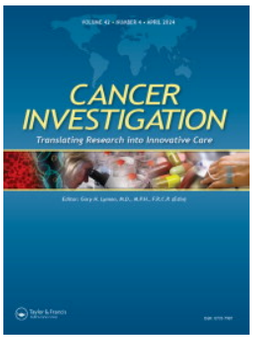

Cancer Investigation

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/icnv20

Identifying Optimal Candidates for Primary Tumor Resection Among Metastatic Pancreatic Cancer Patients: A Population-Based Predictive Model

Kaifeng Su, Ruifeng Duan & Yang Wu

To cite this article: Kaifeng Su, Ruifeng Duan & Yang Wu (2024) Identifying Optimal Candidates for Primary Tumor Resection Among Metastatic Pancreatic Cancer Patients: A Population-Based Predictive Model, Cancer Investigation, 42:4, 333-344, DOI: 10.1080/07357907.2024.2349585

To link to this article: https://doi.org/10.1080/07357907.2024.2349585

Published online: 07 May 2024.

CANCER INVESTIGATION
2024, VOL. 42, NO. 4, 333–344
https://doi.org/10.1080/07357907.2024.2349585

Identifying Optimal Candidates for Primary Tumor Resection Among Metastatic Pancreatic Cancer Patients: A Population-Based Predictive Model

Kaifeng Su[a], Ruifeng Duan[b] and Yang Wu[c]

[a]Medical Faculty of Ludwig Maximilians University of Munich, University Hospital of LMU Munich, Munich, Germany; [b]Department of Gastroenterology and Digestive Endoscopy Center, The Second Hospital of Jilin University, Changchun, China; [c]Pancreas Center, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China

ABSTRACT

Background: There is a controversy about whether surgery should proceed among metastatic pancreatic cancer (mPC) patients. A survival benefit was observed in mPC patients who underwent primary tumor resection; however, determining which patients would benefit from surgery is complex. For this purpose, we created a model to identify mPC patients who may benefit from primary tumor excision.

Methods: Patients with mPC were extracted from the Surveillance, Epidemiology, and End Results database, and separated into surgery and nonsurgery groups based on whether the primary tumor was resected. Propensity score matching (PSM) was applied to balance confounding factors between the two groups. A nomogram was developed using multivariable logistic regression to estimate surgical benefit. Our model is evaluated using multiple methods.

Results: About 662 of 14,183 mPC patients had primary tumor surgery. Kaplan–Meier analyses showed that the surgery group had a better prognosis. After PSM, a survival benefit was still observed in the surgery group. Among the surgery cohort, 202 patients survived longer than 4 months (surgery-beneficial group). The nomogram discriminated better in training and validation sets under the receiver operating characteristic (ROC) curve (AUC), and calibration curves were consistent. Decision curve analysis (DCA) revealed that it was clinically valuable. This model is better at identifying candidates for primary tumor excision.

Conclusion: A helpful prediction model was developed and validated to identify ideal candidates who may benefit from primary tumor resection in mPC.

ARTICLE HISTORY
Received 8 July 2023
Accepted 25 April 2024

KEYWORDS
Metastatic pancreatic cancer; surgery; nomogram; SEER database; primary tumor resection

Introduction

Worldwide, pancreatic cancer (PC) is one of the most lethal gastrointestinal malignancies, with an inferior prognosis; more than 490,000 patients are diagnosed annually with similar mortality (1). The incidence and mortality of PC have shown a stable upward trend, and PC is estimated to become the second leading cause of cancer-related death in the United States by 2030 (2). Despite many efforts, the prognosis is still extremely poor, with a lower than 7% average 5-year survival rate (3). The early stage of PC is usually asymptomatic, resulting in advanced cancer at the first diagnosis. Furthermore, nearly half of PC patients were found to have metastatic disease (4). The overall survival of patients with stage IV metastatic disease is worse than that of stage I–III in PC (5). The median survival of locally advanced PC is approximately 6–10 months, while it is only 3–6 months for mPC (6). Although treatment methods have evolved rapidly, the prognosis of mPC is still disappointing (4).

Surgery is considered the only potentially curative treatment; however, it is not recommended once distant metastasis is found (5). Currently, chemotherapy is the primary treatment for mPC (3). According to the patient's performance status and comorbidity profile, FOLFIRINOX

CONTACT Kaifeng Su kaifeng.su@outlook.com Medical Faculty of Ludwig Maximilians University of Munich, University Hospital of LMU Munich, Munich, Germany

(leucovorin, fluorouracil, irinotecan, and oxaliplatin) regimens and gemcitabine alone or in combination with other chemotherapeutic medicines are recommended (7). Although surgery is not recommended for metastatic tumors in clinical guidelines, increasing evidence suggests that some solid metastatic malignancies, such as breast cancer (8), renal cell cancer (9), colorectal cancer (10), and prostate cancer (11, 12), can achieve favorable outcomes from primary tumor resection. Some data showed that PC patients with liver metastasis who underwent synchronous resection of the primary tumor and liver metastasis had a significant survival benefit and acceptable morbidity and mortality compared to PC patients with liver metastasis who did not undergo resection (13, 14).

Thus, the question of whether all mPC patients could have a survival benefit from resection arises. However, the existing data are minimal, perhaps due to a skeptical attitude about the safety and efficiency of surgery for PC (15). An extensive national database showed that the resection rate has increased to approximately 60%, and operation indications have been extended with the regionalization of pancreatic surgery into high-volume medical centers (16). Surgery has been performed safely with low mortality and morbidity rates in recent progression (17). These findings may provide a potential implication for the surgical management of mPC; however, there has been no consensus on the eligible criteria for surgical resection for mPC until now. Therefore, surgeons often encounter dilemmas when meeting mPC patients with primary tumors that appear resectable. In most cases, based on clinical experience, for example, the patients can tolerate the operation, the patients have firm wishes to undergo the operation, and surgery may solve other symptoms, such as obstruction. However, the impact of surgery on survival has not been clearly elucidated. A few studies have reported that operation benefits some well-selected patients (18–20). In contrast, a few studies showed that patients did not achieve a survival benefit after resection of the primary tumor and metastatic lesions (21, 22). The above-mentioned studies were all small and non-randomized and selected cohorts from single institutions; hence, the exact role of surgery in mPC needs a more systematic evaluation.

This study investigates the prognostic value of primary tumor resection for mPC using a large population-based cohort based on the Surveillance, Epidemiology, and End Results (SEER) database. Moreover, to address clinical needs, we developed and validated a new predictive model to identify patients with mPC who could potentially benefit from primary tumor surgery. We also constructed a prognostic nomogram to better predict individual survival time in mPC patients after primary tumor resection. The process of this research is shown in Figure 1.

Material and methods

Data source

In this retrospective analysis, patient data were obtained from the SEER database. The SEER database is a definitive U.S. statistical cancer database containing patient baseline data, tumor characteristics, treatment information, and prognosis data (23). The database's information on oncology patients is standardized and regularly updated using SEER*Stat software (version 8.3.4) (National Cancer Institute, Bethesda, MD). The database has a very large sample size and solid statistical validity, making the results of studies based on the SEER database of high clinical reference value. This study was conducted based on data from the SEER database that were allowed to be extracted.

Inclusion and exclusion criteria

The target population of this study was limited to surgically treated PC patients from the SEER database from 2010 to 2018. The study period depends on the American Joint Committee on Cancer (AJCC) tumor stage; also, the based clinicopathological characteristics were collected for each patient (age, race, sex, histology, radiotherapy, chemotherapy, grade, TNM stage, tumor location, and follow-up information).

The inclusion and exclusion criteria were as follows: (1) patients diagnosed with metastatic stage and (2) patients with only one primary tumor were included; and (3) patients with

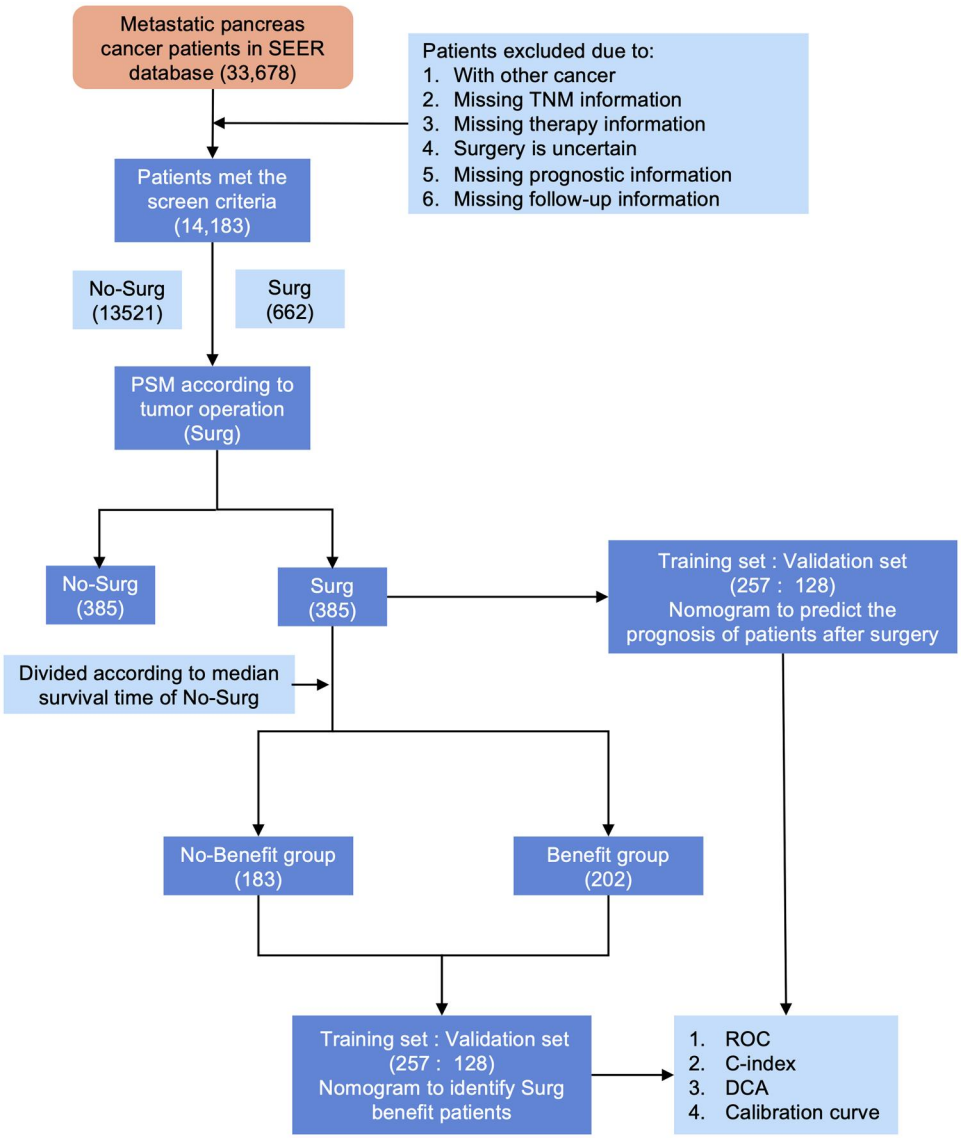

Figure 1. Flowchart of this study. PSM: propensity score matching; Surg: surgery; ROC: receiver operating characteristic; DCA: decision curve analysis.

missing or incomplete data on TNM stage, grading stage, survival status, time, or treatment information were excluded. Surgery was defined as primary site tumor resection. Cancer-specific survival (CSS) was calculated from diagnosis to the date of death attributed to PC. OS was calculated from diagnosis to death, excluding patients alive at the last recording.

Statistical analysis

Propensity score matching (PSM) was performed to reduce confounding bias and facilitate the matching of patients in both treatment groups (R software version 4.0.2 (The R Foundation for Statistical Computing, Vienna, Austria)). Variables that may potentially affect the treatment outcome were used to generate propensity scores by logistic regression, including age, sex, race, tumor T stage, N stage, M stage, histologic grade, tumor location, chemotherapy, and systemic therapy. The patients in the surgery and nonsurgery groups were matched 1:1 using the closest propensity score on the logit scale with a caliper of 0.01 (24). The balance of covariates between the two groups before and after PSM was assessed by standardized differences, and a value of standardized differences $<10\%$ was considered the criterion for adequate balance (25). After PSM, differences in categorical clinical characteristics

were evaluated using chi-square tests. OS and CSS were estimated by the Kaplan–Meier method. Statistical analyses were performed using SPSS 26.0 (IBM Corp., Armonk, NY, USA), and all statistical tests were two-sided, with $p < 0.05$ considered statistically significant.

Construction and validation of the nomogram

We hypothesized that patients who underwent surgery for their primary tumor and had a longer median OS time than patients in the nonsurgery group benefitted from surgery. Based on these assumptions, participants in the surgery group were divided into two categories: the surgery benefit group (median OS >4 months) and the surgery nonbenefit group (median OS ≤4 months), according to the median OS time in the nonsurgery group (results from the matched cohort). Patients for whom surgery for the primary tumor was beneficial were identified as clinically significant. Participants in the surgery group were randomized into training and validation sets based on a 2:1 ratio. Our study developed a nomogram prediction model based on logistic regression to provide a quantitative tool to predict which patients with mPC would benefit from primary site surgery.

In addition, a nomogram prediction model containing data on age, sex, race, tumor T stage, N stage, histological grade, and tumor location was constructed for the prognostic prediction of surgery for patients with mPC.

The area under the receiver operating characteristic (ROC) curve (AUC) was used to assess the predictive performance of the nomogram in the training and validation sets. The calibration of the nomogram was evaluated using calibration plots and the Hosmer–Lemeshow goodness-of-fit test ($p > 0.05$ indicates a nonsignificant deviation from the perfect theoretical calibration). Clinical usefulness and net benefit were estimated using decision curve analysis (DCA).

Result

Patients and baseline characteristics

Of the 14,183 patients who met the inclusion criteria, 662 underwent primary tumor surgery. After 1:1 PSM, a sample of 770 patients with mPC treated with or without primary site surgery was included in the following analysis. After PSM, all baseline characteristics were well balanced (all $p > 0.05$). Table 1 shows the baseline population data before and after matching.

Correlation between surgery and survival in mPC

The patients were grouped by whether they underwent primary site tumor surgery, and Kaplan–Meier analysis was performed to determine whether there were significant differences in OS and CSS between the two groups. Based on the OS curves and subgroup analysis, we observed a good prognosis in the primary site surgery group, as shown in Figure 2.

Nomogram to identify beneficial candidates for primary tumor surgery

In the study mentioned above, it was observed that some patients with mPC could benefit from surgery for their primary tumor. A new nomogram including age, sex, race, T stage, N stage, histological grade, and tumor location was developed to identify these patients (Figure 3(A)). The AUC was used to assess the predictive ability in the training set (AUC = 0.814) and validation set (AUC = 0.825), and the results showed that the model had good predictive efficacy (Figure 3(B,C)). The calibration curves confirmed the excellent agreement between the actual observations and the predictions of the nomogram (Figure 3(D,E)). DCA demonstrated the good clinical utility of the nomogram (Figure 3(F,G)).

Prediction nomogram of OS after primary tumor surgery

We developed a new nomogram based on the above results, including age, sex, race, T stage, N stage, histological grade, and tumor location, for predicting OS in postoperative patients (Figure 4(A)). The predictive ability was evaluated by the ROC curves of the training set (AUC = 0.757 for 1-year OS, and AUC = 0.730 for 2-year OS) and validation set (AUC = 0.744 for 1-year OS, and AUC = 0.707 for 2-year OS), and the results

Table 1. Characteristics of the study population by study group before and after PSM.

	Before PSM			After PSM		
	Primay site resection	Nonprimay site resection		Primay site resection	Nonprimay site resection	
Variable	662	13,521	*p* Value	385	385	*p* Value
Gender			0.425			0.665
Male	340	7161		188	191	
Female	322	6360		197	194	
Age			0.001			0.546
≤65	308	8035		191	183	
>65	354	5486		194	202	
Race			0.004			0.728
W	537	10,696		306	309	
B	67	1832		48	43	
AI	0	79		0	1	
API	58	914		31	32	
T Stage			0.001			0.928
T1	17	499		14	12	
T2	92	4982		80	85	
T3	481	5107		234	228	
T4	72	2933		57	60	
N Stage			0.001			0.345
N0	222	8269		174	161	
N1	440	5252		211	224	
Grade			0.001			0.474
G1	107	264		53	56	
G2	233	1022		123	136	
G3	202	1417		101	96	
G4	21	118		13	6	
Gx	99	10,700		95	91	
Primary site			0.001			0.836
Pancreas head	323	5833		193	190	
Pancreas body	64	2713		45	42	
Pancreas tail	208	3085		106	104	
Pancreas other	67	1890		41	49	
Chemotherapy			0.034			0.714
YES	395	8626		230	225	
NO/UNK	267	4895		155	160	
Systemic			0.001			0.769
YES	404	379		229	223	
NO/UNK	258	13,142		156	152	

PSM: propensity score matching; Race (W: White; B: Black; AI: American Indian/Alaska Native; API: Asian or Pacific Islander); UNK: unknown

showed that the model had good predictive efficacy (Figure 4(B,C)). The calibration curves for 1-year and 2-year OS confirmed the excellent agreement between the actual observations and the predictions of the nomogram (Figure 4(D,E)). DCA for 1- and 2-year OS confirmed the good clinical utility of the nomogram (Figure 4(F,G)).

Prediction nomogram of CSS after primary tumor surgery

We also developed another nomogram based on above results, including age, sex, race, T stage, N stage, histological grade, and tumor location, for predicting CSS in postoperative patients (Figure 5(A)). The predictive ability was evaluated by the ROC curves of the training set (AUC = 0.778 for 1-year CSS, and AUC = 0.811 for 2-year CSS) and validation set (AUC = 0.857 for 1-year CSS, and AUC = 0.832 for 2-year CSS), and the results showed that the model had good predictive efficacy (Figure 5(B,C)). The calibration curves for 1- and 2-year CSS confirmed the excellent agreement between the actual observations and the predictions of the nomogram (Figure 5(D,E)). DCA for 1- and 2-year CSS confirmed the good clinical utility of the nomogram (Figure 5(F, G)).

Discussion

In this study, we observed that mPC patients who underwent primary tumor resection had a better prognosis by using PSM to assess its effect. Hence, primary tumor surgery could potentially have a beneficial impact on survival outcomes in mPC. We first established and validated a novel nomogram to identify this group of patients with mPC who could gain a beneficial prognosis. Furthermore, we constructed a prognostic

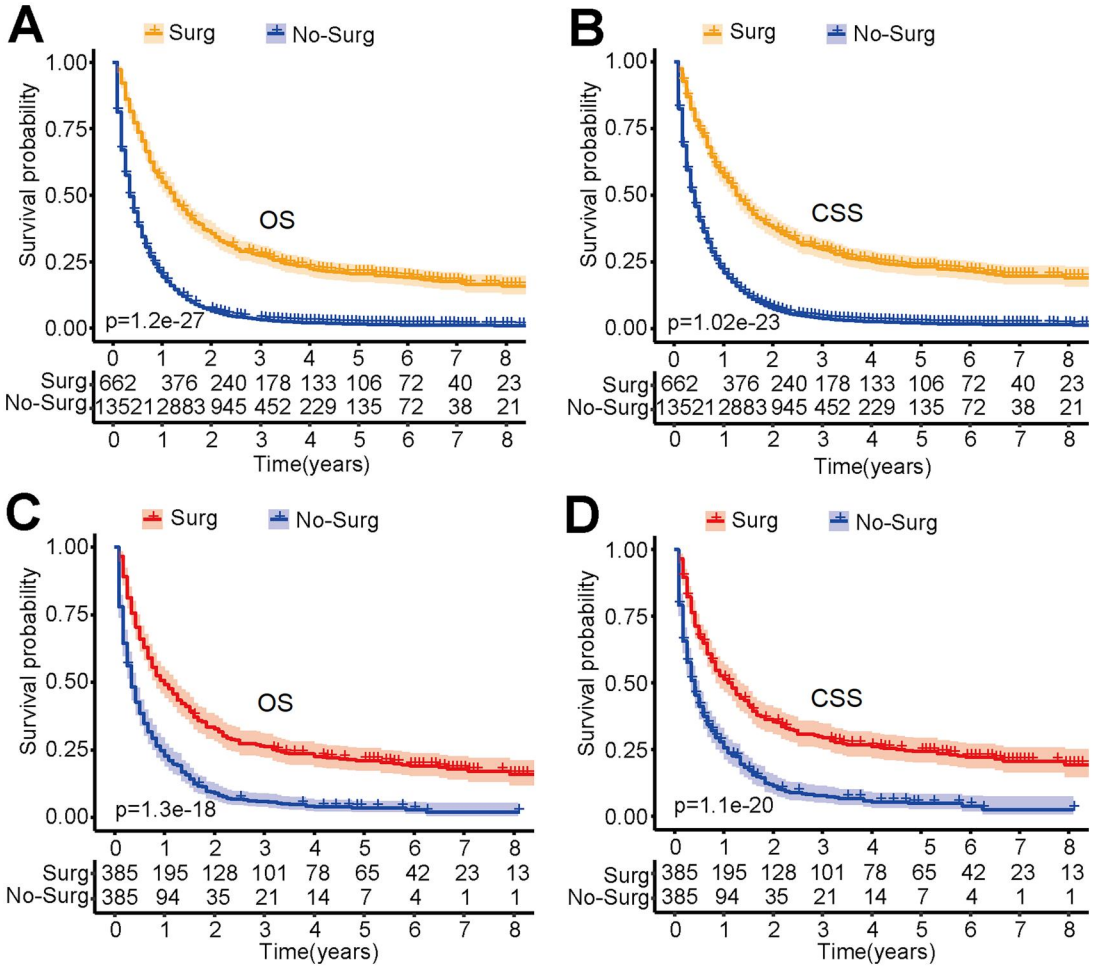

Figure 2. Kaplan–Meier (KM) plots show the OS and CSS of mPC patients according to the group. (A) KM curves of OS for the surgery and nonsurgery groups before PSM, (B) KM curves of CSS for the surgery and nonsurgery groups before PSM, (C) KM curves of OS for the surgery and nonsurgery groups after PSM, (D) KM curves of CSS for the surgery and nonsurgery groups after PSM ($p < 0.001$). Surg: Surgery.

nomogram to better predict the survival time of beneficial candidates. The parameters included in the nomogram are readily accessible in clinical practice, and the validation of the prediction nomogram using different analyses proved its efficacy and usefulness.

For mPC patients, current international guidelines do not recommend performing an operation (26, 27). Systemic treatment plays a crucial role in the treatment of mPC; it should be started immediately when detecting metastasis (28). According to traditional beliefs, primary tumor resection is mostly palliative in nature for mPC. However, the efficacy of primary tumor resection in patients with metastatic cancer has been shown in many systemic malignancies, including mPC (29). Our research showed that primary tumor resection was linked with considerably improved OS and CSS compared to no resection before and after PSM. Wang et al. also reported a similar CSS result for mPC (29). Another study reported that individuals with mPC who underwent primary tumor resection had a survival advantage of 4.7 months compared to those who did not undergo surgical resection (30). Hence, as surgical and diagnostic techniques continue to improve, we should revalue the impact of primary tumor resection on patients with mPC.

From the standpoint of tumor pathophysiology, primary tumor resection also has a theoretical foundation. First, PC is a dense, stroma-rich tumor; the extensive fibrotic stroma impedes the entrance of chemotherapeutic agents into the tumor, resulting in an inadequate

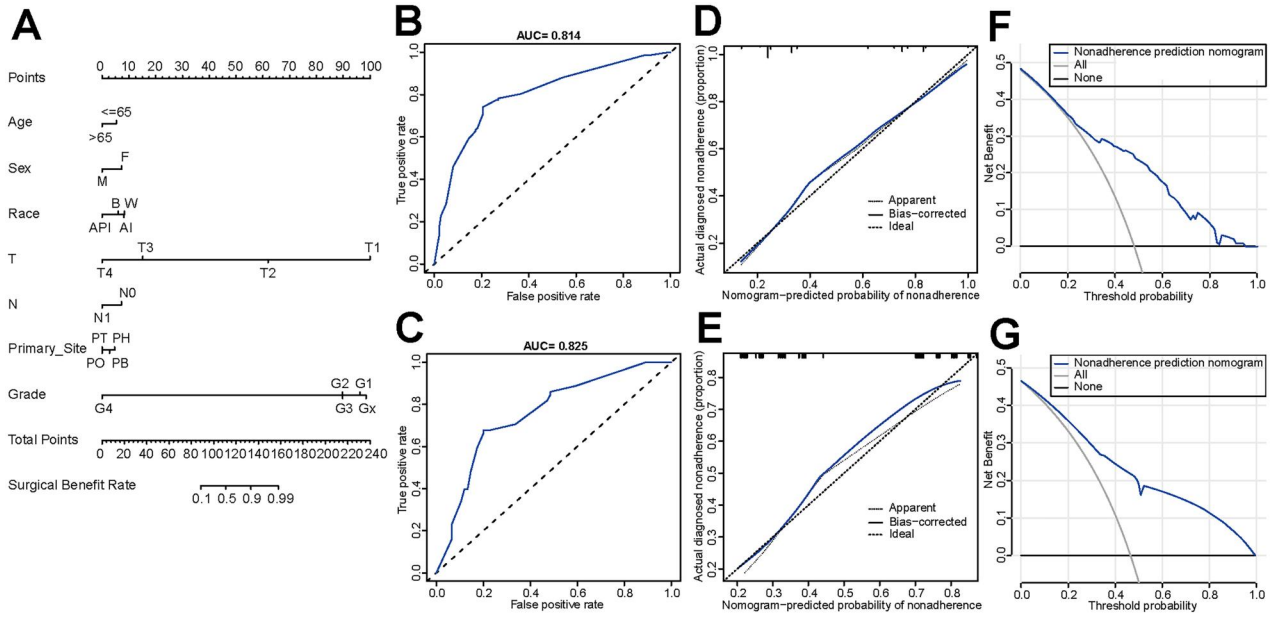

Figure 3. Nomogram to identify beneficial candidates for primary tumor surgery. (A) Nomogram for predicting which patients with mPC might benefit from primary tumor resection. The cutoff point of the nomogram was 0.5. The patient would be a benefit candidate when the overall prediction probability exceeds the threshold and vice versa. (B) ROC curve of the training set. (C) ROC curve of the validation set. (D) Calibration curve of the training set. (E) Calibration curve of the validation set. (F) DCA of the training set. (E) DCA of the validation set. Sex (F: female; M: male), Race (W: White; B: Black; AI: American Indian/Alaska Native; API: Asian or Pacific Islander), T: T Stage; N: N stage; Primary Site (PH: Pancreas head; PB: Pancreas body; PT: Pancreas tail; PO: Pancreas other); AUC: area under the receiver operating characteristic curve.

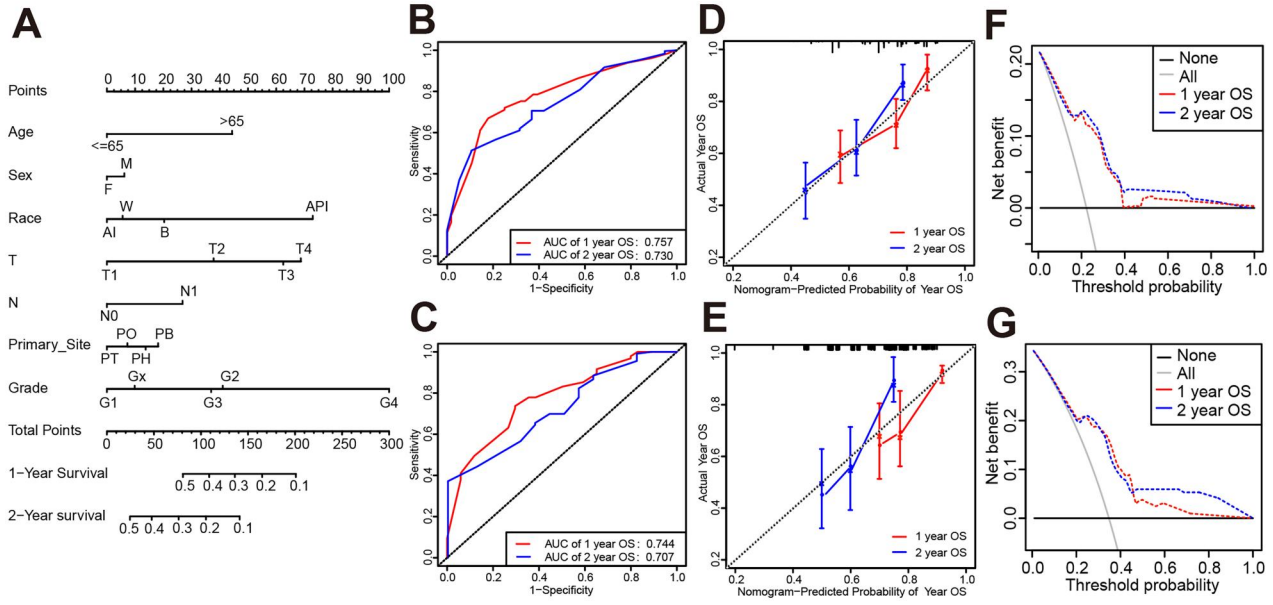

Figure 4. Prediction nomogram of OS after primary tumor surgery. (A) The nomogram includes age, sex, race, T stage, N stage, histological grade, and tumor location for predicting OS in postoperative patients. (B) ROC curves for 1-year OS and 2-year OS in the training set. (C) ROC curves for 1-year OS and 2-year OS in the validation set. (D) Calibration curves for 1-year OS and 2-year OS in the training set. (E) Calibration curves for 1-year OS and 2-year OS in the validation set. (F) DCA for 1-year OS and 2-year OS in the training set. (G) DCA for 1-year OS and 2-year OS in the validation set. Sex (F: female; M: male), Race (W: White; B: Black; AI: American Indian/Alaska Native; API: Asian or Pacific Islander); T: T Stage; N: N stage; Primary Site (PH: Pancreas head; PB: Pancreas body; PT: Pancreas tail; PO: Pancreas other); AUC: area under the receiver operating characteristic curve; OS: overall survival.

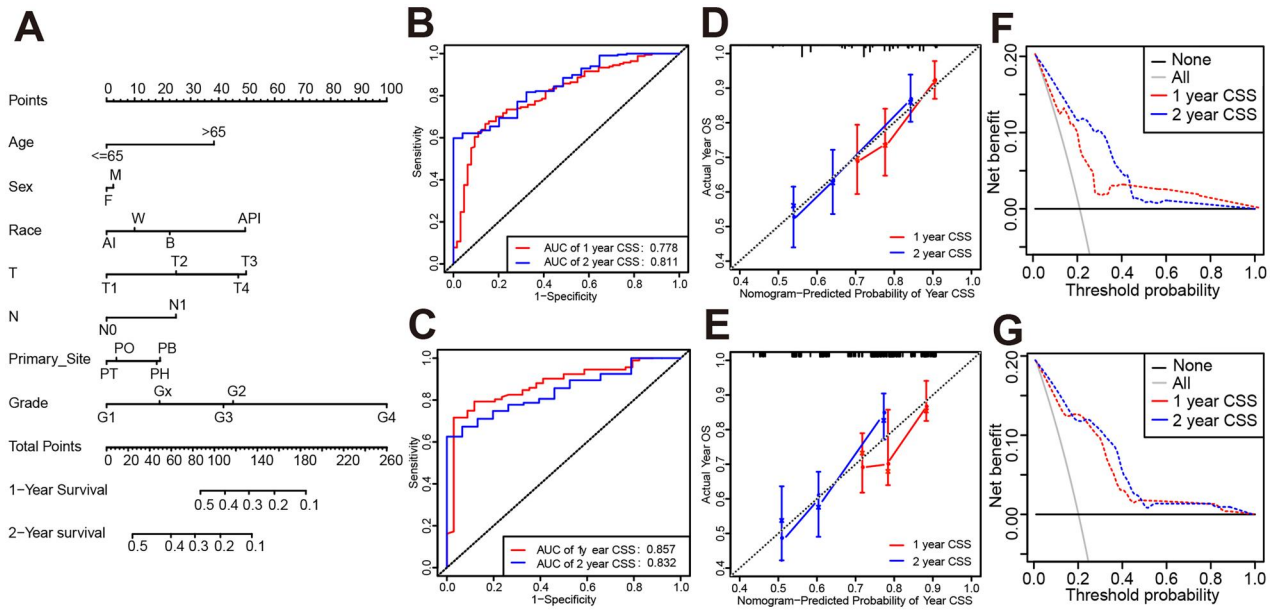

Figure 5. Prediction nomogram of CSS after primary tumor surgery. (A) The nomogram includes age, sex, race, T stage, N stage, histological grade, and tumor location for predicting CSS in postoperative patients. (B) ROC curves for 1-year CSS and 2-year CSS in the training set. (C) ROC curves for 1-year CSS and 2-year CSS in the validation set. (D) Calibration curves for 1-year CSS and 2-year CSS in the training set. (E) Calibration curves for 1-year CSS and 2-year CSS in the validation set. (F) DCA for 1-year CSS and 2-year CSS in the training set. (G) DCA for 1-year CSS and 2-year CSS in the validation set. Sex (F: female; M: male), Race (W: White; B: Black, AI: American Indian/Alaska Native; API: Asian or Pacific Islander); T: T Stage; N: N stage; Primary Site (PH: Pancreas head; PB: Pancreas body; PT: Pancreas tail; PO: Pancreas other); AUC: area under the receiver operating characteristic curve; CSS: cancer-specific survival.

treatment response (31). In addition, the stroma has significant biochemical and physical impacts that promote tumor survival, growth, and metastasis (32). Variations in stromal density between primary and metastatic lesions may lead to treatment response disparities. Therefore, it is reasonable that a reduced tumor load after primary tumor resection could improve the efficacy of chemotherapy for mPC. Evidence showed that the presence of a primary tumor reduced T-cell and antigen-specific antibody responses, whereas surgical excision of the primary tumor restored immunocompetence and improved anticancer immune activity (33). It was reported that circulating tumor cells (CTCs) might colonize their originating tumors, a phenomenon known as tumor self-seeding (34). Comen et al. found that surgical excision of the initial tumor could limit or delay the process of "self-seeding," resulting in a better prognosis for individuals undergoing surgical resection (35).

Although our research shows that primary tumor resection could prolong the survival outcomes of mPC patients, the median OS of patients who undergo primary tumor resection is one year (12 months), which is almost 0.7 years (8 months) longer than that of patients who do not undergo surgery. Of note, not all patients who could undergo surgery would benefit from it in terms of survival; the results revealed that some individuals who underwent surgery did not achieve the median OS time (4 months) of those who did not. Hence, this finding suggests that the surgical advice is insufficient. Based on this, we established a novel prediction model to maximize the selection of candidates who would benefit most from primary tumor surgery. Using this prediction nomogram, mPC patients who are surgical candidates can be selected based on their individual surgery benefit potential projection. Therefore, our prediction nomogram is a useful supplemental tool for selecting mPC patients most suitable for surgical intervention at the time of diagnosis. Clinicians may utilize the prediction nomogram to determine each patient's possible surgical benefit. According to our prediction nomogram, individuals designated as surgery benefit candidates are more likely to benefit from primary tumor surgery. Surgical therapy may be advised in addition to nonsurgical therapy in

these cases. A nonsurgical treatment plan would be a suitable suggestion for people who are considered surgery nonbenefit candidates. We believe that doctors will be better informed when they calculate the estimated benefit for each patient and make choices based on the cooperation of a diverse team.

In our model, tumor grade, size, and local extension of the primary tumor (T stage) were the most prominent predictors of patients who would benefit from primary tumor excision. Under a microscope, the grade of the tumor indicates how normal or aberrant the cells seem. It may estimate the cancer's growth rate and likelihood of spreading (36). By multivariate analysis, previous studies also showed that tumor grade was an independent predictor of PC patient survival after resection (37, 38). Crippa et al. studied a group of 502 resected PC patients and found that those with G3 exhibited larger pathologic sizes, a higher incidence of T3/T4 tumors, more lymph node metastases, and more microvascular/perineural invasion than those with G1 and G2 (39). In PC, tumor grade can be determined safely before surgery using minimally invasive techniques such as endoscopic ultrasonography-guided fine-needle aspiration (40). Therefore, patients with mPC should undergo a preoperative cytologic/histologic evaluation and grading of the primary tumor site as an essential part of their preoperative evaluation.

Similarly, several multivariate analyses have revealed that T stage is an independent risk factor for survival in patients with PC (41–43). Specifically, PC size >2 cm was an independent predictor associated with poor postsurgical prognosis, and this category has been included in the eighth TNM staging system (44, 45). Han et al. reported that patients in stage T1/T2 had a significantly better prognosis by performing a retrospective analysis of 433 patients with PC who underwent resection (46). However, the diagnosis of stage T1/T2 is infrequent. Consequently, early identification is a crucial element of PC therapy.

There are currently no definitive selection criteria for mPC patients who may benefit from surgical treatment. Moreover, as a result of extensive variabilities, such as age, sex, grade, and stage, the prognosis for mPC patients varies. The combination of individualized analysis of patient outcomes and treatment methods with primary tumor resection might improve the prognosis of specific individuals with mPC. Consequently, our research developed and verified the first nomogram based on a population to identify mPC patients who would benefit most from primary tumor resection. We expect to be able to complement the guidelines further and provide a new therapy option for individuals with mPC.

Notably, based on the surgical benefit group, we further developed a nomogram to predict the survival outcome of patients after surgery. Using this supplemental tool, surgeons could evaluate the prolonged survival probability of patients who underwent the procedure. Meanwhile, they can also comprehensively analyze the necessity of surgery by combining it with the desire of patients and relatives. We expect that employing these prediction tools in the clinic without incurring extra costs may assist surgeons with decision-making and treatment for certain patients.

We acknowledge the following limitations in our research. First, as with all observational studies, this research was a retrospective analysis with inherent bias. Second, some details were not provided in the SEER database, such as comorbidities, the specific chemotherapy drugs, and systematic therapy. Third, our nomogram was only validated in a split subgroup of participants, so it is necessary to validate the nomogram in an external cohort in the future.

Conclusion

In summary, our research developed a validated nomogram to aid surgeons in selecting optimally operable mPC patients who could potentially benefit from primary tumor resection in terms of survival. Therefore, presenting them with an extra practical therapeutic choice may improve their prognosis. The prediction model deserves more prospective validation and future enhancement.

Acknowledgments

We are grateful to have the SEER database as an open platform to facilitate our data collection and analysis.

Ethical approval statement

Not applicable.

Authors' contributions

K.S. conceived the study. K.S. and R.D. collected and analyzed the data. K.S. wrote the manuscript. K.S., R.D., and Y.W. collaborated in the discussion. All the authors read and approved the final manuscript.

Conflicts of interest statement

The authors declare that they have no conflicting interests.

Funding

China Scholarship Council (CSC) supported the research and work of K.S. (No. 201908440264).

Availability of data and materials

All data generated or analyzed during this study are included in this published article and raw data can download from Surveillance, Epidemiology, and End Results (SEER) database (www.seer.cancer.gov).

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–249. doi:10.3322/caac.21660.
2. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 2014;74(11):2913–2921. doi:10.1158/0008-5472.CAN-14-0155.
3. Kleeff J, Korc M, Apte M, La Vecchia C, Johnson CD, Biankin AV, et al. Pancreatic cancer. Nat Rev Dis Primers. 2016;2(1):16022. doi:10.1038/nrdp.2016.22.
4. He C, Huang X, Zhang Y, Lin X, Li S. The impact of different metastatic patterns on survival in patients with pancreatic cancer. Pancreatology. 2021;21(3):556–563. doi:10.1016/j.pan.2021.01.014.
5. Su BB, Bai DS, Yu JQ, Zhang C, Jin SJ, Zhou BH, et al. Can patients with pancreatic cancer and liver metastases obtain survival benefit from surgery? A population-based study. J Cancer. 2021;12(2):539–552. doi:10.7150/jca.51218.
6. Allendorf JD, Lauerman M, Bill A, DiGiorgi M, Goetz N, Vakiani E, et al. Neoadjuvant chemotherapy and radiation for patients with locally unresectable pancreatic adenocarcinoma: feasibility, efficacy, and survival. J Gastrointest Surg. 2008;12(1):91–100. doi:10.1007/s11605-007-0296-7.
7. Sohal DP, Mangu PB, Khorana AA, Shah MA, Philip PA, O'Reilly EM, et al. Metastatic pancreatic cancer: American society of clinical oncology clinical practice guideline. J Clin Oncol. 2016;34(23):2784–2796. doi:10.1200/JCO.2016.67.1412.
8. Warschkow R, Güller U, Tarantino I, Cerny T, Schmied BM, Thuerlimann B, et al. Improved survival after primary tumor surgery in metastatic breast cancer: a propensity-adjusted, population-based SEER trend analysis. Ann Surg. 2016;263(6):1188–1198. doi:10.1097/SLA.0000000000001302.
9. Flanigan RC, Salmon SE, Blumenstein BA, Bearman SI, Roy V, McGrath PC, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. N Engl J Med. 2001;345(23):1655–1659. doi:10.1056/NEJMoa003013.
10. Rosen SA, Buell JF, Yoshida A, Kazsuba S, Hurst R, Michelassi F, et al. Initial presentation with stage IV colorectal cancer: how aggressive should we be? Arch Surg. 2000;135(5):530–534. doi:10.1001/archsurg.135.5.530.
11. Fossati N, Trinh QD, Sammon J, Sood A, Larcher A, Sun M, et al. Identifying optimal candidates for local treatment of the primary tumor among patients diagnosed with metastatic prostate cancer: a SEER-based study. Eur Urol. 2015;67(1):3–6. doi:10.1016/j.eururo.2014.08.056.
12. Culp SH, Schellhammer PF, Williams MB. Might men diagnosed with metastatic prostate cancer benefit from definitive treatment of the primary tumor? A SEER-based study. Eur Urol. 2014;65(6):1058–1066. doi:10.1016/j.eururo.2013.11.012.
13. Shrikhande SV, Kleeff J, Reiser C, Weitz J, Hinz U, Esposito I, et al. Pancreatic resection for M1 pancreatic ductal adenocarcinoma. Ann Surg Oncol. 2007;14(1):118–127. doi:10.1245/s10434-006-9131-8.
14. Tachezy M, Gebauer F, Janot M, Uhl W, Zerbi A, Montorsi M, et al. Synchronous resections of hepatic oligometastatic pancreatic cancer: disputing a principle in a time of safe pancreatic operations in a retrospective multicenter analysis. Surgery. 2016;160(1):136–144. doi:10.1016/j.surg.2016.02.019.
15. Strobel O, Neoptolemos J, Jäger D, Büchler MW. Optimizing the outcomes of pancreatic cancer surgery. Nat Rev Clin Oncol. 2019;16(1):11–26. doi:10.1038/s41571-018-0112-1.
16. McPhee JT, Hill JS, Whalen GF, Zayaruzny M, Litwin DE, Sullivan ME, et al. Perioperative mortality for pancreatectomy: a national perspective. Ann Surg. 2007;246(2):246–253. doi:10.1097/01.sla.0000259993.17350.3a.
17. Hackert T, Büchler MW. Pancreatic cancer: advances in treatment, results and limitations. Dig Dis. 2013;31(1):51–56. doi:10.1159/000347178.

18. Seelig SK, Burkert B, Chromik AM, Tannapfel A, Uhl W, Seelig MH. Pancreatic resections for advanced M1-pancreatic carcinoma: the value of synchronous metastasectomy. HPB Surg. 2010;2010:579672–579676. doi:10.1155/2010/579672.
19. Singh A, Singh T, Chaudhary A. Synchronous resection of solitary liver metastases with pancreaticoduodenectomy. JOP. 2010;11(5):434–438.
20. Lemke J, Barth TF, Juchems M, Kapapa T, Henne-Bruns D, Kornmann M. Long-term survival following resection of brain metastases from pancreatic cancer. Anticancer Res. 2011;31(12):4599–4603.
21. Dünschede F, Will L, von Langsdorf C, Möhler M, Galle PR, Otto G, et al. Treatment of metachronous and simultaneous liver metastases of pancreatic cancer. Eur Surg Res. 2010;44(3–4):209–213. doi:10.1159/000313532.
22. Gleisner AL, Assumpcao L, Cameron JL, Wolfgang CL, Choti MA, Herman JM, et al. Is resection of periampullary or pancreatic adenocarcinoma with synchronous hepatic metastasis justified? Cancer. 2007;110(11):2484–2492. doi:10.1002/cncr.23074.
23. Doll KM, Rademaker A, Sosa JA. Practical guide to surgical data sets: surveillance, epidemiology, and end results (SEER) database. JAMA Surg. 2018;153(6):588–589. doi:10.1001/jamasurg.2018.0501.
24. McCaffrey DF, Ridgeway G, Morral AR. Propensity score estimation with boosted regression for evaluating causal effects in observational studies. Psychol Methods. 2004;9(4):403–425. doi:10.1037/1082-989X.9.4.403.
25. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med. 2009;28(25):3083–3107. doi:10.1002/sim.3697.
26. Tempero MA. NCCN guidelines updates: pancreatic cancer. J Natl Compr Canc Netw. 2019;17(1):1. doi:10.6004/jnccn.2019.0003.
27. Tempero MA, Malafa MP, Behrman SW, Benson AB, 3rd, Casper ES, Chiorean EG, et al. Pancreatic adenocarcinoma, version 2.2014: featured updates to the NCCN guidelines. J Natl Compr Canc Netw. 2014;12(8):1083–1093. doi:10.6004/jnccn.2014.0106.
28. Ettrich TJ, Seufferlein T. Systemic therapy for metastatic pancreatic cancer. Curr Treat Options Oncol. 2021;22(11):106. doi:10.1007/s11864-021-00895-4.
29. Wang L, Yang L, Chen L, Chen Z. Do patients diagnosed with metastatic pancreatic cancer benefit from primary tumor surgery? A propensity-adjusted, population-based surveillance, epidemiology and end results (SEER) analysis. Med Sci Monit. 2019;25:8230–8241. doi:10.12659/MSM.917106.
30. McKenzie S, Mailey B, Artinyan A, Kim J, Ellenhorn JD. The incidence and outcomes of pancreatectomy in patients with metastatic pancreatic adenocarcinoma. JOP. 2010;11(4):341–347.
31. Neesse A, Algül H, Tuveson DA, Gress TM. Stromal biology and therapy in pancreatic cancer: a changing paradigm. Gut. 2015;64(9):1476–1484. doi:10.1136/gutjnl-2015-309304.
32. Weniger M, Honselmann KC, Liss AS. The extracellular matrix and pancreatic cancer: a complex relationship. Cancers (Basel). 2018;10(9):316. doi:10.3390/cancers10090316.
33. Danna EA, Sinha P, Gilbert M, Clements VK, Pulaski BA, Ostrand-Rosenberg S. Surgical removal of primary tumor reverses tumor-induced immunosuppression despite the presence of metastatic disease. Cancer Res. 2004;64(6):2205–2211. doi:10.1158/0008-5472.can-03-2646.
34. Kim MY, Oskarsson T, Acharyya S, Nguyen DX, Zhang XHF, Norton L, Massagué J. Tumor self-seeding by circulating cancer cells. Cell. 2009;139(7):1315–1326. doi:10.1016/j.cell.2009.11.025.
35. Comen E, Norton L, Massagué J. Clinical implications of cancer self-seeding. Nat Rev Clin Oncol. 2011;8(6):369–377. doi:10.1038/nrclinonc.2011.64.
36. Marusyk A, Polyak K. Tumor heterogeneity: causes and consequences. Biochim Biophys Acta. 2010;1805(1):105–117. doi:10.1016/j.bbcan.2009.11.002.
37. Rochefort MM, Ankeny JS, Kadera BE, Donald GW, Isacoff W, Wainberg ZA, et al. Impact of tumor grade on pancreatic cancer prognosis: validation of a novel TNMG staging system. Ann Surg Oncol. 2013;20(13):4322–4329. doi:10.1245/s10434-013-3159-3.
38. Wu H, Guo JC, Yang SH, Tien YW, Kuo SH. Postoperative imaging and tumor marker surveillance in resected pancreatic cancer. J Clin Med. 2019;8(8):1115. doi:10.3390/jcm8081115.
39. Crippa S, Partelli S, Zamboni G, Barugola G, Capelli P, Inama M, et al. Poorly differentiated resectable pancreatic cancer: is upfront resection worthwhile? Surgery. 2012;152(1):S112–S119. doi:10.1016/j.surg.2012.05.017.
40. Mizuno N, Hara K, Hijioka S, Bhatia V, Shimizu Y, Yatabe Y, et al. Current concept of endoscopic ultrasound-guided fine needle aspiration for pancreatic cancer. Pancreatology. 2011;11(2):40–46. doi:10.1159/000323502.
41. Lim JE, Chien MW, Earle CC. Prognostic factors following curative resection for pancreatic adenocarcinoma: a population-based, linked database analysis of 396 patients. Ann Surg. 2003;237(1):74–85. doi:10.1097/00000658-200301000-00011.
42. Takahashi C, Shridhar R, Huston J, Meredith K. Correlation of tumor size and survival in pancreatic cancer. J Gastrointest Oncol. 2018;9(5):910–921. doi:10.21037/jgo.2018.08.06.

43. Zhang S, Huang X, Tian Y, Aimaiti S, Zhang J, Zhao J, et al. Clinicopathologic characteristics, laboratory parameters, treatment protocols, and outcomes of pancreatic cancer: a retrospective cohort study of 1433 patients in China. PeerJ. 2018;6:e4893. doi:10.7717/peerj.4893.
44. Li D, Hu B, Zhou Y, Wan T, Si X. Impact of tumor size on survival of patients with resected pancreatic ductal adenocarcinoma: a systematic review and meta-analysis. BMC Cancer. 2018;18(1):985. doi:10.1186/s12885-018-4901-9.
45. Allen PJ, Kuk D, Castillo CF, Basturk O, Wolfgang CL, Cameron JL, et al. Multi-institutional validation study of the American Joint Commission on Cancer (8th Edition) changes for T and N staging in patients with pancreatic adenocarcinoma. Ann Surg. 2017;265(1):185–191. doi:10.1097/SLA.0000000000001763.
46. Han SH, Heo JS, Choi SH, Choi DW, Han IW, Han S, et al. Actual long-term outcome of T1 and T2 pancreatic ductal adenocarcinoma after surgical resection. Int J Surg. 2017;40:68–72. doi:10.1016/j.ijsu.2017.02.007.