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ORIGINAL ARTICLE

Predictive factors of actual 5-y recurrence-free survival after upfront surgery for resectable pancreatic cancer

Exploration of patients who did not require neoadjuvant treatment

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Abstract

Aim: The present study investigated the prognostic factors associated with actual 5-y recurrence-free survival (RFS) after upfront surgery for resectable pancreatic cancer (R-PC) in patients who were deemed not to require neoadjuvant treatment.

Methods: Between 2007 and 2016, 316 patients who underwent pancreatectomy for radiologically R-PC were retrospectively reviewed to evaluate the predictors of actual 5-y RFS. Predictors were identified using logistic regression analysis of preoperative evaluable factors. The cutoff values for continuous variables were determined based on a minimum *p*-value approach (model 1) or the value that maximized the rate of 5-y RFS survivors (model 2).

Results: Fifty-one patients (16.1%) achieved a 5-y RFS. A tumor size ≤23 mm, the absence of serosal invasion on computed tomography (CT), and Neutrophil-to-Lymphocyte Ratio <1.0, were significantly associated with the 5-y RFS in model 1. A Prognostic Nutritional Index ≥58 and the absence of serosal invasion and extra-pancreatic nerve plexus invasion on CT were significantly associated with 5-y RFS in model 2. Only six (11.8%, model 1) and four (7.8%, model 2) patients had all three prognostic factors, and their 5-y RFS rates were 83.3% and 100%, respectively.

Conclusions: A modest number of patients who underwent upfront surgery achieved 5-y RFS, but only ~10% of them could be identified preoperatively. Based on these results, almost all R-PC patients are forced to undergo neoadjuvant treatment in daily practice.

KEYWORDS
neoadjuvant treatment, pancreatic cancer, recurrence-free survival

1 | INTRODUCTION

Pancreatic cancer (PC) is one of the most aggressive cancers worldwide. Surgery is the most effective treatment and offers the only chance for a cure for PC; however, recurrence rates are high, even after curative resection. Adjuvant therapy after surgery for PC has long been proven to prolong the prognosis.[1,2] In recent years, interest in PC treatment has shifted to preoperative treatment. One report noted that neoadjuvant treatment (NAT) significantly prolonged the disease-free survival of patients with PC.[3] The National Comprehensive Cancer Network (NCCN) presents upfront surgery and NAT as treatment options for resectable PC (R-PC).[4] The current NCCN guidelines show that the characteristics of high-risk cases include large primary tumors, elevated carbohydrate antigen 19-9 (CA 19-9) levels, enlarged regional lymph nodes, excessive weight loss, and extreme pain.[4] In these cases, NAT should be considered, but is not recommended in all cases. In Japan, NAT has become the standard treatment for R-PC in daily practice. However, some patients who underwent upfront surgery achieved long-term survival without any signs of recurrence.[5,6] Therefore, the necessity of NAT for all patients with R-PC remains unclear. If preoperative predictors of long-term recurrence-free survival (RFS) after upfront surgery can be identified, patients with these predictors might be able to avoid NAT.

The present study aimed to investigate the details of patients with actual 5-y RFS after upfront surgery for R-PC and objective prognostic factors, focusing on preoperative patient factors and computed tomography (CT) findings.

2 | MATERIALS AND METHODS

This retrospective review was conducted using a prospectively maintained PC database at the Shizuoka Cancer Center. Patients who underwent upfront surgery for radiological R-PC between 2007 and 2016 were studied. Due to the nature of the analysis method, which uses preoperative factors, not only patients with curative resection, but also patients with noncurative resection, who were identified intraoperatively and postoperatively, were included. We investigated whether 5-y RFS could be predicted using preoperative factors in these patients. The relationship between nutritional predictors and completion of adjuvant chemotherapy was also evaluated.

The present study was approved by the Institutional Review Board of Shizuoka Cancer Center (J2020-84-2021-1-3). This study was conducted in accordance with the STROBE guidelines.[7]

2.1 | Preoperative factors

Preoperative findings included the following parameters: age, sex, serum albumin levels, CA 19-9 values after biliary drainage in patients with jaundice, modified Glasgow Prognostic Score (mGPS), Neutrophil-to-Lymphocyte Ratio (NLR), Prognostic Nutritional Index (PNI), and radiological findings on multidetector-row CT. NLR, PNI, and mGPS were calculated as previously reported.[8–10] All preoperative values were obtained within 1 mo before surgery.

2.2 | Radiological evaluations

Preoperative tumor assessment was performed with CT using a standard protocol optimized for imaging pancreatic tumors. CT was performed in the early arterial phase (20 s), late arterial phase (40 s), portal venous phase (70 s), and delayed phase (120 s). The raw data were reconstructed at 2-mm thickness for transverse CT. All images of each eligible patient were reviewed by an experienced radiologist (T.A.) and another radiologist, who was blinded to the clinical course of the patients. Resectability was defined according to the NCCN guidelines.[4] Regarding radiological findings, the presence of lymph nodes larger than 10 mm in diameter was considered a potential sign of metastasis.[11] Vascular invasion was defined as the absence of fat tissue between the tumor and major vessels (splenic artery and portal vein system including portal vein or superior mesenteric vein and splenic vein). Anterior serosal and retroperitoneal tissue invasion was defined as tumors extending to the surface of the pancreas and peripancreatic fat tissue, respectively. Extrapancreatic nerve plexus invasion was defined as a mass and strand pattern or coarse reticular pattern with continuity from the main tumor.[12]

2.3 | Surgery and adjuvant therapy

In general, all patients underwent pancreatectomy with regional lymph node dissection without NAT. Adjuvant therapy was performed as a standard strategy after resection in patients who could tolerate it and was started within 2 mo after the operation, unless contraindicated by the patient's condition or for some other reason. Generally, S-1 is administered; in cases where it is not tolerated, gemcitabine is administered. The administration of S-1 (80 mg/m^2/d for 28 consecutive d followed by a 14-d rest period for four cycles) or gemcitabine (1000 mg/m^2 of gemcitabine intravenously on days 1, 8, and 15, followed by a 1-week rest period for six cycles) was defined as the completion of adjuvant therapy. Patients with M1 disease were given adjuvant therapy whenever possible.

2.4 | Follow-up and definition of recurrence

Follow-up at 3-mo intervals comprised physical examination, laboratory tests, measurement of tumor biomarkers, and CT for the first 3 y. Three years after surgery, if patients had no sign of recurrence, they were followed-up at 6-mo intervals. The events affecting survival were death and recurrence, including local recurrence and distant metastasis. Recurrence was defined on the basis of radiological or biopsy-proven evidence. Agreement was obtained from the institutional cancer board of hepato-biliary-pancreatic

malignancy. Patients with pathological M1 disease who underwent pancreatectomy were considered to have recurrent disease on day 0. The recurrence pattern was assessed by the initial site, including duplications, categorized into "lymph node," "local region," "liver," "lung," "peritoneum," "remnant pancreas," and "other distant." "Lymph node" recurrence was defined as metastasis to the intraabdominal lymph nodes, including the para-aortic lymph nodes. "Local region" recurrence was defined as a local ill-defined mass on CT with positive findings on positron emission tomography or elevated tumor marker levels.

2.5 | Statistical analyses

All continuous variables are expressed as medians with ranges and compared using the Mann–Whitney *U* test. Chi-square test or Fisher's exact test was used to compare categorical variables where appropriate. The cutoff values for continuous variables were determined using two analytical models: the value that minimized the *p*-value (model 1),[13] which used a purely statistical measure, and the value that maximized the rate of 5-y RFS (model 2), which used a purely clinical measure. Multivariate logistic regression analysis was performed using variables shown to be statistically significant in the univariate analysis. RFS and overall survival (OS) rates were calculated using the Kaplan–Meier method, and differences were evaluated using a log-rank test. Statistical significance was defined as a two-sided *p*-value of <0.05. The association between CT and pathological findings or recurrence sites was also evaluated. All statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

3 | RESULTS

A total of 316 patients were included in the study, excluding 93 ineligible patients (Figure 1). Of these, 242 patients underwent curative resection, and 74 underwent noncurative resection: positive surgical margin in 26, distant lymph node metastases in 26, peritoneal dissemination in two, and positive peritoneal lavage cytology in 20 patients. In this cohort, 51 (16.1%) patients survived for 5 y without any signs of recurrence. Table 1 presents a comparison between patients with and without recurrence. Higher CA 19-9 levels, lower serum albumin levels, lower PNI, larger tumor size, pathologically more advanced disease, and the absence or interruption of adjuvant chemotherapy were significantly correlated with recurrence within 5 y after surgery.

The cutoff value for each model was calculated as follows. In model 1, the cutoff values were 120 units/mL for CA 19-9, 23 mm for tumor size, 1.0 for NLR, and 45 for PNI. In model 2, the cutoff values were 120 units/mL for CA 19-9, 12 mm for tumor size, 1.0 for NLR, and 58 for PNI. Therefore, our further analyses were based on these cutoff values.

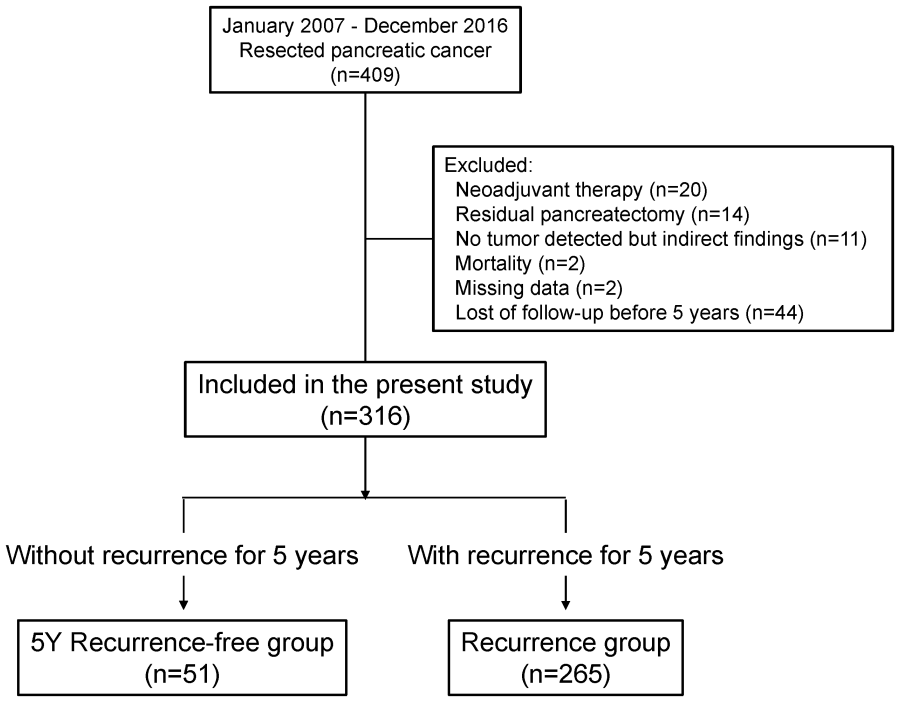

FIGURE 1 Inclusion criteria. A total of 409 patients with radiological resectable pancreatic cancer underwent pancreatectomy between January 2007 and December 2016. The patients who received neoadjuvant therapy, patients who underwent residual pancreatectomy, patients who had no tumor detected on preoperative computed tomography, patients who died in the perioperative period, patients who had insufficient data, and patients who were lost to follow-up <5 y after surgery were excluded. Consequently, 316 patients were included in this study.

TABLE 1 Clinicopathological characteristics in patients with radiological resectable pancreatic cancer.

	5-Year recurrence-free	Recurrence	
	N = 51	*N* = 265	*p* Value
Clinical variables			
Age, y[a]	66 (43–88)	68 (38–87)	0.295
Sex, male	26 (51)	156 (59)	0.297
CA 19-9, U/mL[a]	58 (2–1152)	123 (2–17 324)	0.025
Albumin level (g/dL)[a]	4.2 (2.8–5.1)	4.0 (2.5–5.1)	0.019
mGPS			
0	41 (80)	187 (71)	0.152
1/2	10 (20)	78 (29)	
NLR[a]	2.0 (0.5–5.2)	2.3 (0.6–12.6)	0.145
PNI[a]	50 (28–61)	48 (30–63)	0.001
Tumor location			
Head	34 (67)	210 (79)	0.075
Body and tail	17 (33)	55 (21)	
Tumor size, mm[a]	20 (10–50)	25 (5–90)	<0.001
Surgical procedure			
PD/TP	35 (69)	214 (81)	0.052
DP	16 (31)	51 (19)	
Adjuvant chemotherapy			
Complete	38 (75)	150 (57)	0.017
Interruption/none	13 (25)	115 (43)	
Pathological findings			
Histology			
Well differentiated type	15 (29)	64 (24)	0.427
Mod/por/others	36 (71)	201 (76)	
TNM classification (UICC8th)			
pT category			
pT1	6 (12)	12 (5)	0.051
pT2/T3	45 (88)	253 (95)	
pN category			
pN0	33 (65)	43 (16)	<0.001
pN1/N2	18 (35)	222 (84)	
pM category			
pM0	51 (100)	217 (82)	<0.001
pM1	0 (0)	48 (18)	
Surgical margin positive	4 (8)	22 (8)	1

Note: Values in parentheses are percentages unless otherwise indicated.

Abbreviations: CA 19-9, carbohydrate antigen 19-9; DP, distal pancreatectomy; mGPS, modified Glasgow Prognostic Score; Mod, moderately differentiated type; NLR, Neutrophil-to-Lymphocyte Ratio; PD, pancreaticoduodenectomy; PNI, Prognostic Nutritional Index; Por, poorly differentiated type; TP, total pancreatectomy.

[a]Median (range).

The predictors of 5-y RFS in model 1 are shown in Table 2. A tumor size ≤23 mm, the absence of serosal invasion on CT, and NLR <1.0 were significantly associated with 5-y RFS. RFS and OS according to the number of predictors are shown in Figure 2. The 5-y RFS rates of patients with three ($n = 6$), two ($n = 75$), one ($n = 107$), and zero ($n = 128$) predictors were 83.3%, 29.3%, 12.1%, and 8.6%, respectively (three factors vs others, $p = 0.006$). The OS rates of patients in the four categories were 100%, 44.1%, 29.7%, and 18.1%,

TABLE 2 Predictors of the 5-y recurrence-free survival according to preoperative findings in model 1.

		Univariate analysis		Multivariate analysis	
	n	5-Year recurrence-free	*p* Value	Odds ratio (95% CI)	*p* Value
CA 19-9 (units/mL)					
<120	166	36 (22)	0.005	–	–
≥120	150	15 (9)			
mGPS					
0	228	41 (18)	0.152		
1 or 2	88	10 (11)			
NLR					
<1.0	12	6 (50)	0.006	3.75 (1.02–13.70)	0.046
≥1.0	304	45 (15)		1	
PNI					
≥45	228	46 (20)	0.001	–	–
<45	88	5 (6)			
Tumor size (mm)					
≤23	139	36 (26)	<0.001	2.28 (1.10–4.71)	0.026
>23	177	15 (9)		1	
Tumor location					
Head	244	34 (14)	0.075		
Body and tail	72	17 (24)			
Bile duct invasion					
Absent	130	30 (23)	0.005	–	–
Present	186	21 (11)			
Duodenum invasion					
Absent	194	40 (21)	0.006	–	–
Present	122	11 (9)			
Serosal invasion					
Absent	124	30 (24)	0.002	2.08 (1.01–4.29)	0.047
Present	192	21 (11)		1	
Retroperitoneal invasion					
Absent	102	16 (16)	0.880		
Present	214	35 (16)			
Portal vein invasion					
Absent	163	32 (20)	0.082		
Present	153	19 (12)			
Arterial invasion					
Absent	278	45 (16)	0.989		
Present	38	6 (16)			
Nerve plexus invasion					
Absent	274	50 (18)	0.006	–	–
Present	42	1 (2)			
Other organs invasion					
Absent	303	48 (16)	0.448		
Present	13	3 (23)			
Lymph node metastasis					
Absent	257	46 (18)	0.080		
Present	59	5 (8)			

Note: Values in parentheses are percentages unless otherwise indicated.

Abbreviations: CA 19-9, carbohydrate antigen 19-9; mGPS, modified Glasgow Prognostic Score; NLR, Neutrophil-to-Lymphocyte Ratio; PNI, Prognostic Nutritional Index.

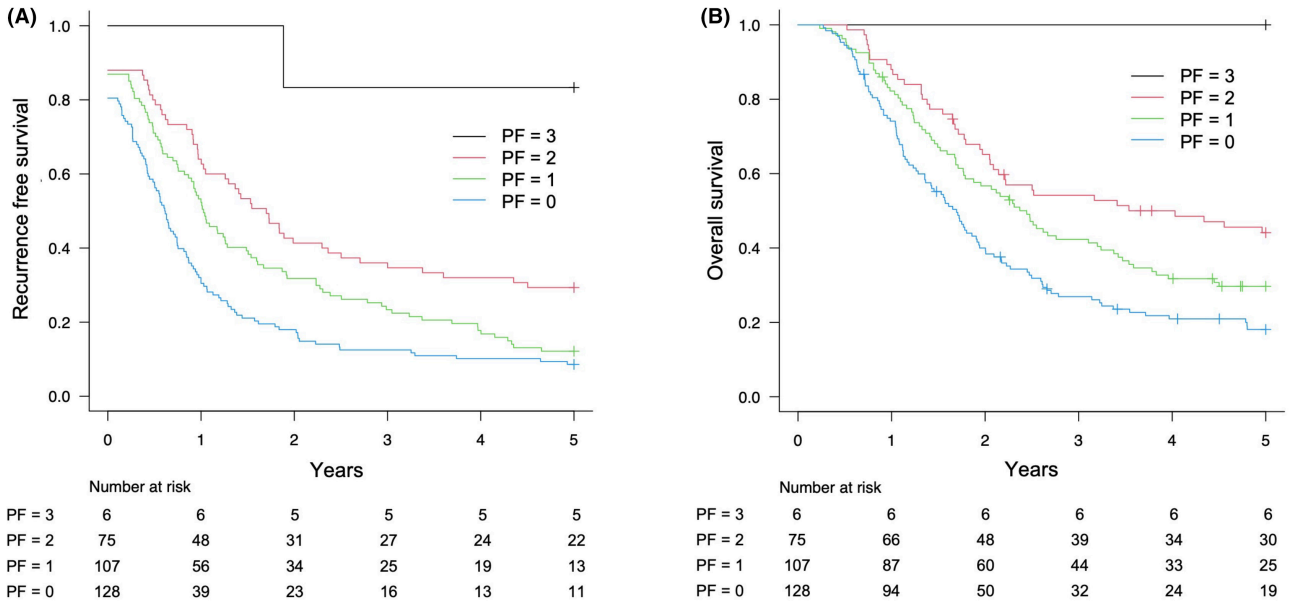

FIGURE 2 Survival curves according to the number of predictive factors in model 1. (A) The recurrence-free survival rate was significantly better in the PF = 3 than in the PF <3 group ($p = 0.006$). (B) The overall survival rate was significantly better in the PF = 3 than in the PF <3 group ($p = 0.003$). PF, predictive factors.

respectively (three factors vs others, $p = 0.003$). One patient with three predictors experienced recurrence in the left lung 23 mo after surgery and underwent partial lung resection.

The predictors of the maximum 5-y RFS in model 2 are shown in Table 3. The absence of radiological serosal invasion, radiological extrapancreatic nerve plexus invasion (PL), and a PNI ≥58 were significantly associated with the 5-y RFS. RFS and OS according to the number of predictors are shown in Figure 3. The 5-y RFS rates of patients with three ($n = 4$), two ($n = 109$), one ($n = 180$), and zero ($n = 23$) predictors were 100%, 24.8%, 11.1%, and 0%, respectively (three factors vs others, $p = 0.012$). The OS rates of patients in the four categories were 100%, 38.7%, 23.7%, and 23.0%, respectively (three factors vs others, $p = 0.042$). Only one patient had all predictors from models 1 and 2.

The diagnostic capabilities of the three predictors in the two models were evaluated. These variables in models 1 and 2 showed satisfactory positive predictive values of 83.3% and 100%, but unsatisfactory false negatives of 90.2% and 92.1%, respectively.

The concordance rates between CT and pathological findings are shown in Table 4. The negative predictive values (NPVs) for serosal invasion and PL invasion were 95.2% and 75.5%, respectively, whereas the NPV for regional lymph node metastasis was low (28.0%).

The recurrence sites according to serosal invasion or PL invasion on CT are shown in Table 5. Patients with radiological serosal invasion had a significantly higher incidence of peritoneal and liver recurrences than those without serosal invasion. Furthermore, patients with radiological PL invasion had a significantly higher incidence of local regional recurrence than those without PL invasion.

The relationship between nutritional status and the completion of adjuvant chemotherapy was also evaluated. The completion rate of adjuvant chemotherapy was significantly lower in malnourished patients (NLR <1.0, 17% vs NLR ≥1.0, 60%, $p = 0.005$; and PNI ≥58, 25% vs PNI <58, 60%, $p = 0.032$, respectively).

4 | DISCUSSION

The present study showed that 16.7% of patients who underwent upfront surgery for R-PC achieved an actual 5-y RFS. To identify long-term recurrence-free survivors, prognostic factors were investigated using actual survival, excluding censoring before the end of observation. In model 1, a tumor size ≤23 mm, absence of radiological serosal invasion, and NLR <1.0 were identified as independent predictors for the 5-y RFS. In model 2, the absence of serosal invasion, absence of PL invasion, and PNI ≥58 were identified. These preoperative predictors focusing on peripancreatic tissue invasion and a nutritional index could identify the groups with an extremely favorable RFS among patients treated with upfront surgery and could be feasible in many centers without specific tests, tools, or additional costs. Patients who fulfill these predictors are likely to achieve 5-y RFS, even if upfront surgery is performed without NAT and to be a population that does not require NAT.

In this study, we used 5-y RFS as the clinical outcome. In general, the RFS curve appears to reach a gradual plateau around 3 y postoperatively.[14] PC is characterized by a short survival after recurrence, which may not lead to overall survival beyond 5 y postoperatively.[15] Therefore, we decided to examine the need for NAT in patients after upfront surgery for R-PC, using 5-y RFS as the outcome, which is the time when PC is considered to be oncologically cured.

In the present study, the absence of serosal invasion on CT was related to the 5-y RFS. Serosal invasion in pathological specimens is

TABLE 3 Predictors of the 5-y recurrence-free survival according to preoperative findings in model 2.

		Univariate analysis		Multivariate analysis	
	n	5-Year recurrence-free	*p* Value	Odds ratio (95% CI)	*p* Value
Patient factors					
CA 19-9 (units/mL)					
<120	166	36 (22)	0.005	–	–
≥120	150	15 (10)			
mGPS					
0	228	41 (18)	0.152		
1 or 2	88	10 (11)			
NLR					
<1.0	12	6 (50)	0.006	–	–
≥1.0	304	45 (15)			
PNI					
≥58	12	6 (50)	0.005	5.30 (1.25–22.50)	0.023
<58	304	45 (6)		1	
CT findings					
Tumor size (mm)					
≤12	18	7 (39)	0.015	–	–
<12	298	44 (15)			
Tumor location					
Head	244	34 (14)	0.075		
Body and tail	72	17 (24)			
Bile duct invasion					
Absent	130	30 (23)	0.005	–	–
Present	186	21 (11)			
Duodenum invasion					
Absent	194	40 (21)	0.006	–	–
Present	122	11 (9)			
Serosal invasion					
Absent	124	30 (24)	0.002	2.59 (1.26–5.32)	0.009
Present	192	21 (11)		1	
Retroperitoneal invasion					
Absent	102	16 (16)	0.880		
Present	214	35 (16)			
Portal vein invasion					
Absent	163	32 (20)	0.082		
Present	153	19 (12)			
Arterial invasion					
Absent	278	45 (16)	0.989		
Present	38	6 (16)			
Nerve plexus invasion					
Absent	274	50 (18)	0.006	8.17 (1.03–64.90)	0.046
Present	42	1 (2)		1	
Other organs invasion					
Absent	303	48 (16)	0.448		
Present	13	3 (23)			

TABLE 3 (Continued)

		Univariate analysis		Multivariate analysis	
	n	5-Year recurrence-free	*p* Value	Odds ratio (95% CI)	*p* Value
Lymph node metastasis					
Absent	257	46 (18)	0.080		
Present	59	5 (8)			

Note: Values in parentheses are percentages unless otherwise indicated.

Abbreviations: CA 19-9, carbohydrate antigen 19-9; mGPS, modified Glasgow Prognostic Score; NLR, Neutrophil-to-Lymphocyte Ratio; PNI, Prognostic Nutritional Index.

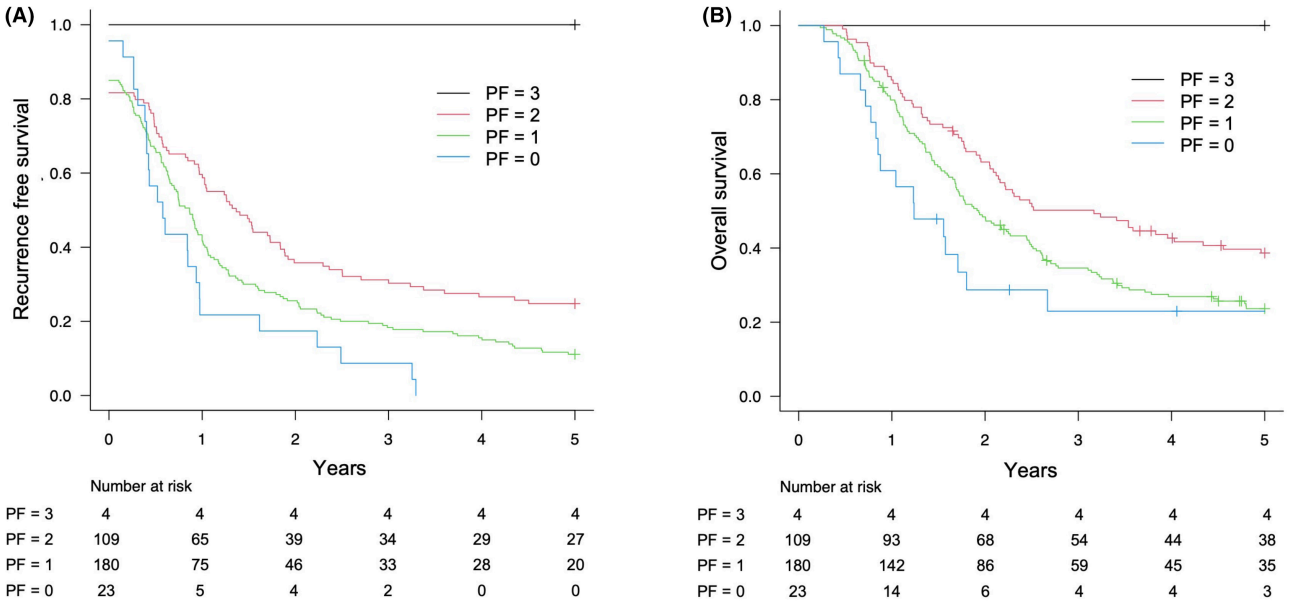

FIGURE 3 Survival curves according to the number of predictive factors in model 2. (A) The recurrence-free survival rate was significantly better in the PF = 3 than in the PF <3 group ($p = 0.012$). (B) The overall survival rate was significantly better in the PF = 3 than in the PF <3 group ($p = 0.042$). PF, predictive factors.

considered an important prognostic factor, showing a different extension pattern from lymphatic and hematological extension. The PC easily extends beyond the anterior surface of the pancreas, as it is an elongated 2-cm-thick organ. Serosal invasion leads to dissemination of cancer cells into the peritoneal cavity. Previous studies have reported that a positive peritoneal cytology is significantly correlated with the development of peritoneal recurrence.[16,17] Patients with positive peritoneal cytology were also more likely to be positive for serosal invasion than those with negative peritoneal cytology.[17] The results of this study supported the tendency for patients with serosal invasion on CT to have more peritoneal recurrence than those without invasion. Therefore, serosal invasion on CT is an important preoperative prognostic factor.

The current results in model 2 indicated that the absence of PL invasion on CT was also related to the 5-y RFS. Several studies have focused on the imaging findings of PL invasion in PC.[12,18] PL invasion can be a cause of positive surgical margins and local recurrence after surgical resection,[19] as supported by the significantly higher incidence of local recurrence in PC patients with PL invasion on CT than those without PL invasion in our study. In previous studies, the presence of PL invasion was confirmed in pathological specimens in 50%–80% of resected patients with pancreatic head cancer.[20,21] However, the rate of invasion was as low as 30% in our study because we included only patients with potentially R-PC who had undergone resection. The NPV of PL invasion was 75.5%, making it a good preoperative prognostic factor.

Lymph node metastasis is one of the strongest prognostic factors for poor prognosis. However, CT findings in the absence of lymph node metastasis were not found to be a predictor of the 5-y RFS due to its low negative predictive value. In contrast, its positive predictive value was high (93.2%). Therefore, the presence of lymph node metastasis on CT findings is accurate and generally used to predict poor prognosis in patients. Recently, Bian et al[22] reported that an automated preoperative artificial intelligence (AI) algorithm for lymph nodes showed favorable accuracy in predicting lymph node metastasis on CT in patients with PC. In the future, AI may be able to predict patient prognosis even more accurately using preoperative images.

A high NLR or low PNI is a well-known nutritional index associated with poor RFS after surgical resection.[23–25] The present study also showed that a low NLR or high PNI was significantly associated with the 5-y RFS. Systemic inflammation, which is associated

TABLE 4 Concordance rates between CT findings and pathological findings.

	CT findings	Pathological findings	PPV	NPV	Accuracy
Tumor extension and LN status					
Bile duct invasion	58.9	59.5	89.2	83.1	86.7
Duodenum invasion	38.6	51.6	89.3	72.2	78.8
Serosal invasion	60.8	27.5	42.2	95.2	63.0
Retroperitoneal invasion	67.7	96.5	98.1	6.9	68.7
Portal vein invasion	48.4	38.0	66.7	89.0	78.2
Arterial invasion	12.0	11.4	50.0	93.9	88.6
Nerve plexus invasion	13.3	30.1	66.7	75.5	74.4
Other organs invasion	4.1	3.8	23.1	97.0	94.0
Regional LN metastasis	18.7	75.9	93.2	28.0	40.2

Note: Values are presented as percentage.

Abbreviations: CT, computed tomography; LN, lymph node; PPV, positive predictive value; NPV, negative predictive value.

TABLE 5 Recurrence sites according to serosal invasion or extrapancreatic nerve plexus invasion on CT.

	Serosal invasion (+)	Serosal invasion (−)		Extrapancreatic nerve plexus invasion (+)	Extrapancreatic nerve plexus invasion (−)	
	n = 192	*n* = 124	*p* Value	*n* = 42	*n* = 274	*p* Value
Recurrence site						
Lymph node	45 (23)	27 (22)	0.731	10 (24)	62 (23)	0.865
Local region	39 (20)	19 (15)	0.263	19 (45)	39 (14)	<0.001
Liver	71 (37)	31 (25)	0.026	13 (31)	89 (32)	0.844
Lung	22 (11)	21 (17)	0.166	7 (17)	36 (13)	0.535
Peritoneum	36 (19)	12 (10)	0.028	7 (17)	41 (15)	0.775
Remnant pancreas	14 (7)	7 (6)	0.566	4 (10)	17 (6)	0.500
Other distant	2 (1)	1 (1)	1	0 (0)	3 (1)	1

Note: Values in parentheses are percentages unless otherwise indicated.

with the disturbance of various hematological components such as neutrophils, lymphocytes, monocytes, and platelets, plays a critical role in cancer progression.[26] Hypoalbuminemia indicates chronic malnutrition, which is also correlated with immunosuppression.[27] Therefore, NLR and PNI are indicators that change in accordance with cancer progression and the host immune condition, and their maintenance in a good status may indicate a low probability of occult invasion or metastasis in PC. In addition, nutritional status may be important in tolerating chemotherapy without severe adverse events. Xiao et al[28] demonstrated that nutritional status affects the tolerability of adjuvant therapy after gastrectomy in patients with gastric cancer. In the current study, malnutrition status influenced the tolerability of adjuvant chemotherapy, resulting in a low completion rate. This may be another possible reason for the poor RFS in patients with a high NLR or low PNI.

CA 19-9 is also well known to be associated with early recurrence and poor prognosis[29,30]; however, we failed to detect it as a predictor of 5-y RFS. In fact, in the current series, the higher the CA 19-9 value, the higher was the rate of early recurrence (data not shown). However, among 166 patients with a preoperative CA 19-9 value <120 U/mL, 130 (78%) experienced recurrence within 5 y after surgery. Given these results, tumor biomarkers, primarily CA 19-9, appear to be useful in predicting early recurrence and survival, but have limited power in predicting long-term RFS.

We used two methods for determining the cutoff value that was used to divide continuous variables into two groups: the minimum *p*-value method (model 1) and a method in which the cutoff value was the value that maximized the proportion of objective cases (model 2). In that case, the only difference between models 1 and 2 was how the cutoff value was determined, not which one was better. The validity of a model is determined by whether the predictors are successful or not. If the predictions are successful, it means that a good model has been created. Conversely, if the predictors are unsuccessful, it means that the model is bad. In the present study, prediction models were created to identify groups with a good prognosis, but the numbers of people in those group

were only about 10% of the 5-y recurrence-free group. Therefore, it cannot be said to be good prognostic models for 5-y recurrence-free patients.

Several limitations of the present study warrant mention. This was a retrospective study conducted at a single institution. In the present study, two models were used to determine the optimal cut-off value to achieve our objectives, but predictions that could change actual clinical practice were difficult to make. Predictors stratifying RFS were extracted for each patient. However, these predictors differed between the models, except for serosal invasion, indicating that almost completely different groups were extracted. Further exploration is therefore needed to determine the cutoff values for selecting a favorable prognosis group, as in this study.

5 | CONCLUSION

A modest number of patients who underwent upfront surgery achieved a 5-y RFS, but only ~10% of them were identifiable. Based on these results, almost all patients with R-PC are forced to undergo NAT in daily practice.

AUTHOR CONTRIBUTIONS

Study conception and design: MU and TS. Acquisition of data: MU, TS, RA, KO, MY, SO, TA, and KU. Analysis and interpretation of data: MU, TS, and AN. Drafting of article: MU and TS. Critical revision of article: all authors.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest for this article.

ETHICS STATEMENTS

The study was approved by the Institutional Research Ethics Committee (J2020-84-2021-1-3) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Approval of the research protocol: N/A.

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