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ORIGINAL ARTICLE

A Preoperative Prognostic Scoring System to Predict Prognosis for Resectable Pancreatic Cancer: Who Will Benefit from Upfront Surgery?

Toru Nakamura[1] · Toshimichi Asano[1] · Keisuke Okamura[1] · Takahiro Tsuchikawa[1] · Soichi Murakami[1] · Yo Kurashima[1] · Yuma Ebihara[1] · Takehiro Noji[1] · Yoshitsugu Nakanishi[1] · Kimitaka Tanaka[1] · Toshiaki Shichinohe[1] · Satoshi Hirano[1]

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Abstract

Background Upfront surgery is recommended in patients with potentially resectable pancreatic ductal adenocarcinoma (R-PDAC) by National Comprehensive Center Network (NCCN) guidelines. However, even among R-PDACs, there is a subset that demonstrates extremely poor prognosis. The purpose of this study was to identify preoperative prognostic factors for upfront surgical resection of R-PDACs.

Methods The records of 278 consecutive patients with PDAC who underwent curative resection between 2001 and 2015 in a single institution were retrospectively reviewed. Preoperative factors to predict prognosis in patients with R-PDAC according to the NCCN guidelines were analyzed.

Results Of the 278 patients who underwent resection, 153 R-PDACs received upfront surgery with a median survival time (MST) of 26.4 months. Tumor location (pancreatic head) (odds ratio [OR] 1.97, 95% confidence interval [CI] 1.14–3.40; $P = 0.015$), preoperative cancer antigen 19–9 (CA19–9) > 100 U/mL (OR 1.92, 1.31–2.80; $P = 0.0009$), and tumor size > 20 mm (OR 1.50, 1.02–2.19; $P = 0.038$) were identified as preoperative independent predictive risk factors for poor prognosis in patients with R-PDACs. In the patients with R-PDAC, 5-year survival was 60.7%, 21.5%, and 0% in patients with 0, 1 or 2, and 3 risk factors, respectively. There were significant differences in overall survival between the three groups ($P < .0001$).

Conclusions A preoperative prognostic scoring system using preoperative tumor location, tumor size, and CA19-9 enables preoperative prediction of prognosis and facilitates selection of appropriate treatment for resectable pancreatic cancer.

Keywords Resectable pancreatic cancer · Preoperative prognostic scoring · Upfront surgery

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive malignancies.[1, 2] In 2017, it is estimated that there will be 53,670 new cases of pancreatic cancer in the USA, and PDAC is the fourth leading cause of cancer-related death.[2] Furthermore, in the USA, the number of patients with PDAC is expected to increase from 43,000 in 2010 to 88,000 by 2030, an increase projected to result in 63,000 deaths in 2030 compared to 36,888 in 2010.[1]

National Comprehensive Center Network (NCCN) guidelines recommend upfront surgery for potentially resectable pancreatic cancer (R-PDAC), followed by postoperative adjuvant therapy, owing to the expectation of R0 resection and better prognosis.[3] However, in reality, upfront surgery for R-PDAC resulted in R0 resection in 81–88% of cases, postoperative recurrence was observed in 66–85% of cases, and the 5-year overall survival rate was 20.7–44.1%.[4,5] These findings indicate that a subset of tumors with poor prognosis is included within R-PDACs. Several clinicopathological factors

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✉ Toru Nakamura
torunakamura@med.hokudai.ac.jp

1 Department of Gastroenterological Surgery II, Faculty of Medicine, Hokkaido University, N-15 W-7, Kita-Ku, Sapporo 060-8638, Japan

have been associated with prognosis following pancreatectomy for PDAC. These factors include the classical clinical factors such as tumor size, lymph node metastasis, surgical margin status, and tumor markers, as well as the recently recognized role played by the host systemic inflammatory response.[6–8] The combination of C-reactive protein (CRP) and albumin, known as the Glasgow Prognostic Score (GPS), has been evaluated preoperatively in patients undergoing potentially curative pancreatectomy for PDAC.[9–12]

The goal of the present study was to establish a prognostic prediction system in R-PDAC using preoperatively detectable factors.

Patients and Methods

Patients

Between August 2001 and July 2015, 278 consecutive patients with PDAC underwent curative resection in the Department of Gastroenterological Surgery II, Hokkaido University Hospital. According to NCCN guidelines,[3] 164 tumors were categorized as resectable (R-PDACs), 74 were borderline resectable (BR-PDACs), and 40 were unresectable (UR-PDACs). Of the 164 patients with R-PDACs, 11 patients who received preoperative adjuvant therapy were excluded, and a total of 153 patients with R-PDACs who received upfront surgery were retrospectively analyzed. Preoperative workup was performed with multidetector computed tomography (MDCT) using a standard protocol optimized for pancreatic tumors. Patients were followed for a median of 72 months (range, 15.3–171) or until death. Postoperative follow-up investigations consisted of physical examination, laboratory studies, and CT imaging at 3- to 4-month intervals for the first 2 years, at 6-month intervals for years 3 through 5, and then at yearly intervals. In principle, preoperative laboratory tests were measured within 14 days before surgery. For patients with biliary obstruction, CA19-9 was measured after biliary drainage with a total bilirubin under 3.0 mg/dL.

Surgery and Adjuvant Chemotherapy

Surgical resection with lymph node dissection was performed in all patients. Lymph node dissection around the celiac artery, common hepatic artery (CHA), superior mesenteric artery (SMA), superior mesenteric vein (SMV), and hepatoduodenal ligament was performed in patients who underwent pancreaticoduodenectomy. In patients who underwent distal pancreatectomy, lymph node dissection around the celiac artery, CHA, SMA, and SMV was performed. When the primary tumor was adherent to the portal vein (PV)/SMV, venous resection and reconstruction were performed at the surgeon's discretion. When a primary tumor located in the pancreatic body was adherent to the root of the splenic artery (generally within 10 mm), concomitant resection of the celiac artery and CHA were performed.[13,14] Adjuvant therapy was initiated within 2 months after the operation unless contraindicated by the patient's condition or rejection. Most commonly, gemcitabine or S-1 (oral fluoropyrimidine agent containing tegafur, gimeracil, and oteracil potassium) was administered.[5]

Statistical Analysis

Cumulative overall survival was estimated with the Kaplan-Meier method, and a comparison of the survival curves was performed using the log-rank test. Factors significant on univariate analysis were entered into the multivariate Cox proportional hazards model, and the hazard ratio (HR) and 95% confidence interval (CI) were calculated. To define the cut-off value of continuous variables, age and body mass index (BMI) were used as median. To define the cut-off value of tumor diameter, we evaluated tumor diameter 20 mm, 25 mm, 30 mm, and 35 mm; as a result, 20 mm was most clearly influenced by the prognosis of R-PDACs. The cut-off value of CA19-9 was also decided by evaluating 100, 150, 200, and 300; as a result, 100 was most clearly influenced by the prognosis of R-PDACs. All survival analyses were calculated from the time of surgery to death from any cause. The significance level was set at $P < 0.05$. Statistical analysis was performed using JMP 10.0 (SAS Institute, Inc., Cary, NC, USA) software for Windows.

Results

Clinical and Pathological Characteristics of Patients

The clinical and pathological characteristics of the 153 patients with R-PDAC are shown in Table 1. There were 92 men (60%) and 61 women (40%), with a median age of 69.0 years (range 43–85). Concomitant portal and/or SMV resection was necessary in 55 (36%) patients, and the artery was concomitantly resected in 22 (14%) patients (celiac artery resection) to maintain the residual margin of the splenic artery during the distal pancreatectomy. The pathological stage was determined according to the 7th Tumor-Node-Metastasis (TNM) classification of the Union for International Cancer Control (UICC).[15] Among the patients, 142 (92.8%) were categorized as having pT3 tumors, and 96 patients (62.7%) had regional lymph node metastases; therefore, 143 patients (93.5%) had stage II disease.

Table 1 Clinical characteristics of patients

Characteristics	Value
Patients	
Age (median) [range], years	69 [43–85]
Men/women	92/61
Tumor location	
Head	103 (67.3)
Body and tail	50 (32.7)
Operative method	
PD	5 (3.3)
SSPPD	98 (64.0)
DP	28 (18.3)
DP-CAR	22 (14.4)
Perioperative data	
Operative time (median) [range], min	472 [208–854]
Blood loss (median) [range], mL	980 [200–3290]
Blood transfusion (%)	13 (8.5)
PV/SMV resection (%)	55 (35.9)
Artery resection (%)	22 (14.4)
Clavien-dindo classification[a] ≥ grade IIIa (%)	41 (26.8)
Pancreatic fistula[b] ≥ grade B or C (%)	32 (20.9)
Adjuvant chemotherapy (%)	91 (59.5)
UICC (7th, 2009) pathologic stage	
Primary tumor	
T1 (%)	6 (3.9)
T2 (%)	5 (3.3)
T3 (%)	142 (92.8)
Lymph node metastasis	
N0 (%)	57 (37.3)
N1 (%)	96 (62.7)
Stage	
I (%)	9 (5.9)
II (%)	143 (93.5)
III (%)	0 (0.0)
IV (%)	1 (0.6)
Histopathologic type	
Well (%)	33 (21.6)
Moderate (%)	98 (64.0)
Poor (%)	22 (14.4)
Residual tumor status	
R0 (%)	138 (90.2)
R1 (%)	15 (9.8)

UICC International Union Against Cancer

[a] Postoperative complications were classified according to the Clavien-Dindo's classification

[b] Pancreatic fistula was defined by the International Study Group on Pancreatic Fistula (ISGPF)

Lymph node metastasis in the paraaortic area that proved to be an M1 lesion was diagnosed as stage IV disease in one patient. R0 resection was achieved in 138 (90.2%) patients. Of the 153 patients, 91 (60%) patients received adjuvant chemotherapy, and the remaining 62 (40%) did not.

Independent Preoperative Prognostic Factors of R-PDAC

To identify the preoperative prognostic factors for postoperative overall survival (OS) in R-PDAC, the clinical factors that can be evaluated preoperatively are shown in Table 2. Univariate analysis revealed that the significant prognostic factors for OS of R-PDAC were sex (male), biliary drainage, tumor location (pancreatic head; ph), tumor size, PV/SMV invasion, and CA19-9. After multivariate analysis, three parameters, including tumor location (ph) ($P = 0.028$), tumor size ($P = 0.012$), and CA19-9 ($P = 0.002$), were identified as the independent prognostic factors for OS. The mGPS showed the possibility of prognostic factors in both univariate ($P = 0.057$) and multivariate analysis ($P = 0.071$), but it did not reach statistical significance.

Overall survival curves were assessed using three independent prognostic factors (Fig. 1). The median survival time for patients in the ph group was 20.5 months, while it was 46.7 months for those in the pancreatic body/tail (pbt) group ($P = 0.0001$). The median survival time for patients in the group with tumor size > 20 mm was 20.6 months, and it was 46.5 months for those in the group with tumor size ≤ 20 mm ($P = 0.0003$). For patients in the CA19-9 > 100 U/mL group, the median survival time was 17.8 months, while it was 34.1 months for those in the CA19-9 ≤ 100 U/mL group ($P = 0.0001$).

Preoperative Prognostic Scoring System

The tumor location, tumor size, and preoperative CA19-9 levels, which could be easily evaluating prior to pancreatectomy, were selected as the independent prognostic factors to establish the preoperative prognostic scoring system. The criteria of the Preoperative Prognostic Score (PPS) are shown in Table 3. Adverse prognostic factors were tumor location in pancreatic head, clinical tumor size > 20 mm, and preoperative CA19-9 levels > 100 U/mL, and these were allocated 1 point each. Tumor location in pancreatic body/tail, clinical tumor size ≤ 20 mm, and preoperative CA19-9 levels < 100 U/mL were allocated 0 points each. The total score was defined as the PPS, with scores ranging from PPS0 to PPS3.

The PPS scores were distributed as follows: PPS0, 19 patients; PPS1, 42 patients; PPS2, 61 patients; and PPS3, 31 patients. Because the survival rates of patients with scores of PPS1 and PPS2 were not statistically different ($P = 0.35$, Supplemental Fig. 1), PPS1 and PPS2 were combined during calculation of survival rates. The prognoses for PPS0, PPS1/2, and PPS3 were estimated with overall survival rates using the

Table 2 Univariate and multivariate analysis of preoperative clinical parameters

	Univariate		Multivariate	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Age (year) (≥ 69 vs < 69)	0.77 (0.53–1.12)	0.17		
Gender (male vs female)	1.48 (1.01–2.19)	0.043	1.37 (0.92–2.08)	0.13
Body mass index (< 22 vs ≥ 22)	1.09 (0.75–1.57)	0.66		
Biliary drainage (+ vs −)	1.53 (1.05–2.22)	0.027	1.04 (0.67–1.62)	0.86
Diabetes (+ vs −)	1.23 (0.82–1.80)	0.31		
Tumor location (Ph vs Pbt)	2.26 (1.50–3.52)	<.0001	1.82 (1.07–3.14)	0.028
Clinical tumor size (> 20 vs ≤ 20 mm)	2.07 (1.39–3.15)	0.0003	1.69 (1.12–2.61)	0.012
Clinical PV/SMV invasion (+ vs −)	1.91 (1.30–2.79)	0.0011	1.34 (0.87–2.05)	0.18
CA19-9 (> 100 vs ≤ 100 U/mL)	2.05 (1.41–2.98)	0.0002	1.87 (1.27–2.73)	0.002
mGPS (2 vs 0/1)	3.15 (0.96–7.60)	0.057	3.03 (0.90–7.71)	0.071
NLR (≥ 3 vs < 3)	0.99 (0.65–1.48)	0.96		
PLR (≥ 150 vs < 150)	0.77 (0.53–1.12)	0.18		
PNI (< 45 vs ≥ 45)	0.83 (0.53–1.26)	0.39		

PV portal vein, *SMV* superior mesenteric vein, *CA19-9* carbohydrate antigen 19-9, *m GPS* modified Glasgow prognostic score, *NLR* nentrophil lymphocyte ratio, *PLR* platelet lymphocyte ratio, *PNI* prognostic nutritional index

Modified Glasgow prognostic score was defined as follows: patients with both an elevated C-reactive protein (> 1.0 mg/dL) and hypoalbuminemia (< 3.5 g/dL) were allocated a score of 2. Patients with only one of these biochemical abnormalities were given a score of 1. Patients with neither of these abnormalities were given a score of 0

PNI was calculated as follows: 10 × albumin (g/dL) + 0.005 × total lymphocyte count (/μL)

Kaplan–Meier method (Fig. 2). The estimated overall 1-, 3-, and 5-year survival rates for the 19 patients with PPS0 were 94.7%, 94.7%, and 65.1%, respectively, while for the 103 patients with PPS1/2, they were 84.5%, 35.2%, and 22.7%, respectively. The median survival times for PPS0 and PPS1/2 were not reached and 26.0 months, respectively. In contrast, the prognosis was worse in the 31 patients with PPS3, with overall 1-, 3-, and 5-year survival rates of 61.3%, 9.7%, and 3.2%, respectively. The median survival time was 13.3 months. Patients with PPS3 had a significantly worse survival than patients with PPS0 or PPS1/2 (log-rank, $P < .0001$ and $P < .0001$, respectively) (Table 4). Recurrence occurred in 90.3% (28/31) of the patients in the PPS 3 group. The primary recurrence sites of them were liver (19/28: 67.9%), peritoneum (8/28: 28.6%), local (3/28: 10.7%), lung (3/28: 10.7%), and lymph node (5/28: 17.9%) with overlaps. The median period to having recurrences after surgery was 5.6 months (1.4–34.7) in the liver, 5.4 months (3.5–34.7) in the peritoneum, 6.2 months (5.3–8.1) in the lung, and 7.6 months (3.3–14.7) in lymph node. These data suggest that the patients in the PPS3 group suffered systemic disease at the time of surgery.

Discussion

The rate of PPS scores of PPS3 in our study population was 20.3% among patients with R-PDAC, and the median survival time was 13.3 months, representing a worse prognosis than that of patients with locally advanced unresectable (UR-LA) PDAC.[16,17] This result indicates a limitation of the treatment strategy according to the NCCN guidelines, because it includes a subset of patients with poor prognosis who derive no benefit from surgery even if diagnosed with R-PDAC. “Resctable” according to traditional imaging studies means surgically resectable but does not guarantee a survival benefit from surgery. The modern regimens such as Gemcitabine plus nab-PTX or FOLFIRINOX used in patients with high-risk factors PPS1/2 might prolong the survival time. However, enforcing such powerful regimens could be used only for patients with fair systemic condition. The prognosis of patients in the PPS 3 group is almost comparable to that of patients with borderline resectable (BR) or some with unresectable (UR) pancreatic cancer. As the status of tumor progression is resectable in imaging study even in the PPS 3 group, the main cause of poor prognosis might be potential metastasis. Therefore, for the patients in the PPS 3 group, we recommend systemic chemotherapy first according to the strategy for BR or locally advanced UR patients. Some reports indicated that prognosis of patients having BR PC who received preoperative treatment could be improved.[18,19] On the other hand, there is a subset of patients with good prognosis, such as the PPS0 group (5-year survival, 65.1%). Recently, several clinical trials of neoadjuvant therapy have been conducted in R-PDAC to achieve better survival compared with an upfront

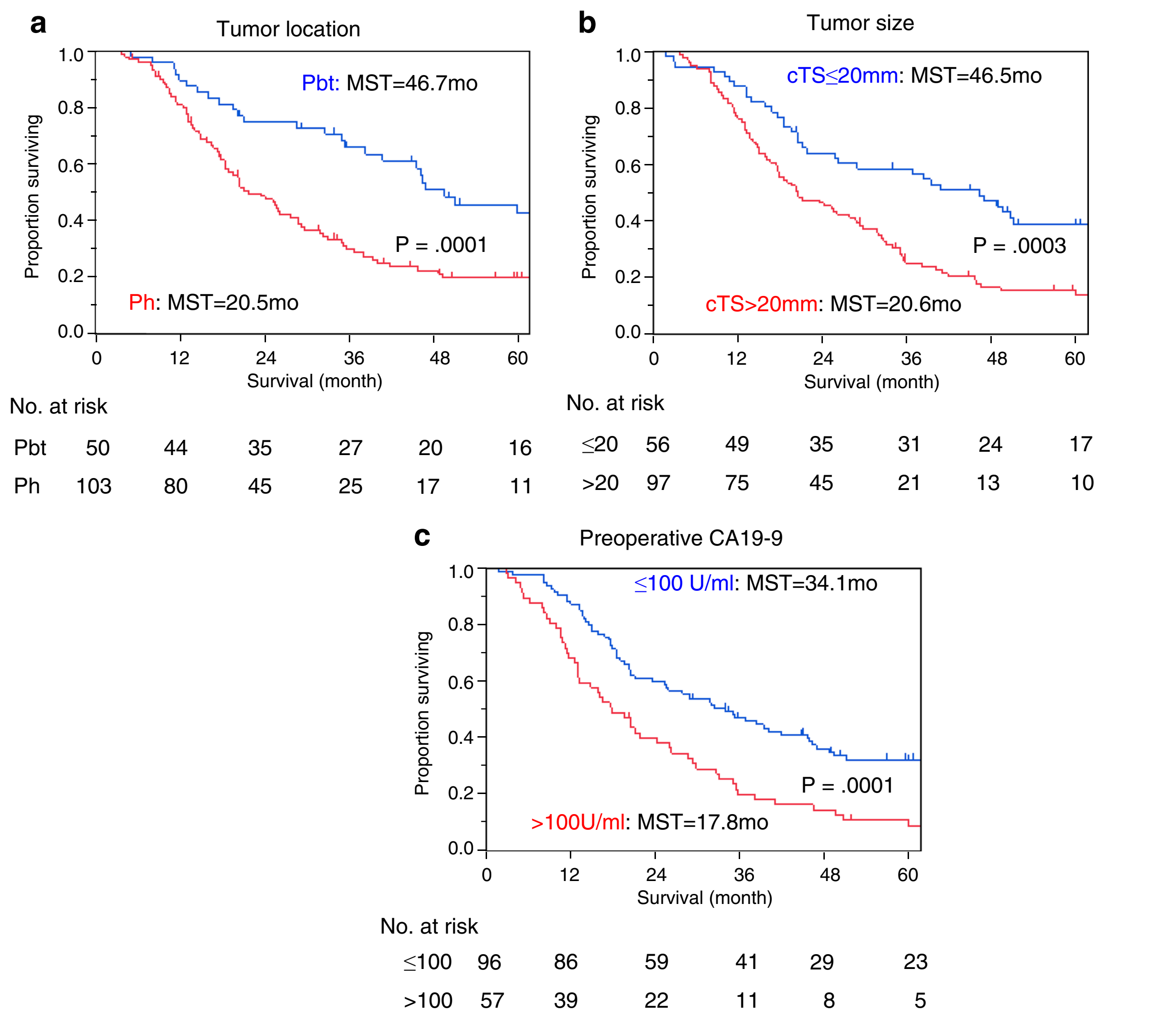


Fig. 1 Overall survival in 153 patients with pancreatic cancer was statistically analyzed on the basis of **a** tumor location, **b** clinical tumor size, and **c** preoperative CA19-9. MST = median survival time

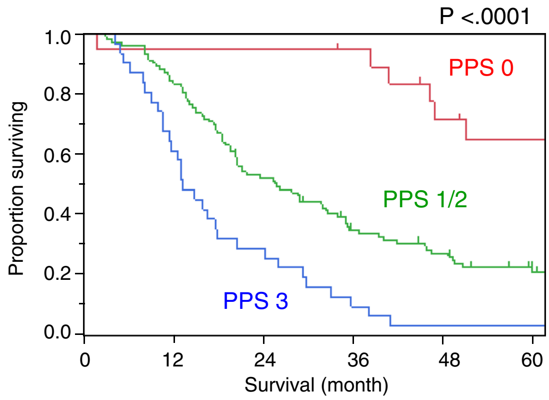
surgical approach.[20,21] In construction of a randomized controlled trial for R-PDAC in a neoadjuvant setting, a bias in the direction of the subsets with either poor or good prognosis could lead to misdirection in the results.

There have been several studies to identify factors to predict postoperative early recurrence of PDAC.[9,22,23] Matsumoto and colleagues reported a simple scoring system using three preoperative predictive risk factors including mGPS = 2, CA19-9 ≥ 300 U/mL, and tumor size ≥ 30 mm that predicts early recurrence from analysis of R-PDAC and BR-PDAC.[9] Of the three factors, tumor size and CA19-9 were also identified in the present study, but m-GPS was not. A value of mGPS = 2 showed possibility as a prognostic factor in both univariate ($P = 0.057$) and multivariate analysis ($P = 0.071$), but it did not achieve statistical significance in our study. Because the proportion of patients with m-GPS = 2 in our study was 2.6% (4 out of 153), the statistical power may be low. Our study was limited to R-PDAC only; therefore, the m-GPS score was relatively preserved (91.5%, score 0). We felt that these differences regarding independent factors might be caused by the analysis set (including BR-PDAC or limited to R-PDAC) and outcome setting (early recurrence or prognosis).

Table 3 Criteria of the preoperative prognostic score

Factors	Points
Tumor location	
Body and tail	0
Head	1
Tumor size (clinical)	
≤ 20 mm	0
> 20 mm	1
Preoperative CA19-9 (U/mL)	
≤ 100	0
> 100	1

CA19-9 carbohydrate antigen 19-9



No. at risk

PPS 0	19	18	18	17	12	10
PPS 1/2	103	87	53	32	24	16
PPS 3	31	19	9	3	1	1

Fig. 2 Estimated overall survival curves for patients with resectable pancreatic cancer according to preoperative prognostic scoring system. Because patients in PPS1 and PPS2 groups were not statistically different in prognosis, PPS1 and PPS2 were combined. There were significant differences in overall survival between PPS0, PPS1/2, and PPS3 groups ($P < .0001$, log rank test). PPS = preoperative prognostic score

In the present study, cancer in the pancreatic body/tail was associated with better prognosis than cancer in the pancreatic head, and tumor location was an independent prognostic factor. It is frequently mentioned that pancreatic body/tail cancer is diagnosed at an advanced stage, which leads to worse prognosis. However, there is a lack of data regarding stage at diagnosis and survival of pancreatic body/tail cancer compared to those of pancreatic head cancer. Moreover, there are increasing reports that pancreatic body/tail cancer may have good prognosis. Lau et al. reported that the incidence of pancreatic head cancer had remained stable, whereas the incidence of pancreatic body/tail cancers has been rising in the last 3 decades, and the authors also showed that the 3-year survival rate for local-stage pancreatic body/tail cancer is 20.0% compared with 9% for local-stage pancreatic head cancer.[24] In our study, the artery was concomitantly resected in 22 (14%) patients (celiac artery resection) to maintain the residual margin of the splenic artery during the distal pancreatectomy. When a primary tumor located in the pancreatic body was adherent to the root of the splenic artery (generally within 10 mm), we routinely performed distal pancreatectomy with en bloc celiac axis resection (DP-CAR). DP-CAR was developed for locally advanced pancreatic body cancer and was resulted in the high R0 rate.[13,14] Therefore, one of the reasons for good prognosis in the pancreatic body-tail tumor in this study might be achieved by local control in DP-CAR. On the other hand, when the tumor is located at the pancreatic head, it becomes adaptation of pancreaticoduodenectomy (PD). Since PD has higher hospitalization days and complication rates than distal pancreatectomy (DP), it seems that the tumor location has become a prognostic factor because adjuvant chemotherapy is difficult to introduce in PD cases. However, in our study, there was no difference between PD and DP in performed adjuvant therapy (PD: 58/103(56%), DP: 33/50 (66%), $P = 0.25$, data not shown in the results). Hence, the tumor location could not be influenced by the rate of adjuvant therapy, but might have other oncological behavior for the patient prognosis. Recently, Ling et al. showed that overall and disease-free survival were significantly higher in patients with pancreatic body/tail cancer compared to those with pancreatic head cancer at stage II. The researchers found lower expression of miR-501-3p and higher expression of miR-375 in pancreatic body/tail cancer tissues compared with pancreatic head cancer tissues. The pancreatic body/tail cancer demonstrated a less malignant phenotype associated with deregulation of miR-501-3p compared with pancreatic head cancer.[25] Further oncological research will elucidate the differences in malignant phenotype related to the tumor location.

This study was based on data from 153 resected pancreatic cancer patients over the course of 15 years. Indeed, it is one of the limitations of this study that the data was collected for the long period from the single institution. However, the surgical procedure had not changed in the period. The other limitation is heterogeneity of adjuvant therapy. Of course, the multi-institutional study including much more patients during shorter collection period should be done so as to make the results more definite.

Table 4 Results of preoperative prognostic score (PPS)

PPS	Survival rate, year (%)			Median survival time (month)
	1	2	3	
0 ($n = 19$)	94.7	94.7	65.1	not reached
1/2 ($n = 103$)	84.5	35.2	22.7	26.0
3 ($n = 31$)	61.3	9.7	3.2	13.3

Conclusion

Based on the results of the present study, three factors, tumor location in the pancreatic head, tumor size (> 20 mm), and CA19-9 (> 100 U/mL), can be used to distinguish a subset with poor prognosis in R-PDAC. Future clinical trials of neoadjuvant therapy targeting the subset of R-PDAC with poor prognosis should be performed.

Authors' Contribution Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: Toru Nakamura, Toshimichi Asano, Keisuke Okamura, Takahiro Tsuchikawa, Takehiro Noji, Yoshitsugu Nakanishi, Kimitaka Tanaka, Soichi Murakami, Yuma Ebihara, Yo Kurashima, Toshiaki Shichinohe.

Drafting the work or revising it critically for important intellectual content: Toru Nakamura.

Final approval of the version to be submitted: Toru Nakamura, Satoshi Hirano.

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: Toru Nakamura, Satoshi Hirano.

Compliance with Ethical Standards

This study was conducted in accordance with the ethical standards of the Committee on Human Experimentation of our institution and was approved by the Institutional Review Board of Hokkaido University Hospital (No. 017-0363).

References

1. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM and 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; 74:2913–21.
2. Siegel RL, Miller KD and Jemal A. Cancer Statistics, 2017. CA: a cancer journal for clinicians. 2017.
3. National Comprehensive Cancer Network. NCCN practice guidelines for pancreatic cancer, version 2. Available from: http://www.nccn.org/professionals/physician_gls/recently_ updated.asp.
4. Oettle H, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. JAMA. 2013; 310:1473–81.
5. Uesaka K, Boku N, Fukutomi A, Okamura Y, Konishi M, Matsumoto I, JASPAC 01 Study Group et al.. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). Lancet. 2016; 388:248–57.
6. Brennan MF, Kattan MW, Klimstra D, Conlon K. Prognostic nomogram for patients undergoing resection for adenocarcinoma of the pancreas. Ann Surg. 2004; 240:293–98.
7. Åkerberg D, Ansari D, Andersson R. Re-evaluation of classical prognostic factors in resectable ductal adenocarcinoma of the pancreas. World J Gastroenterol. 2016; 22:6424–33.
8. Sierzega M, Lenart M, Rutkowska M, Surman M, Mytar B, Matyja A, et al. Preoperative Neutrophil-Lymphocyte and Lymphocyte-Monocyte Ratios Reflect Immune Cell Population Rearrangement in Resectable Pancreatic Cancer. Ann Surg Oncol. 2017; 24:808–15.
9. Matsumoto I, Murakami Y, Shinzeki M, Asari S, Goto T, Tani M, et al. Proposed preoperative risk factors for early recurrence in patients with resectable pancreatic ductal adenocarcinoma after surgical resection: A multi-center retrospective study. Pancreatology. 2015; 15:674–80.
10. La Torre M, Nigri G, Cavallini M, Mercantini P, Ziparo V, Ramacciato G. The glasgow prognostic score as a predictor of survival in patients with potentially resectable pancreatic adenocarcinoma. Ann Surg Oncol. 2012; 19:2917–23.
11. Yamada S, Fujii T, Yabusaki N, Murotani K, Iwata N, Kanda M, et al. Clinical Implication of Inflammation-Based Prognostic Score in Pancreatic Cancer: Glasgow Prognostic Score Is the Most Reliable Parameter. Medicine (Baltimore). 2016; 95:e3582. https://doi.org/10.1097/MD.0000000000003582.
12. Jamieson NB, Denley SM, Logue J, MacKenzie DJ, Foulis AK, Dickson EJ, et al. A prospective comparison of the prognostic value of tumor- and patient-related factors in patients undergoing potentially curative surgery for pancreatic ductal adenocarcinoma. Ann Surg Oncol. 2011; 18:2318–28.
13. Hirano S, Kondo S, Hara T, Ambo Y, Tanaka E, Shichinohe T, et al. Distal pancreatectomy with en bloc celiac axis resection for locally advanced pancreatic body cancer: long-term results. Ann Surg. 2007; 246:46–51.
14. Nakamura T, Hirano S, Noji T, Asano T, Okamura K, Tsuchikawa T, et al. Distal Pancreatectomy with en Bloc Celiac Axis Resection (Modified Appleby Procedure) for Locally Advanced Pancreatic Body Cancer: A Single-Center Review of 80 Consecutive Patients. Ann Surg Oncol. 2016; 23:969–75.
15. Sobin LH, Gospodarowicz MK, Wittekind Ch (eds). TNM Classification of Malignant Tumours. 7th ed. Wiley-Blackwell, Oxford, 2009
16. Mukherjee S, Hurt CN, Bridgewater J, Falk S, Cummins S, Wasan H, et al. Gemcitabine-based or capecitabine-based chemoradiotherapy for locally advanced pancreatic cancer (SCALOP): a multicentre, randomised, phase 2 trial. Lancet Oncol. 2013; 14: 317–26.
17. Suker M, Beumer BR, Sadot E, Marthey L, Faris JE, Mellon EA, et al. FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. Lancet Oncol. 2016; 17:801–10.
18. Jang JY, Han Y, Lee H, Kim SW, Kwon W, Lee KH, et al. Oncological Benefits of Neoadjuvant Chemoradiation With Gemcitabine Versus Upfront Surgery in Patients With Borderline Resectable Pancreatic Cancer: A Prospective, Randomized, Open-label, Multicenter Phase 2/3 Trial. Ann Surg. 2018; 268:215–22.
19. Versteijne E, Vogel JA, Besselink MG, Busch ORC, Wilmink JW, Daams JG, Dutch Pancreatic Cancer Group. et al; Meta-analysis comparing upfront surgery with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic cancer. Br J Surg. 2018; 105:946–58. **Review**.
20. Palmer DH, Stocken DD, Hewitt H, Markham CE, Hassan AB, Johnson PJ, et al. A randomized phase 2 trial of neoadjuvant chemotherapy in resectable pancreatic cancer: gemcitabine alone versus gemcitabine combined with cisplatin. Ann Surg Oncol. 2007; 14:2088–96.
21. Heinrich S, Pestalozzi B, Lesurtel M, Berrevoet F, Laurent S, Delpero JR, et al. Adjuvant gemcitabine versus NEOadjuvant gemcitabine/oxaliplatin plus adjuvant gemcitabine in resectable pancreatic cancer: a randomized multicenter phase III study (NEOPAC study). BMC Cancer. 2011; 11:346.
22. Sugiura T, Uesaka K, Kanemoto H, Mizuno T, Sasaki K, Furukawa H, et al. Serum CA19-9 is a significant predictor among preoperative parameters for early recurrence after resection of pancreatic adenocarcinoma. J Gastrointest Surg. 2012; 16:977–85.
23. Kim TH, Han SS, Park SJ, Lee WJ, Woo SM, Yoo T, et al. CA 19-9 level as indicator of early distant metastasis and therapeutic selection in resected pancreatic cancer. Int J Radiat Oncol Biol Phys. 2011; 81:e743–8.
24. 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; 39:458–62.
25. 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; 8: 15159–67.