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Combination of Distance from Superior Mesenteric Artery and Serum CA19-9 as a Novel Prediction of Local Recurrence in Patients With Pancreatic Cancer Following Resection

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Abstract. *Background/Aim: Prediction of local recurrence and distant metastasis is important for patients with pancreatic cancer following pancreatic resection. The aims of this study were to identify a novel prognostic score which combines distance from common hepatic artery (CHA) or superior mesenteric artery (SMA) and examine serum CA19-9 for predicting local recurrence in patients with pancreatic cancer following resection. Patients and Methods: This retrospective study comprised 149 patients who went through elective pancreatic resection for pancreatic cancer between June 2007 and December, 2017. We established new scores (CHA score and SMA score) using the distance between CHA or SMA and the tumor measured by preoperative CT scan in combination with preoperative serum CA19-9 values. We evaluated the relationship between the scores and local recurrence of pancreatic cancer. Finally, we investigated the relationship between the scores and local recurrence-free survival as well as the overall survival. Results: The optimal cut-off levels of the distance between CHA or SMA and the tumor, as determined by ROC analysis, were 20.55 and 10.9 mm, respectively. In a logistic progression model, demonstrated by multivariate analysis, lymphatic invasion (p=0.002), preoperative serum CA19-9 (p=0.007) and SMA score (p=0.004) were identified to be independent predictors of local recurrence in patients with pancreatic cancer following resection. In a Cox progression model, demonstrated by multivariate analysis, intraoperative blood loss (p=0.022), lymphatic invasion (p=0.001) and SMA score (p<0.001) were identified as independent factors of local recurrence. The independent predictors of poor overall survival by multivariate analysis consisted of intraoperative blood loss (p=0.045), intraoperative transfusion (p=0.026) and SMA score (p<0.001). Conclusion: The SMA score may be an independent preoperative predictor of local recurrence and prognosis in patients with pancreatic cancer.*

Pancreatic cancer is one of the most fatal human malignant cancers of the digestive system and the fourth leading cause of cancer-related deaths worldwide (1). Pancreatic cancer is predicted to become the second leading cause of cancer-death in the United States by 2030 (2). Only 10-25% of patients with pancreatic cancer are eligible for curative resection due to the lack of screening methods with high sensitivity and specificity that allow early detection (3, 4). The overall survival rate of patients who undergo such curative surgical resection remains poor, despite of improvements in surgical techniques, instruments, and postoperative management. Most patients will develop disease recurrence resulting in a 5-year survival of only about 10 to 25% (5-7). Well-known prognostic factors of long-term survival in patients undergoing resection of pancreatic cancer include small tumor size, absence of lymph node involvement, curative (R0) resection and adjuvant chemotherapy (8, 9).

The time and location pattern of cancer recurrence following pancreatic resection is unique and variable. Isolated local recurrence accounts for 30% in patients with cancer following pancreatic resection in the absence of distant metastasis (10, 11). Locally destructive tumor growth has been shown to be the probable cause of death in up to 30% of patients with pancreatic cancer (12). This suggests that, in addition to distant metastasis, management and prediction of local recurrence is also important to get long-term survival of patients with pancreatic cancer after resection. Unfortunately, despite the high local recurrence rate, there are no established strategies to deal with the local recurrence of pancreatic cancer. As local recurrence of pancreatic cancer is closely linked to the surgical procedure,

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Key Words: Pancreatic cancer, local recurrence, elective pancreatic resection, distance from SMA.

the identification of risk factors for local recurrence using preoperative variables may be critical for deciding the degree of lymphadenectomy and plexus resection during pancreatic resection.

The aims of this study were to identify a novel prognostic score for predicting local recurrence in patients with pancreatic cancer using preoperative variables.

Patients and Methods

Study population. Between June 2007 and December 2017, 153 patients who underwent elective pancreatic resection for pancreatic cancer at the Department of Surgery, Jikei University Hospital in Tokyo, Japan, were retrospectively reviewed. Of these, 4 patients were excluded for lack of data or lost follow-up. We performed a retrospective review of a prospectively maintained database of patients. Of the 149 patients, 38 (25%) were without recurrence, 44 developed local recurrence (30.0%) and 67 developed distant metastases (45.0%). Eight patients had both local recurrence and distant metastases, and were classified as a local recurrence group, because the primary endpoint of this study was occurrence of local recurrence. This study was approved by the Ethics Committee of the Jikei University School of Medicine (Approval number: 21-121). All patients were assessed at a preoperative disciplinary meeting and received: i) routine preoperative workups using computed tomography (CT) of the abdomen and chest, ii) endoscopic ultrasound (EUS) and iii) magnetic resonance cholangiopancreatography (MRCP). The preoperative hemogram and chemistry profile including the serum carcinoembryonic antigen (CEA) and the carbohydrate antigen 19-9 (CA19-9) were also measured in each patient. If the tumor was in the pancreatic head, endoscopic retrograde cholangiopancreatography (ERCP) was often performed for cytology or obstructive jaundice.

Perioperative management and follow-up following elective pancreatic resection. All patients underwent pacreaticoduodenectomy (PD) (n=92), distal pancreatectomy (DP) (n=51) or total pancreatectomy (TP) (n=6) with lymphadenectomy, depending on the location of the pancreatic tumor. Twenty-two patients went through portal vein resection and reconstruction. To accomplish radical lymphadenectomy, common hepatic artery (CHA), proper hepatic artery (PHA), left hepatic artery (LHA), right hepatic artery (RHA), common bile duct and portal vein in the hepatoduodenal ligand were skeletonized, and the right-side plexus of the superior mesenteric artery (SMA) was dissected in case of pancreatic head cancer. In case of pancreatic body or tail cancer, CHA and splenic artery (SA) were skeletonized, and the left-side plexus of SMA was dissected. If distant metastases were identified during the operation, pancreatectomy was abandoned (13).

Perioperative use of blood products and dose were determined by the attending surgeons, based on guidelines for the administration of blood products by the Japanese Ministry of Health and Welfare settled in 2005 (14), as well as on intraoperative blood loss, postoperative hemoglobin, serum albumin and prothrombin time. Postoperative patients were followed carefully as outpatients in our department. The tumor recurrence was defined as newly detected local or distant metastatic tumors by ultrasonography, computed tomography, or magnetic resonance image with or without an increase in serum carcinoembryonic antigen (CEA) or carbohydrate antigen 19-9 (CA19-9). In this study, local recurrences were identified as follows: i) perivascular (CHA or SMA) recurrence, ii) pancreaticojejunal anastomotic recurrence, iii) retroperitoneal recurrence and iv) regional lymph node recurrence. Other types of recurrence were defined as distant metastases. One hundred and seven patients (71.8%) received adjuvant chemotherapy following pancreatic resection (either gemcitabine or S-1, for six months), excluding the patients diagnosed as stage 0, poor performance status (PS) or patients who refused therapy.

Identification of a novel score to predict local recurrence of pancreatic cancer. We calculated the distance from CHA or SMA to the edge of the tumor using preoperative CT imaging in all patients. The shortest distance was measured from CHA or SMA to the edge of tumor (CHA: Figure 1A and B, SMA: Figure 1C and 1D). The optimal cut-off level of the distance from CHA or SMA was determined by ROC analysis. The area under ROC (AUC) was measured and was compared to the presence of local recurrence of pancreatic cancer to evaluate the discrimination ability. After deciding the optimal cut-off value in each distance using ROC analysis, novel CHA or SMA scores were constructed to stratify the risk of local recurrence by combining the distance from CHA or SMA with the preoperative serum CA19-9 value. These are described in Table I. Next, to identify risk factors that can predict the local recurrence of pancreatic cancer, we investigated the relationship between clinicopathological variables and the occurrence of local recurrence in all patients with pancreatic cancer (n=149), by using the logistic regression model. The following 17 variables were evaluated: age, gender, type of operation (PD or others), resection of portal vein, duration of operation, intraoperative blood loss, intraoperative RCC and FFP transfusion, differentiation of the tumor, TNM classification based on the Union for International Cancer Control (UICC) 8th edition (3), resection margin, lymphatic invasion (ly), venous invasion (v), distance from CHA or SMA, preoperative CA19-9 values, CHA score and SMA score. Finally, we investigated the relationship between clinicopathological variables and SMA score by univariate analysis. The variables consisted of the following 12 factors: age, gender, type of operation (PD or others), resection of portal vein, duration of operation, intraoperative blood loss, intraoperative RCC and FFP transfusion, differentiation of the tumor, TNM classification based on UICC 8th edition, resection margin, lymphatic invasion (ly) and venous invasion (v).

Effects of the novel scores on local recurrence-free survival and overall survival. We investigated the relationship between clinicopathological variables, local recurrence-free survival (LFS) and overall survival (OS) in patients with pancreatic cancer following elective pancreatic resection by univariate and multivariate analyses. Both the local recurrence group (n=44) and recurrence-free group (n=38) were used for this analysis. The following 14 variables were evaluated: age, gender, type of operation (PD or others), resection of the portal vein, duration of operation, intraoperative blood loss, intraoperative transfusion of RCC or FFP, differentiation of the tumor, TNM classification based on UICC 8th edition, resected margin, lymphatic invasion (ly), venous invasion (v), CHA score and SMA score.

Statistical analysis. Data were expressed as a median with an interquartile range (IQR) or ratio. Univariate analysis was performed using the Mann-Whitney's *U*-test, Kruskal-Wallis test, or Chi-square test, as appropriate. A logistic regression model with a backward elimination stepwise approach was used for the univariate

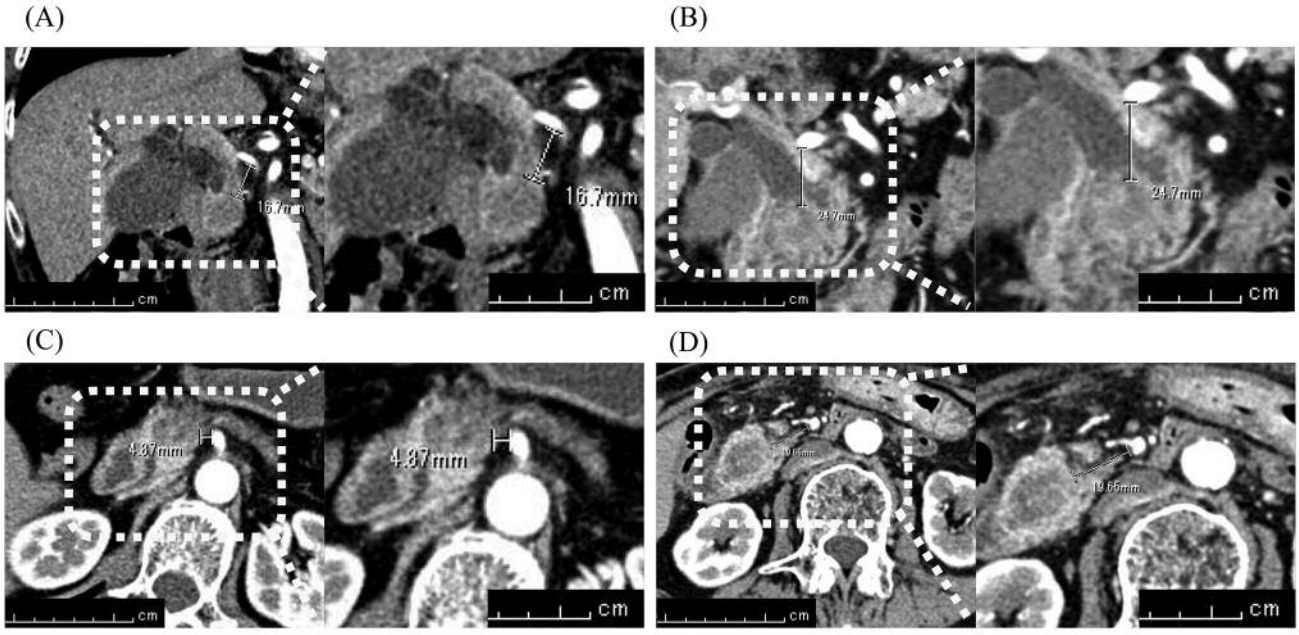

Figure 1. *The shortest distance from CHA to the edge of the tumor (A: under 20.55 mm, B: over 20.55 mm). The shortest distance from SMA to the edge of the tumor (C: under 10.9 mm, D: over 10.9 mm). Scale bars: Centimeters are shown in each image.*

and multivariate analyses of local recurrence. Both univariate and multivariate analyses of LFS or OS were performed using the Cox proportional regression model with a backward elimination stepwise approach. These analyses were conducted using IBM SPSS statistics version 24 (IBM Japan, Tokyo Japan). All *p*-values were considered statistically significant when the association probability was less than 0.05.

Results

Patient characteristics. All patients' characteristics are outlined in Table I as a median, interquartile range, or ratio. The median DFS and OS of the entire study population were 1.03 years (0.86 to 1.21 years) and 2.48 years (1.60 to 3.35 years), respectively. In the current study, 5-year DFS and OS rate in patients with pancreatic cancer following pancreatic resection were 13.8% and 32.6%, respectively. For the CHA or SMA distance from the edge of the tumor, based on the ROC analysis of the local recurrence, the optimal cut-off level of CHA distance was set as 20.55 mm with the AUC of 0.617 [95% confidence interval (CI)=0.519-0.715, p=0.025). For SMA distance, the cut-off value was 10.9 mm with the AUC of 0.670 (95%CI=0.578-0.761, p=0.001) (Figure 2A). The AUC value of SMA distance was greater than that of CHA distance. The relationship between the distance from CHA or SMA and the type of recurrence is shown in Figure 2B and C. SMA distance in the local recurrence group was significantly shorter compared to the two other groups (p=0.004), while the CHA distance was comparable in each group.

Table I. *The novel scores combining distance from main abdominal artery and pancreatic tumor with preoperative serum CA19-9 values.*

Index		
CHA score	Distance from CHA (mm)	Preoperative serum CA19-9 (Uml^{-1})
0	≥20.55 mm	≤200 Uml^{-1}
1	<20.55 mm	≤200 Uml^{-1}
1	≥20.55 mm	>200 Uml^{-1}
2	<20.55 mm	>200 Uml^{-1}
SMA score	Distance from SMA (mm)	Preoperative serum CA19-9 (Uml^{-1})
0	≥10.9 mm	≤200 Uml^{-1}
1	<10.9 mm	≤200 Uml^{-1}
1	≥10.9 mm	>200 Uml^{-1}
2	<10.9 mm	>200 Uml^{-1}

CHA: Common hepatic artery; SMA: superior mesenteric artery; CA19-9: carbohydrate antigen 19-9.

Univariate and multivariate analyses of clinicopathological variables in relation to the occurrence of local recurrence following pancreatic resection. Novel CHA or SMA scores using the optimal cut-off values were constructed, as described in Table II. Table III lists the relationship between the clinical variables and the occurrence of local recurrence following pancreatic resection using a logistic progression analysis. In the univariate analysis, factors that positively associated with the occurrence of local recurrence consisted of: i) lymphatic

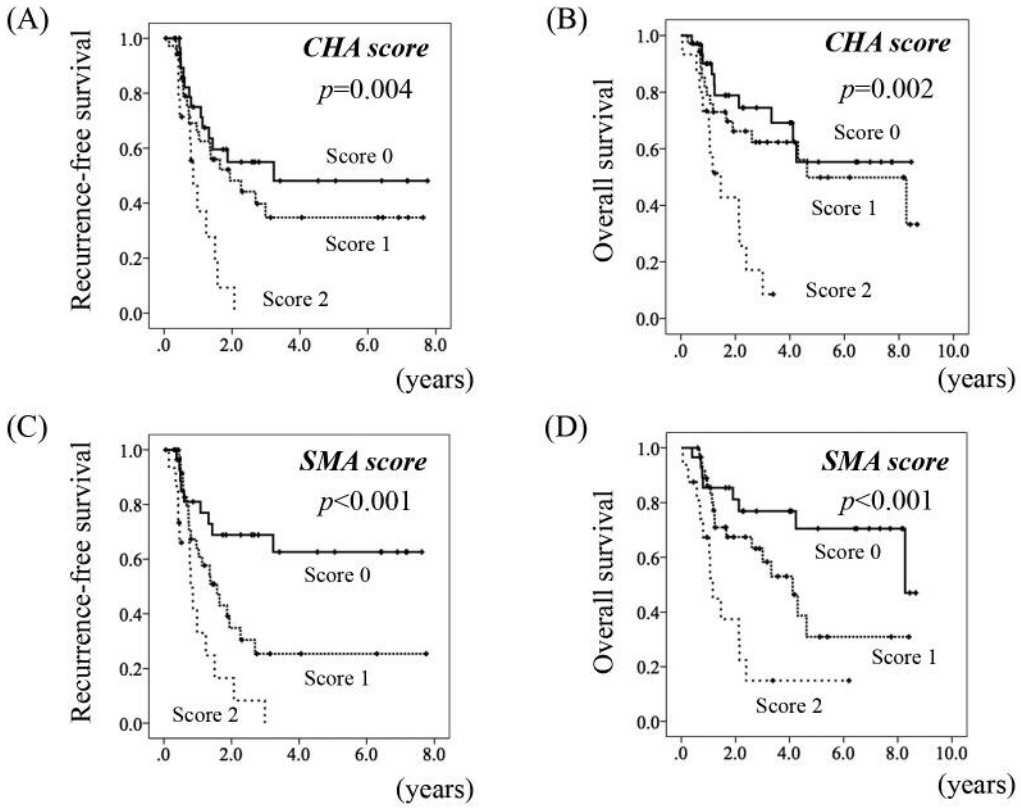

Figure 2. *(A) ROC curve of distance from CHA or SMA in relation to the local recurrence after pancreatic resection. The optimal cut-off level for the distance from CHA was 20.55 mm, with an AUC of 0.617 (95%CI=0.519-0.715, p=0.025). On the other hand, the distance from SMA was 10.9 mm, with the AUC of 0.670 (95%CI=0.578-0.761, p=0.001). Relationship between distance from CHA (B) or SMA (C) and the type of recurrence.*

invasion (p=0.003), ii) distance from CHA (p=0.030), iii) distance from SMA (p=0.017), iv) CHA score (p=0.042) and v) SMA score (p=0.004). In the multivariate analysis, lymphatic invasion (p=0.002), preoperative elevated serum CA19-9 ≥200 Uml^{-1} (p=0.007) and SMA score (p=0.004) were independent predictors of local recurrence, while SMA distance alone was not an independent predictor of local recurrence. The hazard ratio of SMA score 2 was 29.28, which was greater than that of preoperative elevated serum CA19-9 (hazard ratio=13.32) using multivariate analysis. These results showed that a novel SMA score combining SMA distance and preoperative serum CA19-9 values was superior to SMA distance or preoperative serum CA19-9 values alone for predicting the occurrence of local recurrence.

Table IV lists the relationship between the clinico-pathological variables and the SMA score. In the univariate analysis, factors that positively correlated with SMA score 2 consisted of duration of operation (p=0.007), intraoperative RCC and FFP transfusion (p=0.016).

Univariate and multivariate analyses of clinicopathological variables in relation to local recurrence-free survival (LFS), as well as to overall survival in both local recurrence and recurrence-free groups, following elective pancreatic resection. Table V lists the relationship between the clinical variables and LFS as well as OS in pancreatic cancer patients with pancreatic cancer after pancreatic resection. The samples were separated in a local recurrence group and a recurrence-free group in this analysis. In the univariate analysis, factors positively associated with local recurrence DFS were: i) resection of portal vein (p=0.008), ii) advanced TNM classification based on UICC 8th edition (p=0.008), iii) lymphatic invasion (p<0.001), and iv) CHA score (p=0.004) (Figure 3A) and SMA score (p<0.001) (Figure 3C). In the multivariate analysis, intraoperative blood loss ≥1,000 ml (p=0.022), lymphatic invasion (p=0.001) and SMA score (p<0.001) were independent factors associated with local recurrence. Using a univariate analysis, reconstruction of portal vein (p=0.011), differentiation of the tumor (modulate and poor) (p=0.046), lymphatic invasion (p=0.025), CHA score (p=0.002) (Figure 3B) and SMA score (p<0.001) (Figure 3D) were positively associated with OS. In the multivariate analysis, intraoperative blood loss ≥1,000 ml (p=0.045), intraoperative RCC or FFP transfusion (p=0.026) and SMA score (p<0.001) were independent factors of OS.

Table II. *Patient characteristics*.

Characteristic	Median or rate	IQR
Age		
years	69.0	62-75
Gender		
Male/Female	87/62	
Disease-free survival		
years	1.03*	0.86-1.21**
Overall survival		
years	2.48*	1.60-3.35**
Type of recurrence		
No recurrence/Local recurrence/		
Distant Metastasis	38/44/67	
Type of operation		
PD/non-PD	92 /57	
Resection of portal vein		
Present/Absent	127/22	
Duration of operation		
min	504.0	428-590.5
Intraoperative blood loss		
ml	680.0	380-1,265
Intraoperative transfusion of RCC or FFP		
Present/Absent	31/118	
Differentiation of the tumor		
Well/Others	47/102	
TNM classification based on UICC		
I/II, III or IV	46/103	
Resection margin		
R0/Others	111/38	
Lymphatic invasion (ly)		
ly0/Others	52/97	
Venous invasion (v)		
v0/Others	42/107	
Preoperative serum CA19-9		
Uml^{-1}	93.0	28-262
Distance from CHA		
mm	22.4	13.1-34
Distance from SMA		
mm	11.2	7.9-20.2

*Median survival time. **95%CI. IQR: Interquartile range; CA19-9: carbohydrate antigen 19-9; UICC: the Union for International Cancer Control.

Discussion

Our novel SMA score combining distance from SMA and preoperative serum CA19-9 values is simple and seems to be useful for predicting local recurrence of pancreatic cancer. In the literature, independent predictors of local recurrence following pancreatic resection included male gender, perineural invasion, resected margin and adjuvant chemotherapy (10, 15). All factors, except for gender, were postoperative factors, and were, therefore, not known before resection. To our knowledge, the current study is the first report that identifies a predictor of local recurrence using preoperative variables in patients with pancreatic cancer.

To overcome the aggressive progression of pancreatic cancer, many surgeons have tried more aggressive and extended pancreatic resections, including extensive lymph node dissection, excision of the nerve plexus and combined vascular resection (16, 17). The approaches have been supported by some retrospective reports, which showed that negative margins are associated with longer survival in patients with pancreatic cancer (18, 19). Some other studies have shown that extended pancreatic resection fails to demonstrate an improved tumor-related survival in all RCTs and tends to increase postoperative morbidity and mortality, as well as to worsen the quality of patients' life (QOL) (20-23). It appears that extended pancreatic resection in patients with pancreatic cancer is not a standard treatment worldwide. On the other hand, besides lymphadenectomy, dissection of the nerve plexus has been considered important in increasing the R0 resection and reducing the local recurrence (17, 24, 25). Kimura *et al*., have reported that both extra-pancreatic nerve plexus and perineural invasion were poor prognostic factors in patients with pancreatic cancer (24). However, total circumferential dissection of the nerve plexus around the celiac axis or the SMA induces severe and intractable diarrhea, malnutrition and lower QOL following pancreatic resection (23, 24). To minimize these adverse effects of total circumferential nerve plexus dissection, right-sided 180-degree dissection of the nerve plexus for pancreatic head cancer and left-sided for pancreatic body or tail cancer has been widely practiced in Japan (24).

One of the reasons why extended pancreatic resection has not improve prognosis and tends to increase morbidity, is that almost all patients with resectable pancreatic cancer are included in these trials. Many patients with low risk of local recurrence do not undergo extended lymph nodes and nerve plexus dissection. To minimize the adverse effects and maximize the oncological effects using extended pancreatic resection, a preoperatively risk stratification of local recurrence in patients with pancreatic cancer, using preoperative variables, is important to determine the degree of invasiveness of pancreatic resection preoperatively. To predict the time to recurrence of pancreatic cancer is also important for postoperative management and treatment. Groot *et al*. has already reported the relationship between time to recurrence and location of recurrence (10), of which the shortest time to recurrence after pancreatic resection was liver (median; 6.9 months) and longest was local recurrence (median=9.5 months). Our novel SMA score was not positively associated with the time to recurrence (data was not shown).

Recently, National Comprehensive Cancer Network (NCCN) provided clinical guidelines for the classification of pancreatic cancer into i) resectable, ii) borderline resectable (BRPC) and iii) unresectable pancreatic cancer (26). BRPC with arterial involvement (BR-A) is associated with poor prognosis, as compared to BRPC with portal or superior mesenteric vein involvement (BR-PV) (27, 28). Resection of BRPC without any

Table III. *Univariate and multivariate analyses of clinicopathological variables in relation to local recurrence including in patients with pancreatic cancer.*

	Univariate		Multivariate	
Factor	Hazard ratio (95%CI)	*p*-Value	Hazard ratio (95%CI)	*p*-Value
Age				
years	1.026 (0.989-1.066)	0.173	1.040 (0.911-1.091)	0.111
Gender				
Male	1 (reference)	0.401	1 (reference)	0.082
Female	0.733 (0.355-1.514)		0.454 (0.187-1.104)	
Type of operation				
PD	1 (reference)	0.297		NS
Others	0.673 (0.320-1.416)			
Resection of portal vein				
Absent	1 (reference)	0.448		NS
Present	1.444 (0.558-3.737)			
Duration of operation				
min	1.002 (1.000-1.005)	0.085		NS
Intraoperative Blood loss				
ml	1.000 (1.000-1.001)	0.212		NS
Intraoperative transfusion of RCC or FFP				
Absent	1 (reference)	0.211		NS
Present	1.697 (0.741-3.888)			
Differentiation of the tumor				
Well	1 (reference)	0.665		NS
Others	1.180 (0.558-2.496)			
TNM classification based on UICC classification				
Stage I	1 (reference)	0.820	1 (reference)	0.137
Stage II, III or IV	1.093 (0.507-2.355)		2.165 (0.782-5.998)	
Resected margin				
R0	1 (reference)	2.519	1 (reference)	0.071
R1 or R2	2.519 (1.163-5.454)		2.375 (0.930-6.067)	
Lymphatic invasion (ly)				
Ly 0	1 (reference)	0.003	1 (reference)	0.002
Ly 1, 2 and 3	3.964 (1.619-9.707)		5.386 (1.889-15.356)	
Venous invasion (v)				
v0	1 (reference)	0.178		NS
v1, 2 and 3	1.782 (0.769-4.131)			
Distance from CHA				
mm	0.974 (0.951-0.997)	0.030		NS
Distance from SMA				
mm	0.952 (0.915-0.991)	0.017		NS
Preoperative serum CA19-9				
<200Uml^{-1}	1 (reference)	0.484	1 (reference)	0.007
≥200Uml^{-1}	1.304 (0.621-2.737)		13.32 (2.207-87.59)	
CHA score				
0	1 (reference)	0.042	1 (reference)	0.089
1	1.131 (0.501-2.554)		0.998 (0.355-2.808)	
2	3.441 (1.230-9.626)		6.122 (0.883-42.436)	
SMA score				
0	1 (reference)	0.004	1 (reference)	0.004
1	2.109 (0.880-5.055)		3.369 (1.165-9.742)	
2	6.356 (2.131-18.95)		29.48 (3.90-222.9)	

PD: Pancreaticoduodenectomy; RCC: red blood cell concentrate; FFP: fresh frozen plasma; CHA: common hepatic artery; SMA: superior mesenteric artery; UICC: Union for International Cancer Control; CA19-9: carbohydrate antigen 19-9.

neoadjuvant therapy is at high risk for margin-positive resection and postoperative local recurrence (29). Other reports agree on the effectiveness of neoadjuvant chemoradiotherapy for BRPC or stage III pancreatic cancer (30, 31). Hackert *et al*. has also reported that the resection rate of patients with locally advanced pancreatic cancer following FOLFIRINOX was 61%, compared to 41% following gemcitabine with radiotherapy (32). Therefore, neoadjuvant therapy for patients with BRPC may

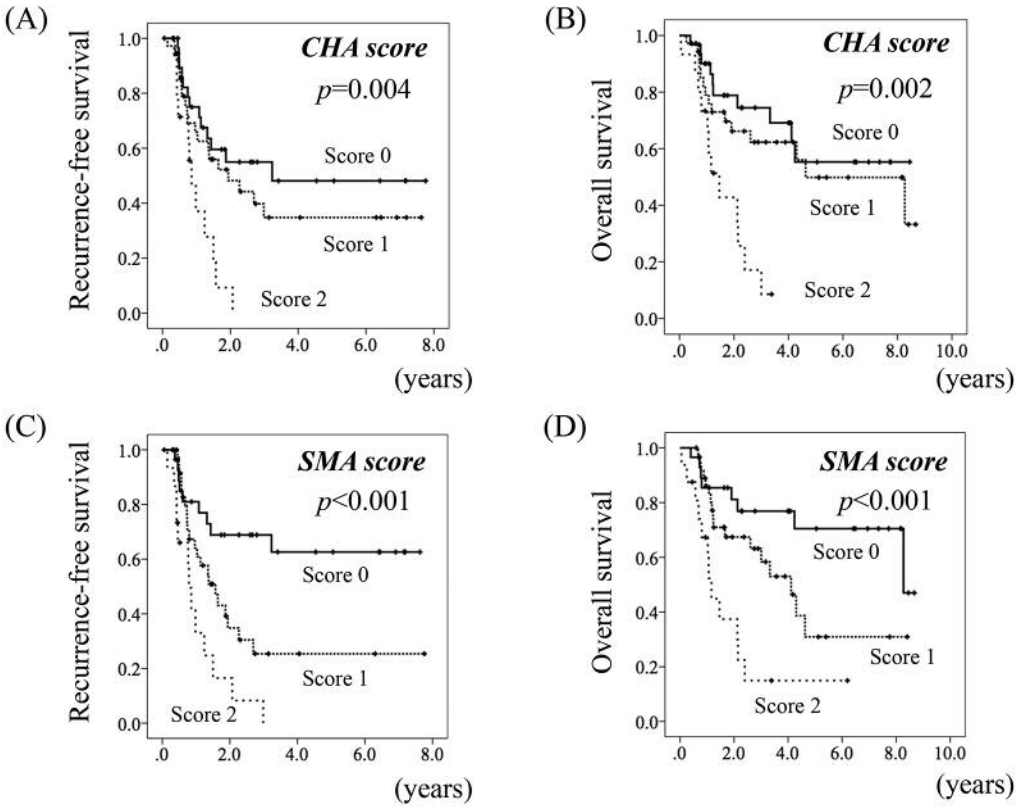

Figure 3. *Kaplan-Meier curves of local recurrence-free survival (A and C, respectively) and overall survival (B and D, respectively) in relation to CHA score and SMA score, respectively. Patients in this analysis were classified as recurrence-free and local recurrence group. Both CHA and SMA scores were negatively associated with local recurrence-free survival (p=0.004, p<0.001) and overall survival (p=0.002, p<0.001), respectively.*

Table IV. *Univariate analysis of patients' characteristics in relation to SMA score in patients with pancreatic cancer.*

Factor	SMA score (n=149)			*p*-Value
	0 (N=53)	1 (N=73)	2 (N=23)	
Age (years)	69 (61.5-76.0)*	68.0 (61.5-74.0)*	72.0 (62.0-77.0)*	0.313
Gender (male/female)	30/23	45/28	12/11	0.686
Type of operation (PD/non-PD)	27/26	47/26	18/5	0.064
Reconstruction of portal vein (present/absent)	49/4	61/12	17/6	0.095
Duration of operation (min)	490.0 (399.5-547.0)*	508.0 (425.0-598.5)*	540.0 (489.-0-641.0)*	0.007
Intraoperative blood loss (ml)	553.0 (300.0-1,170.0)*	690.0 (390.0-1,215.0)*	1,040.0 (600.0-1,810.0)*	0.067
Intraoperative transfusion of RCC or FFP (present/absent)	40/13	64/9	14/9	0.016
Differentiation of the tumor (well/others)	23/30	19/54	5/18	0.064
TNM classification based on UICC (I/II, III or IV)	21/32	22/51	3/20	0.069
Resected margin (R0/R1 or R2)	42/11	55/18	14/9	0.234
Lymphatic invasion (ly) (ly0/ly1, 2 or 3)	22/31	25/48	5/18	0.248
Venous invasion (v) (v0/v1, 2 or 3)	18/35	21/52	3/20	0.175

PD: Pancreaticoduodenectomy; RCC: red blood cell concentrate; FFP: fresh frozen plasma; UICC: Union for International Cancer Control; *Median (IQR: interquartile range).

become the standard therapeutic approach. In this regard, our study showed that neoadjuvant chemotherapy or radiochemotherapy in patients with pancreatic cancer should be supplemented with SMA score 2 prior to extended pancreatic resection to reduce the local recurrence, regardless of the type of pancreatic cancer classified using the NCCN guidelines (26).

There were several limitations to the current study. The study was retrospective, included a small sample size, and was

Table V. *Univariate and multivariate analyses of clinicopathological variables in relation to LFS and OS in patients with pancreatic cancer (recurrence-free group and local recurrence group).*

		LFS				OS			
		Univariate		Multivariate		Univariate		Multivariate	
Factor	N	Hazard ratio (95%CI)	*p*-Value	Hazard ratio (95%CI)	*p*-Value	Hazard ratio (95%CI)	*p*-Value	Hazard ratio (95%CI)	*p*-Value
Age									
<60 years	16	1 (reference)	0.454	Did not remain in this model		1 (reference)	0323	Did not remain in this model	
≥60 years	67	0.746 (0.346-1.607)				0.672 (0.306-1.477)			
Gender									
Male	46	1 (reference)	0.117	Did not remain in this model		1 (reference)	0.055	1 (reference)	0.057
Female	36	0.611 (0.330-1.132)				0.500 (0.246-1.016)		0.495 (0.240-1.021)	
Type of operation									
PD	49	1 (reference)	0.067	Did not remain in this model		1 (reference)	0.197	Did not remain in this model	
Others	33	0.552 (0.292-1.043)				0.641 (0.326-1.260)			
Reconstruction of portal vein									
Absent	71	1 (reference)	0.008	Did not remain in this model		1 (reference)	0.011	Did not remain in this model	
Present	11	2.933 (1.322-6.508)				3.080 (1.290-7.355)			
Duration of operation									
<500 min	40	1 (reference)	0.165	Did not remain in this model		1 (reference)	0.516	Did not remain in this model	
≥500 min	42	1.532 (0.839-2.796)				1.240 (0.647-2.377)			
Intraoperative blood loss									
<1,000 ml	54	1 (reference)	0.503	1 (reference)	0.022	1 (reference)	0.495	1 (reference)	0.045
≥1,000 ml	28	1.228 (0.673-2.242)		2.304 (1.125-4.719)		1.257 (0.652-2.426)		2.189 (1.106-4.716)	
Intraoperative transfusion of RCC or FFP									
Absent	63	1 (reference)	0.407	1 (reference)	0.100	1 (reference)	0.174	1 (reference)	0.026
Present	19	1.326 (0.681-2.580)		1.879 (0.887-3.980)		1.627 (0.807-3.282)		2.465 (1.116-5.443)	
Differentiation of the tumor									
Well	34	1 (reference)	0.059	Did not remain in this model		1 (reference)	0.046	1 (reference)	0.097
Others	48	1.838 (0.976-3.463)				2.081 (1.013-4.279)		1.926 (0.888-4.178)	
TNM classification based on UICC classification									
Stage I	31	1 (reference)	0.028	Did not remain in this model		1 (reference)	0.055	Did not remain in this model	
Stage II, III or IV	51	2.078 (1.083-3.987)				2.039 (0.984-4.226)			
Resection margin									
R0	58	1 (reference)	0.056	Did not remain in this model		1 (reference)	0.081	Did not remain in this model	
R1 or R2	24	1.813 (0.984-3.342)				1.817 (0.929-3.553)			
Lymphatic invasion (ly)									
ly 0	30	1 (reference)	<0.001	1 (reference)	0.001	1 (reference)	0.025	Did not remain in this model	
ly 1, 2 and 3	52	4.741 (2.097-10.718)		4.645 (1.956-11.033)		2.385 (1.118-5.088)			
Venous invasion (v)									
v0	25	1 (reference)	0.065	Did not remain in this model		1 (reference)	0.606	Did not remain in this model	
v1, 2 and 3	57	1.994 (0.957-4.155)				1.211 (0.585-2.506)			

Table V. *Continued*

Table V. *Continued*

CHA score									
0	31	1 (reference)	0.004	Did not remain in this model		1 (reference)	0.002	Did not remain in this model	
1	36	1.400 (0.691-2.836)				1.352 (0.606-3.019)			
2	15	3.710 (1.652-8.332)				4.499 (1.890-10.706)			
SMA score									
0	29	1 (reference)	<0.001	1 (reference)	<0.001	1 (reference)	<0.001	1 (reference)	<0.001
1	37	2.645 (1.203-5.819)		3.666 (1.599-8.404)		2.194 (0.935-5.147)		2.432 (0.973-6.081)	
2	16	6.172 (2.572-14.811)		5.903 (2.286-15.240)		5.967 (2.367-15.048)		7.122 (2.513-20.187)	

The patients of this analysis included in recurrence-free group and local recurrence group. A backward elimination with a threshold of p=0.05 was used to select variables for the final model of the multivariate analysis. PD: Pancreaticoduodenectomy; RCC: red blood cell concentrate; FFP: fresh frozen plasma; CHA: common hepatic artery; SMA: superior mesenteric artery; UICC: Union for International Cancer Control; CA19-9: carbohydrate antigen 19-9; LFS: local recurrence-free survival; OS: overall survival.

a single-institutional design. To prove our hypothesis it seems important to perform a prospective study using the SMA score, in order to determine the invasiveness of pancreatic resection in patients with pancreatic cancer. Risk stratification using the SMA score can be performed easily before surgery, using CT imaging and tumor marker, which are considered as standards in preoperative management. This SMA score could be helpful in clinical decisions, including the administration of neo-adjuvant chemotherapy and surgical treatment. The novel SMA score combining the distance between SMA and tumor with the preoperative serum CA19-9 value may be an independent predictor of local recurrence and prognosis in patients with pancreatic cancer and allow the preoperative determination of the extent of pancreatic resection.

Conflicts of Interest

All authors declare no conflicts of interests.

Authors' Contributions

F.S. and Y.F. designed the study, collected and analyzed the data as well as wrote the manuscript. R.H., K.H., T.S. and H.S. collected the data and helped with the analysis. Y.K. reviewed the manuscript.

Ethics Approval

This study was approved by the Ethics Committee of the Jikei University School of Medicine (21-121).

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