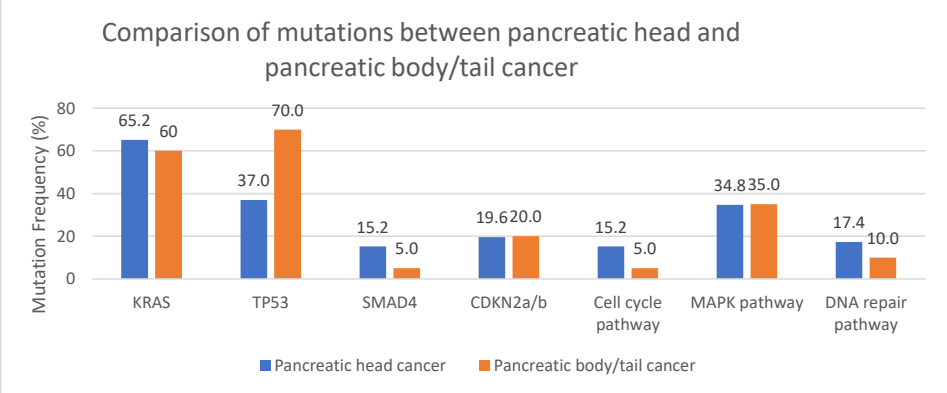

Figure 2. Comparison of mutations between pancreatic head and pancreatic body/tail cancer.

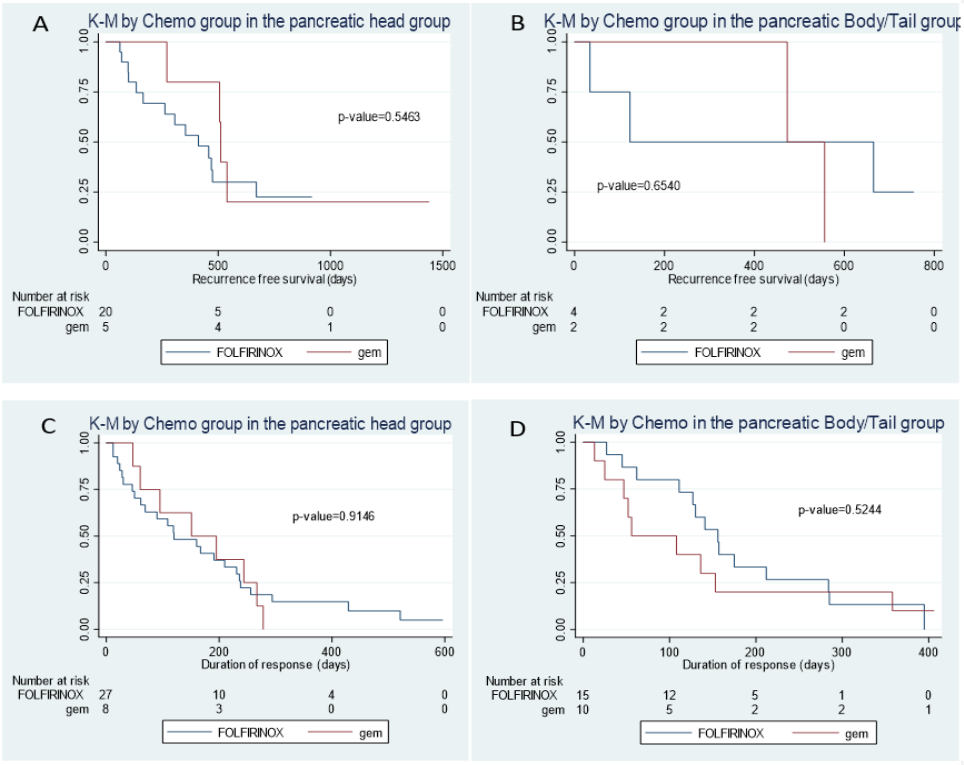

Figure 3. Response to chemotherapy and tumor location. A, Kaplan Meier curve of recurrence free interval in patients with pancreatic head cancer who had resection and received FOLFIRINOX-based therapy versus gemcitabine based therapy (p= 0.5463). B, Kaplan Meier curve of recurrence free interval in patients with pancreatic body/tail cancer who had resection and received FOLFIRINOX-based therapy versus gemcitabine-based therapy (p= 0.6540). C, Kaplan Meier curve of response duration in patients with metastatic pancreatic head cancer who received FOLFIRINOX-based therapy versus gemcitabine-based therapy (p=0,9146). D, Kaplan Meier curve of response duration in patients with metastatic pancreatic body/tail cancer who received FOLFIRINOX-based therapy versus gemcitabine-based therapy (p=0,5244).

References

1. Bastidas-Ponce A, Scheibner K, Lickert H, Bakhti M. Cellular and molecular mechanisms coordinating pancreas development. Development. 2017 15;144(16):2873–88.

2. Lau MK, Davila JA, Shaib YH. Incidence and survival of pancreatic head and body and tail cancers: a population-based study in the United States. Pancreas. 2010 May;39(4):458–62.

3. Matsuno S, Egawa S, Fukuyama S, Motoi F, Sunamura M, Isaji S, et al. Pancreatic Cancer Registry in Japan: 20 years of experience. Pancreas. 2004 Apr;28(3):219–30.

4. Saad AM, Turk T, Al-Husseini MJ, Abdel-Rahman O. Trends in pancreatic adenocarcinoma incidence and mortality in the United States in the last four decades; a SEER-based study. BMC Cancer. 2018 Jun 25;18(1):688.

5. Bailey P, Chang DK, Nones K, Johns AL, Patch A-M, Gingras M-C, et al. Genomic analyses identify molecular subtypes of pancreatic cancer. Nature. 2016 Mar 3;531(7592):47–52.

6. Hoadley KA, Yau C, Wolf DM, Cherniack AD, Tamborero D, Ng S, et al. Multiplatform analysis of 12 cancer types reveals molecular classification within and across tissues of origin. Cell. 2014 Aug 14;158(4):929–44.

7. Birnbaum DJ, Bertucci F, Finetti P, Birnbaum D, Mamessier E. Head and Body/Tail Pancreatic Carcinomas Are Not the Same Tumors. Cancers (Basel). 2019 Apr 8;11(4).

8. Dreyer SB, Jamieson NB, Upstill-Goddard R, Bailey PJ, McKay CJ, Australian Pancreatic Cancer Genome Initiative, et al. Defining the molecular pathology of pancreatic body and tail adenocarcinoma. Br J Surg. 2018;105(2):e183–91.

9. Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol. 2008 Jul 20;26(21):3543–51.

10. Heinemann V, Quietzsch D, Gieseler F, Gonnermann M, Schönekäs H, Rost A, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. J Clin Oncol. 2006 Aug 20;24(24):3946–52.

11. van Erning FN, Mackay TM, van der Geest LGM, Groot Koerkamp B, van Laarhoven HWM, Bonsing BA, et al. Association of the location of pancreatic ductal adenocarcinoma (head, body, tail) with tumor stage, treatment, and survival: a population-based analysis. Acta Oncol. 2018 Dec;57(12):1655–62.

12. Sheng W, Dong M, Wang G, Shi X, Gao W, Wang K, et al. The diversity between curatively resected pancreatic head and body-tail cancers based on the 8th edition of AJCC staging system: a multicenter cohort study. BMC Cancer. 2019 Oct 22;19(1):981.

13. Zhang X, Feng S, Wang Q, Huang H, Chen R, Xie Q, et al. Comparative genomic analysis of head and body/tail of pancreatic ductal adenocarcinoma at early and late stages. J Cell Mol Med. 2021 Feb;25(3):1750–8.

14. Winer LK, Dhar VK, Wima K, Morris MC, Lee TC, Shah SA, et al. The Impact of Tumor Location on Resection and Survival for Pancreatic Ductal Adenocarcinoma. J Surg Res. 2019;239:60–6.

15. Zheng Z, Wang M, Tan C, Chen Y, Ping J, Wang R, et al. Disparities in survival by stage after surgery between pancreatic head and body/tail in patients with nonmetastatic pancreatic cancer. PLoS One. 2019;14(12):e0226726.

16. Ling Q, Xu X, Ye P, Xie H, Gao F, Hu Q, et al. The prognostic relevance of primary tumor location in patients undergoing resection for pancreatic ductal adenocarcinoma. Oncotarget. 2017 Feb 28;8(9):15159–67.

17. Sinn M, Sinn BV, Treue D, Keilholz U, Damm F, Schmuck RB, et al. *TP53* mutations predict sensitivity to adjuvant gemcitabine in patients with pancreatic ductal adenocarcinoma: next-generation sequencing results from the CONKO-001 trial. Clin Cancer Res. 2020 Mar 31;clincanres.3034.2019.