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Prognostic impacts of biological and conditional factors in patients with anatomically resectable pancreatic adenocarcinoma treated with preoperative chemoradiotherapy

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Abstract

The efficacy of preoperative chemoradiotherapy (CRT) for anatomically resectable pancreatic adenocarcinoma (R-PDAC) remains contentious. This study aims to elucidate the treatment outcomes of preoperative CRT for R-PDAC and to identify prognostic factors. This retrospective study included 109 R-PDAC patients treated with gemcitabine- or S-1 plus gemcitabine-based preoperative CRT from February 2005 to April 2023. Cox proportional hazards regression was employed to identify factors associated with worse overall survival (OS). Among the 109 cases, 90 patients (82.6%) underwent curative-intent resection following CRT. The median OS for the entire cohort was 36.5 months, significantly longer in resected cases than in unresected cases (40.6 vs 11.4 months). Multivariate analysis identified pretreatment serum levels of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) and the Eastern Cooperative Oncology Group performance status ≥1 as independent prognostic factors. When these factors were scored (risk score 0–3) using pre-CRT serum CA19-9 level (≥640 U/mL) and CEA (≥6.1 ng/mL), OS for risk scores 1 (n = 41), 2 (n = 20) or 3 (n = 6) was significantly shorter than for risk score 0 (n = 42) (score 0 vs 1 vs 2 vs 3: 49.1 vs 33.8 vs 16.1 vs 16.8 months). The presence of portal vein invasion on imaging and post-CRT serum CA 19-9 level (≥111 U/mL) were independent prognostic factors in resected cases. Biological factors, including serum levels of CA19-9 and CEA, along with conditional factor of Eastern Cooperative Oncology Group performance status ≥1, were identified as independent prognostic factors for R-PDAC patients treated with preoperative CRT. Preoperative CRT is considered effective for cases lacking these risk factors.

Abbreviations: BR-PDAC = borderline resectable pancreatic adenocarcinoma, CA19-9 = carbohydrate antigen 19-9, CEA = carcinoembryonic antigen, cPV1 = portal venous system invasion on imaging, CRT = chemoradiotherapy, ECOG-PS = Eastern Cooperative Oncology Group performance status, G-CRT = gemcitabine-based CRT, GS-CRT = S-1 plus gemcitabine-based CRT, IAP = International Association of Pancreatology, JPS = Japan Pancreas Society, MD-CT = multidetector computed tomography, OS = overall survival, PNI = prognostic nutritional index, PV = portal vein, R-PDAC = resectable pancreatic adenocarcinoma, SMV = superior mesenteric vein, UICC = Union for International Cancer Control.

Keywords: biological factors, conditional factors, pancreatic cancer, pancreatic ductal adenocarcinoma, preoperative chemoradiotherapy

1. Introduction

Pancreatic adenocarcinoma (PDAC) is recognized as one of the most aggressive malignancies worldwide, characterized by a dismal prognosis and the highest mortality rate among cancers.[1] To enhance the outcomes of surgical resection, a neoadjuvant therapeutic approach has been advocated for the management of localized PDAC. Among the various neoadjuvant therapies available, preoperative chemoradiotherapy (CRT) is considered to provide clinical advantages, such as systemic control of micrometastases and downsizing

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of the tumor, thereby mitigating the risks associated with microscopically positive margin resection.[2] Substantial evidence from randomized controlled trials indicates that preoperative CRT provides oncological benefits by improving the R0 resection rate and overall survival (OS) compared to up-front surgery, particularly in patients with borderline resectable PDAC (BR-PDAC).[3–5] Emerging comparative studies suggest similar benefits in anatomically resectable PDAC (R-PDAC). The PREOPANC-1 randomized phase III trial demonstrated that preoperative CRT significantly increases R0 resection rates and trends toward improved OS in R-PDAC cases.[5] Furthermore, retrospective studies have shown that preoperative CRT reduces the incidence of pathological lymph nodal metastasis and positive microscopic surgical margins[6] while providing a significant survival advantage over up-front surgery in R-PDAC.[7,8] Additionally, our prior retrospective studies indicate that a major histological response to preoperative CRT is associated with higher R0 resection rates and improved survival in R-PDAC.[9,10] These findings highlight the potential oncological benefits of preoperative CRT in R-PDAC, though further research is warranted to refine selection criteria and optimize treatment strategies.[11]

Most resectability criteria classify the primary pancreatic tumor based on the extent of tumor contact with major vessels as assessed through radiological imaging, and current treatment guidelines are generally based solely on anatomical criteria.[12,13] Nonetheless, biological and conditional factors are known to significantly influence the prognosis of localized PDAC.[14–17] The International Association of Pancreatology (IAP) has introduced preoperative staging criteria by redefining BR-PDAC to include biological and conditional factors.[18] According to the IAP, biological factors include the preoperative serum level of carbohydrate antigen (CA19-9) and preoperative regional lymph nodal metastasis, while the patients' condition is reflected by the Eastern Cooperative Oncology Group (ECOG) performance status (PS).[18] Notably, a serum CA19-9 level exceeding 500 U/mL has been associated with elevated early recurrence rates and reduced survival outcomes in patients with R-PDAC undergoing up-front surgery.[15–17] However, the applicability of these factors has yet to be validated in patients with R-PDAC who have undergone neoadjuvant therapy, including preoperative CRT. Furthermore, limited evidence exists to inform the optimal neoadjuvant treatment strategy for patients categorized under the biological BR-PDAC classification.

Therefore, the aim of this study was to elucidate the treatment outcomes of preoperative CRT for the patients with R-PDAC and to identify pretreatment prognostic factors, encompassing both biological and conditional factors.

2. Materials and methods

2.1. Study design

This retrospective study was carried out in accordance with the ethical standards stated in the Declaration of Helsinki and approved by the institutional ethics committee (Approval No. H2020-118). Given the retrospective study design, the requirement for informed consent was waived. Patient data was retrieved from a prospectively compiled institutional registry that included individuals with localized PDAC who received preoperative CRT. The dataset was accessed for analysis on August 27th, 2023.

An overview of the study and patient selection process are depicted in Figure 1. A total of 109 consecutive patients with R-PDAC patients who received preoperative CRT between February 2005 and April 2023 were analyzed. Reevaluation of imaging following preoperative CRT identified distant metastases in 13 patients (liver: n = 5, peritoneal: n = 2, lung: n = 2, para-aortic lymph node: n = 2, liver and peritoneal: n = 1, chest wall: n = 1), representing 11.9% of the cohort. PS prior to surgery deteriorated in 1 patient. Among the remaining 95 patients who received laparotomy after preoperative CRT, distant metastases were detected intraoperatively in 5 patients (4.6%; peritoneal: n = 3, liver: n = 2). Consequently, 90 patients (82.6%) proceeded to curative-intent resection. Pretreatment patient demographics and OS following initial treatment were compared between the resection group (n = 90) and no-resection group (n = 19) after CRT. To identify patient baseline factors related to OS after initial treatment in the entire cohort (n = 109), univariate and multivariate analyses were performed. Additionally, corresponding statistical analyses were conducted to identify perioperative predictors of OS after surgery in the resection group following preoperative CRT (n = 90). The last follow-up was conducted on August 21, 2023, with no patients lost to follow-up. The median follow-up period was 29.7 (range, 3.6–165.5) months.

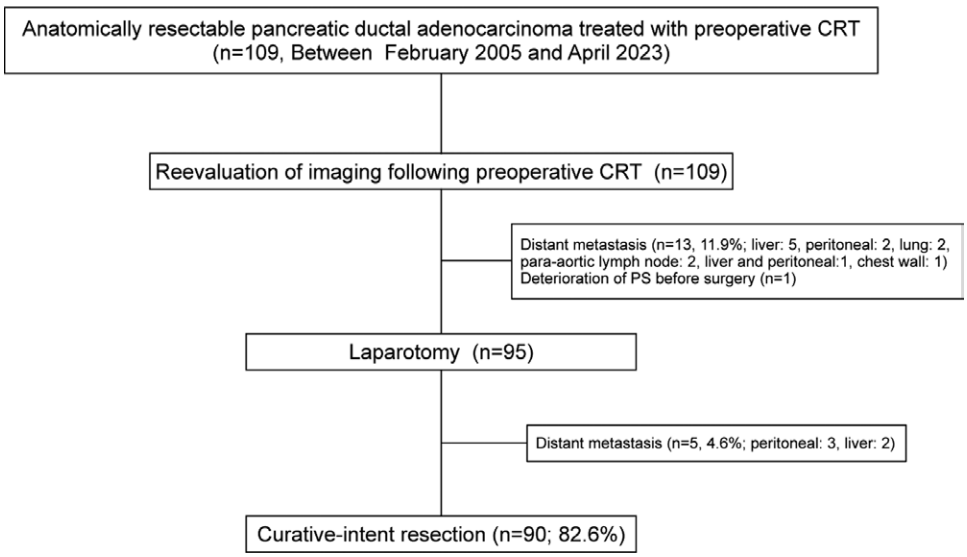

Figure 1. Flowchart of patient selection.

2.2. Radiologic evaluation of tumor resectability

At the time of initial clinical assessment, tumor staging and resectability were evaluated using a pretreatment tetraphasic dynamic contrast-enhanced multidetector computed tomography (MD-CT) scan according to the Japan Pancreas Society (JPS) classification.[19] The initial tumor staging at baseline, based on MD-CT, was reviewed and determined by a multidisciplinary team, which included a radiologist. Specifically, the T category and related local invasions factors were evaluated in accordance with definition of JPS classification. Furthermore, the T category was also assessed based on the Union for International Cancer Control (UICC) TNM classification of malignant tumors and incorporated as a pretreatment baseline factor to analyze its association with OS following both initial treatment and surgery.[20]

2.3. Preoperative CRT protocol and surgical management

Of the 109 patients included in this study, 30 were treated with gemcitabine-based CRT (G-CRT), while the remaining 79 received S-1 plus gemcitabine-based CRT (GS-CRT). The detailed chemotherapeutic protocols for both regimens have been previously described, and all patients received concurrent three-dimensional conformal radiotherapy, as outlined in the same report.[21] Initially, 30 patients treated with G-CRT and 9 treated with GS-CRT received 45 Gy in 25 fractions between February 2005 and September 2013. To enhance treatment efficacy, the protocol was modified in October 2013, increasing the overall radiation dose to 50.4 Gy in 28 fractions for 70 patients treated with GS-CRT until April 2023. After completing CRT, all patients were reevaluated using MD-CT to assess clinical treatment response. Radiographic findings were compared before and after CRT, with particular attention to changes in maximum tumor diameter. In parallel, serum levels of tumor markers including CA19-9 and carcinoembryonic antigen (CEA), were measured at baseline and reassessed after CRT. The neutrophil-to-lymphocyte ratio (NLR) and the prognostic nutritional index (PNI) were calculated using pre-CRT laboratory data according to previously established formulas to assess patient conditional factors.[22,23] PS was assessed by the ECOG scale (ECOG-PS) just before the initiation of preoperative CRT.[24]

Patients who showed no evidence of distant metastasis on post-CRT CT scans were considered eligible for surgical resection. During laparotomy, pancreatectomy was carried out only when the absence of distant metastatic lesions was confirmed intraoperatively. Pancreaticoduodenectomy was performed using the anterior approach in combination with the nerve plexus hanging maneuver, as previously reported.[25] Distal pancreatectomy was executed following the principles of radical antegrade modular pancreatosplenectomy. When the pancreatic head could not be separated from the superior mesenteric vein (SMV) and/or portal vein (PV) without leaving visible tumor tissue, vascular resection followed by reconstruction was undertaken. The Clavien–Dindo grading system was employed to classify postoperative complications.[26] Histopathological evaluation was performed by certified pathologists in accordance with the definition of JPS classification.[19]

2.4. Adjuvant chemotherapy and surveillance

Adjuvant chemotherapy using either gemcitabine or S-1 was scheduled to commence within 6 weeks after surgery and administered for at least 6 months. Postoperative surveillance involved monthly clinical evaluations, including physical examinations and periodic laboratory tests such as serum CA19-9 measurements every 2 or 3 months. Additionally, MD-CT scans were performed every 3 months during the first 2 years after surgery, then every 6 months thereafter. Patients with recurrent disease and preserved PS were typically managed using systemic chemotherapy.

2.5. Statistical analysis

Continuous variables were expressed as medians with interquartile ranges, and categorical variables were summarized as frequencies. Group comparisons of categorical variables were conducted using the chi-square test or Fisher exact test as appropriate. The Mann–Whitney *U* test was applied for comparisons of continuous variables. The interval from the initiation of treatment to either death or last follow-up was defined as OS. Censoring for OS was applied at the time of the last disease follow-up for patients who were alive. Survival distributions were estimated using the Kaplan–Meier method, and differences between groups were tested with the log-rank test. In univariate analysis, potential pretreatment prognostic factors were examined through the log-rank test, followed by multivariate analysis using the Cox proportional hazards regression model. Cutoff values for continuous variables considered as potential prognostic factors were identified using the web-based software tool (Cut-off Finder; https://molpathoheidelberg.shinyapps.io/CutoffFinder_v1/), and all variables were converted into binary categories for further analysis. Statistical analyses were conducted using JMP Pro software (version 17.2.0, SAS Institute Inc, Cary, NC), with significance defined as a *P*-value <.05.

3. Results

Figure 2 displays the OS curves of patients with R-PDAC treated with preoperative CRT, comparing the OS between the resection and no-resection groups following CRT. The median OS after initial treatment for the entire cohort was 36.5 months (Fig. 2A). The OS following initial treatment was significantly longer in the resection group compared to the no-resection group (resection vs no-resection after CRT: 40.6 vs 11.4 months, $P < .001$) (Fig. 2B). Among the 90 patients with curative-intent resection, R0 resection was achieved in 88 (97.8%) cases. The median OS after surgery for the resection group was 37.1 months (Figure S1A, Supplemental Digital Content, https://links.lww.com/MD/O885). The OS after surgery was significantly longer in the patients with R0 resection compared to those with R1 resection (R0 vs R1: 37.9 vs 15.5 months, $P = .021$) (Figure S1B, Supplemental Digital Content, https://links.lww.com/MD/O885). Table 1 provides a comparative analysis of peritreatment factors between the resection and no-resection groups following CRT. Concerning the laboratory data, in terms of patient conditional factors, the PNI before the initiation of CRT was significantly lower in the no-resection group compared to the resection group (resection vs no-resection after CRT: 47.0 vs 42.9, $P = .007$). Additionally, regarding the biological factors, the serum level of CA19-9 after preoperative CRT was significantly higher in the no-resection group than in the resection group (resection vs no-resection after CRT: 35 vs 164.3 U/mL, $P = .008$). Regarding imaging parameters, the incidence of portal venous system invasion before CRT was significantly lower in the no-resection group compared to the resection group (resection vs no-resection after CRT: 65.6 vs 36.8%, $P = .037$). Conversely, the incidence of invasion into other organs before CRT was significantly higher in the no-resection group than in the resection group (resection vs no-resection after CRT: 11.1 vs 36.8%, $P = .011$). Additionally, post-CRT tumor size on imaging was significantly greater in the no-resection group compared to the resection group (resection vs no-resection after CRT: 22.5 vs 26.4 mm, $P = .028$).

Cox proportional hazard models were employed to identify pretreatment baseline factors significantly associated with

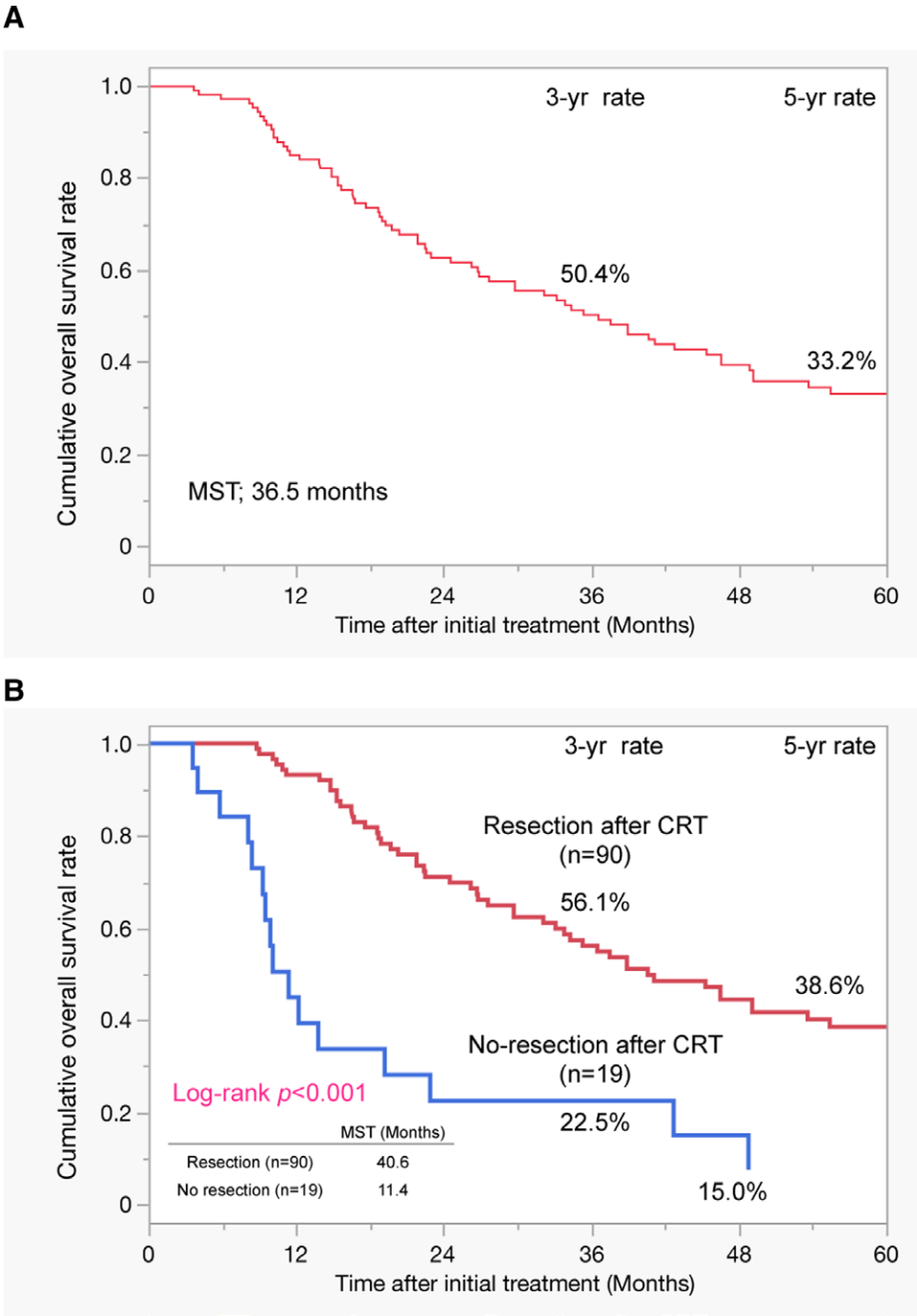

Figure 2. Overall survival curves in the patients with anatomically resectable pancreatic adenocarcinoma who underwent preoperative chemoradiotherapy. (A) Overall survival curve in the 109 patients who underwent preoperative chemoradiotherapy. (B) Comparison of the overall survival curves between the patients who underwent curative-intent resection (resection group, n = 90) and those who underwent nonsurgical treatment after preoperative chemoradiotherapy (no-resection group, n = 19).

OS after the initiation of preoperative CRT. Univariate Cox regression analysis indicated that ECOG-PS ≥ 1, and elevated serum levels of CEA and CA19-9, were prognostic factors significantly associated with shorter OS. Multivariate Cox regression analysis revealed that ECOG-PS ≥ 1, serum levels of CEA, and serum level of CA19-9 were independent prognostic factors associated with shorter OS (ECOG-PS ≥ 1/ECOG-PS 0; HR (95%CI): 1.77 (1.12–2.79), P = .015, serum level of CEA; 1.01 (1.00–1.02), P = .029, serum level of CA19-9 ($\times 10^2$); 1.02 (1.01–1.03), P = .006) (Table 2). Patients with ECOG-PS ≥ 1 (n = 41) exhibited significantly shorter OS compared to those with ECOG-PS 0 (n = 68) (ECOG-PS ≥ 1 vs ECOG-PS 0: 19.7 vs 45.3 months, P = .001) (Fig. 3A). The cutoff values for serum levels of CEA and CA19-9 associated with shorter OS were determined as to be ≥ 6.1 ng/mL and ≥640 U/mL, respectively. OS was significantly worse in patients with CEA levels ≥ 6.1 ng/mL (n = 32) compared to those with CEA levels < 6.1 ng/mL (n = 77) (CEA levels ≥ 6.1 vs <6.1 ng/mL: 20.3 vs 46.5 months, P < .001) (Fig. 3B). Similarly, OS was significantly worse in patients with CA 19-9 levels ≥ 640 U/mL (n = 26) compared to those with CA 19-9 levels < 640 U/mL (n = 83) (CA19-9 levels ≥ 640 vs < 640 U/mL: 17.7 vs 42.7

Table 1

Comparison of the patient peri-treatment factors between the resection and no-resection groups following preoperative chemoradiotherapy.

Variables	All cases (n = 109)	Resection after CRT (n = 90)	No-resection after CRT (n = 19)	*P*-value
Age	69 (63–74)	69 (62–74)	71 (64–76)	.479
Gender (male/female)	64/45	50/40	14/5	.201
ECOG-PS (0/≥1)	68/41	59/31	10/9	.192
Chemotherapeutic agent of CRT (GS/G)	79/30	65/25	14/5	1.000
BMI (kg/m^2)	21.3 (18.9–23.6)	21.1 (18.7–23.5)	22.4 (19.2–25.1)	.114
Laboratory data				
Neutrophil-to-lymphocyte ratio before CRT	2.5 (1.9–3.6)	2.4 (1.8–3.3)	3.2 (1.9–4.3)	.218
Prognostic nutritional index before CRT	46.1 (42.4–50.1)	47.0 (43.3–50.2)	42.9 (39.6–46.3)	**.007**
Serum level of CEA before CRT (ng/mL)	4.1 (2.3–6.4)	4.1 (2.3–6.3)	4.5 (2.6–11.8)	.465
Serum level of CEA after CRT (ng/mL)	3.5 (2.1–5.6)	3.5 (2.1–5.5)	4 (1.9–8.7)	.576
Reduction rate of CEA (%)	7.5 (-19.9–33.2)	5.7 (-18.2–32.3)	16.1 (-30.0–42.3)	.940
Serum level CA19-9 before CRT (U/mL)	144.6 (57.5–582.6)	126.6 (44.2–490.7)	296.7 (83.6–2869.6)	.115
Serum level CA19-9 after CRT (U/mL)	37.3 (19.1–129.6)	35 (17.7–85.0)	164.3 (23.7–1024.8)	**.008**
Reduction rate of CA19-9 (%)	71.4 (37.2–88.4)	74.1 (40.6–89.7)	62.0 (-4.2–78.8)	.105
Imaging parameters				
Tumor location (head/body or tail)	73/36	62/28	11/8	.423
Tumor size before CRT (mm)	25.4 (19.2–32.6)	25.3 (18.6–31.8)	26.1 (22.6–33.2)	.429
Tumor size after CRT (mm)	23.7 (17.8–28.9)	22.5 (16.9–28.4)	26.4 (25.2–32.5)	**.028**
Reduction rate of tumor size (%)	12.1 (-0.5–23.9)	12.4 (-0.33–26.5)	11.2 (-8.9–16.1)	.078
Grade of local invasion before CRT (JPS T1 or T2/T3)	3/106	3/87	0/19	1.000
Bile duct invasion before CRT (no/yes)	57/52	46/44	11/8	.623
Duodenal invasion before CRT (no/yes)	77/32	65/25	12/7	.421
Anterior pancreatic tissue invasion before CRT (no/yes)	31/78	26/64	5/14	1.000
Retropancreatic tissue invasion before CRT (no/yes)	34/75	30/60	4/15	.416
Portal venous system invasion before CRT (no/yes)	43/66	31/59	12/7	**.037**
Arterial invasion before CRT (no/yes)	89/20	75/15	14/5	.336
Extrapancreatic nerve plexus invasion before CRT (no/yes)	84/25	72/18	12/7	.136
Invasion of other organs before CRT (no/yes)	92/17	80/10	12/7	**.011**
Grade of local invasion before CRT (UICC T1 or T2/T3)	97/12	80/10	17/2	1.000
Lymph nodal metastasis before CRT (no/yes)	94/15	80/10	14/5	.134

BMI = body mass index, CA = carbohydrate antigen, CEA = carcinoembryonic antigen, CRT = chemoradiotherapy, ECOG-PS = the Eastern Cooperative Oncology Group performance status, G = gemcitabine-based, GS = gemcitabine plus S-1 based, JPS = the eighth edition of the Japan Pancreas Society classification, UICC = the eighth edition of the International Union Against Cancer TNM classification of Malignant Tumors.

Bold values indicate that the *P*-value is statistically significant.

months, *P* = .001) (Fig 3C). When evaluating these 3 significant pretreatment baseline factors on a scale of 0 to 3, based on the presence of pre-CRT serum CEA levels (cutoff ≥ 6.1 ng/mL), CA19-9 levels (cutoff ≥ 640 U/mL), and ECOG-PS ≥ 1, the OS for a risk score of 1 (n = 41), 2 (n = 20), or 3 (n = 6) was significantly worse than that for a risk score of 0 (n = 42) (risk score 0 vs 1 vs 2. vs 3 points: 49.1 vs 33.8 vs 16.1 vs 16.8 months) (Fig. 4B). The OS for a risk score of either 2 or 3 was notably shorter than that for a risk score of 1. Although not statistically significant, the rate of curative-intent resection after preoperative CRT was markedly lower in patients with a risk score 2 or 3 compared to that with a risk score of 0 or 1 (risk score 0 vs 1 vs 2. vs 3 points:88.1 vs 85.4 vs 70.0 vs 66.7%) (Fig. 4A).

Cox proportional hazard models were employed to identify perioperative factors significantly associated with OS after surgery in R-PDAC patients who underwent curative-intent resection following preoperative CRT. Univariate Cox regression analysis revealed that the serum level of CA19-9 after preoperative CRT, portal venous system invasion on imaging (cPV1) before preoperative CRT, and pathological lymph node metastasis were prognostic factors significantly associated with shorter OS after surgery. Multivariate Cox regression analysis identified that the presence of cPV1 and serum level of CA19-9 (×10^2) after preoperative CRT as independent prognostic factors associated with shorter OS after surgery (cPV1; HR (95% CI): 2.24 (1.19–4.21), *P* = .008, post-CRT serum CA19-9 levels (×10^2); 1.32 (1.11–1.54), *P* = .003) (Table 3). OS in R-PDAC patients with the presence of cPV1 (n = 59) was significantly shorter than in those with the absence of portal venous system invasion (cPV0) before preoperative CRT (n = 31) (cPV0 vs cPV1: 83.2 vs 29.6 months, *P* = .029) (Fig. 5A). The cutoff value for the post-CRT serum CA19-9 level associated with shorter OS was determined as to be≥111 U/mL. OS was significantly shorter in patients with post-CRT serum CA19-9 level ≥ 111 U/mL (n = 19) compared to those with post-CRT serum CA19-9 < 111 U/mL (n = 71) (≥111 vs <111 U/mL: 13.2 vs 43.3 months, *P* = .025) (Fig. 5B).

4. Discussion

The present study aimed to elucidate treatment outcomes and identify significant pretreatment prognostic factors for R-PDAC patients who received preoperative CRT. Multivariate analysis revealed that elevated pre-CRT serum CEA and CA19-9 levels were strong prognostic factors significantly associated with reduced OS. Additionally, a pre-CRT ECOG-PS ≥ 1 was recognized as a crucial factor correlated with diminished OS. The baseline risk scores we defined, which combine pre-CRT CEA and CA19-9 levels with ECOG-PS score, were significantly associated with shorter OS in patients with R-PDAC treated with preoperative CRT. Our findings suggest that preoperative CRT might be advantageous for cases without these risk factors but not for those who exhibit high-risk scores.

In the present study, the serum level of CEA was identified, alongside the well-established role of serum CA19-9, as an independent prognostic indicator in R-PDAC patients undergoing preoperative CRT. To the best of our knowledge, the present study is the first report demonstrating the efficacy of a combined

Table 2

The univariate and multivariate Cox regression analysis of pretreatment baseline factors associated with overall survival after initial treatment in the pancreatic adenocarcinoma patients who underwent preoperative chemoradiotherapy (n = 109).

				Univariate analysis		Multivariate analysis	
Variable		**No. of cases**	**MST (months)**	**Hazard ratio (95% CI)**	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**
Gender	Male	64	36.5	1.18 (0.74–1.88)	.476		
	Female	45	37.5	1			
Age (years)		109	N/A	1.01 (0.99–1.04)	.237		
ECOG-PS	0	68	45.3	1	**.023**	1	**.015**
	≥1	41	19.7	1.70 (1.08–2.66)		1.77 (1.12–2.79)	
BMI (kg/m^2)		109	N/A	1.00 (0.95–1.06)	.999		
Neutrophil lymphocyte ratio		109	N/A	0.99 (0.82–1.14)	.896		
Prognostic nutrition index		109	N/A	0.99 (0.95–1.03)	.602		
Serum level of CEA (ng/mL)		109	N/A	1.01 (1.00–1.02)	**.005**	1.01 (1.00–1.02)	**.029**
Serum level of CA19-9 (×10^2) (U/mL)		109	N/A	1.02 (1.01–1.03)	**.003**	1.02 (1.01–1.03)	**.006**
Chemotherapeutic agent of CRT	GS-CRT	79	41.1	1	.250		
	G-CRT	30	27.2	1.33 (0.82–2.15)			
Tumor location	Head	73	38.9	1	.579		
	Body or tail	36	29.7	1.15 (0.71–1.85)			
Tumor size before CRT (mm)		109	N/A	1.01 (0.99–1.03)	.390		
Grade of local invasion before CRT (JPS)	cT1 or T2	3	74.2	1	.373		
	cT3	106	34.3	1.79 (0.44–7.33)			
Bile duct invasion	no	57	38.9	1	.942		
	yes	52	33.8	0.98 (0.63–1.54)			
Duodenal invasion	no	77	37.5	1	.433		
	yes	32	35.3	1.22 (0.75–2.00)			
Serial side of the anterior pancreatic tissue invasion	no	31	48.8	1	.148		
	yes	78	32.1	1.45 (0.86–2.45)			
Retropancreatic tissue invasion	no	34	49.1	1	.544		
	yes	75	33.1	1.16 (0.71–1.90)			
Portal venous system invasion	no	43	45.3	1	.239		
	yes	66	33.8	1.33 (0.82–2.14)			
Arterial system invasion	no	89	38.9	1	.269		
	yes	20	27.2	1.38 (0.79–2.40)			
Extrapancreatic nerve plexus invasion	no	84	38.9	1	.384		
	yes	25	27.6	1.27 (0.75–2.16)			
Invasion of other organs	no	92	38.9	1	.108		
	yes	17	22.5	1.66 (0.92–2.98)			
Grade of local invasion before CRT (UICC)	cT1 or T2	97	34.3	1	.632		
	cT3	12	45.3	0.84 (0.40–1.75)			
Lymph nodal metastasis before CRT	no	94	57.5	1	.874		
	yes	15	32.1	1.66 (0.92–2.98)			

BMI = body mass index, CA = carbohydrate antigen, CEA = carcinoembryonic antigen, CRT = chemoradiotherapy, ECOG-PS = the Eastern Cooperative Oncology Group performance status, G = gemcitabine-based, GS = gemcitabine plus S-1 based, JPS = the eighth edition of the Japan Pancreas Society classification, MST = median survival time, N/A = not applicable, UICC = the eighth edition of the International Union Against Cancer TNM classification of Malignant Tumors.

Bold values indicate that the *P*-value is statistically significant.

analysis of serum CEA and CA19-9 levels as a predictive tool for patients with anatomically R-PDAC undergoing preoperative CRT. Elevated pretreatment CEA level has been reported as a prognostic factor associated with significantly worse OS in patients with localized PDAC undergoing up-front surgery.[27,28] Importantly, the combined analysis of serum levels of CEA and CA19-9 before surgery is considered effective in prognostic prediction after curative resection for patients with localized PDAC.[27,28] The combined role of serum CEA and CA19-9 levels for predicting resectability has been investigated in patients with R-PDAC, indicating that preoperative CEA and CA19-9 levels are suitable for assessing curability and resectability in patients with anatomicaly R-PDAC.[29,30] Additionally, high preoperative serum CEA and CA19-9 levels have been consistently associated with poor OS in patients with advanced pancreatic cancer.[31] Mansen et al assessed the value of serum CEA and CA19-9 levels at diagnosis as predictors for the advanced stage of PDAC in patients discussed at multidisciplinary team meeting. They found that both CEA and CA19-9 serum levels independently predict advanced disease, defined as either locally advanced PDAC or the presence of distant metastases.[32] Incorporating serum CEA alongside serum CA19-9 levels in the evaluation of PDAC offers several advantages. Firstly, CA19-9 is not expressed in individuals lacking the Lewis antigen, even in the presence of tumors. Given that approximately 4% to 7% of the population lacks this antigen,[33,34] sole reliance on serum CA19-9 must be approached with caution. CEA has been reported to serve as a complement to CA19-9 in Lewis-negative PDAC patients.[35] In our present study, 6 out of 109 R-PDAC patients (5.5%) exhibited CA19-9 values below the assay sensitivity threshold (1 U/mL), likely due to the absence of Lewis antigen. Remarkably, 3 of these patients (50%) displayed elevated serum CEA levels (≥6.1 ng/mL). This finding suggests the utility of a combined approach utilizing both CA19-9 and CEA in the evaluation of PDAC resectability. Secondly, the serum CA19-9 level can be influenced by biliary obstruction, necessitating assessments after correcting for biliary serum levels. Hence, the concurrent utilization of CA19-9 and CEA as biological factors may enhance the accuracy of clinical decision-making.

There exists limited evidence concerning the optimal neoadjuvant regimen for patients diagnosed with anatomically R-PDAC presenting who present positive biological factors,

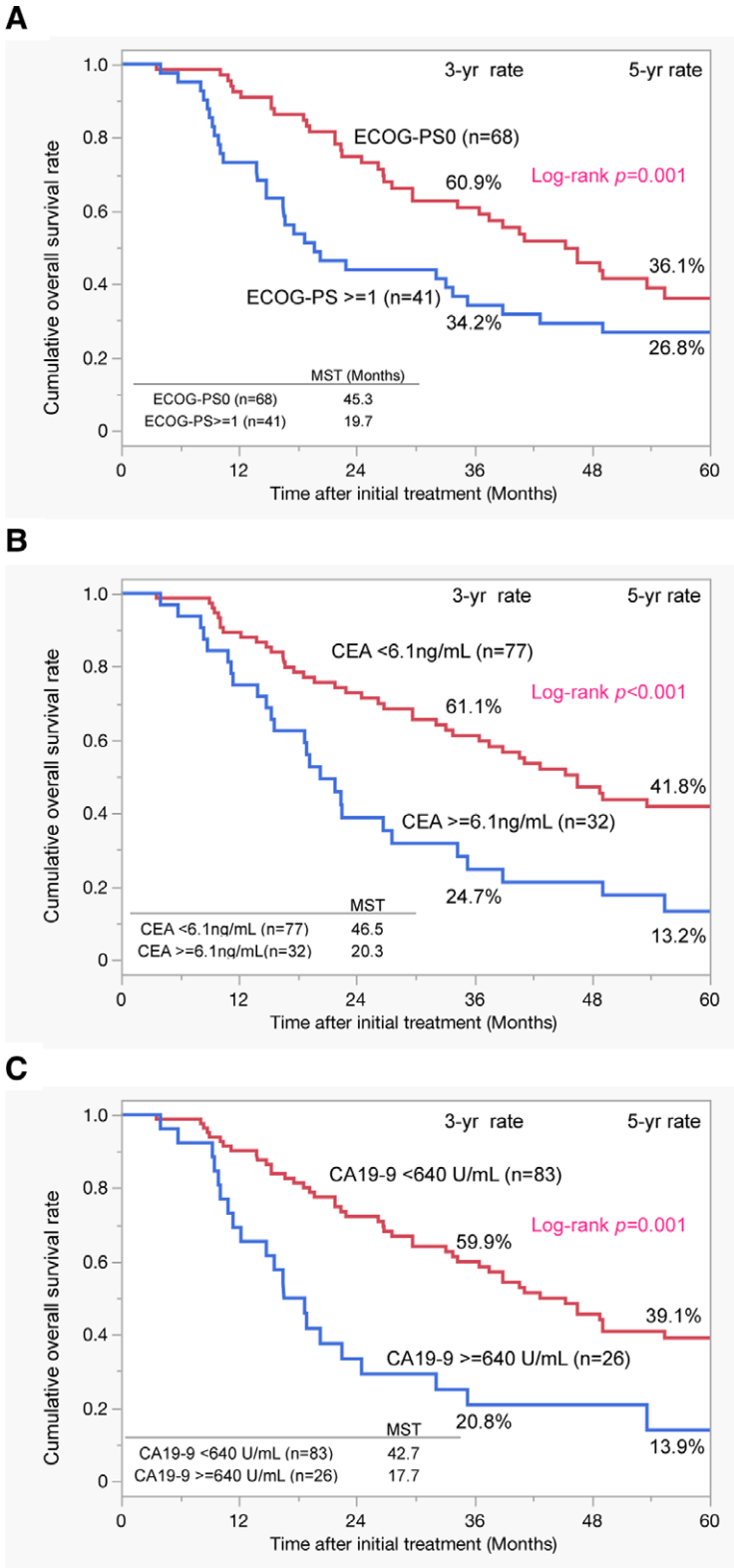

Figure 3. Comparison of the overall survival curves based on the significant pretreatment prognostic factors in the patients with anatomically resectable pancreatic adenocarcinoma who underwent preoperative chemoradiotherapy. (A) ECOG-PS0 (n = 68) vs ECOG-PS≥1 (n = 41); (B) CEA < 6.1 ng/mL (n = 77) vs CEA≥6.1 ng/mL (n = 32); (C) CA19-9 < 640 U/mL (n = 83) vs CA19-9≥640 U/mL (n = 26). CA19-9 = carbohydrate antigen 19-9, CEA = carcinoembryonic antigen, ECOG-PS = Eastern Cooperative Oncology Group performance status.

termed biological BR-PDAC. Given that R-PDAC patients with positive biological factors demonstrated significantly worse OS in comparison to those devoid of such factors in this study, reliance solely on preoperative CRT amay not yield advantages for this patient cohort. Considering that biological BR-PDAC potentially manifests as a systemic disease harboring occult distant metastasis, early systemic treatment, such as neoadjuvant chemotherapy, might offer greater benefits

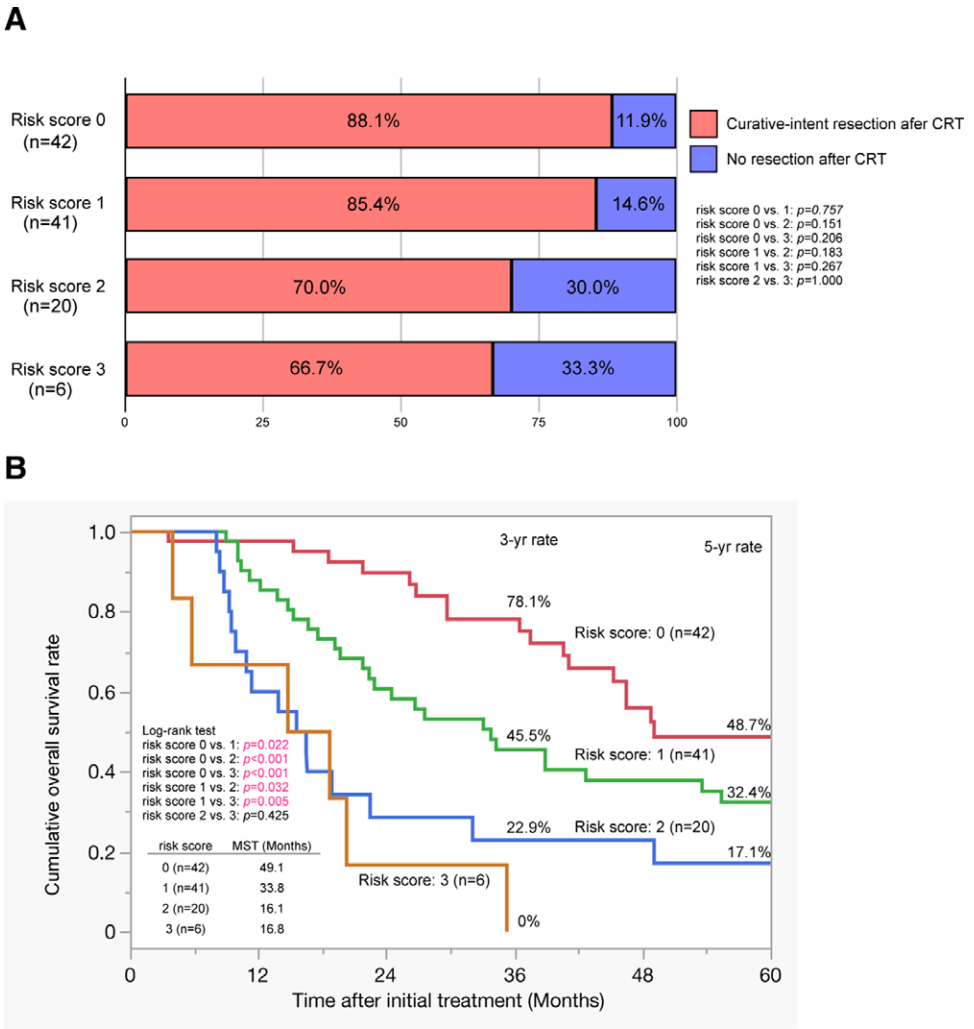

Figure 4. Comparison of the rates of curative-intent resection and overall survival curves after initial treatment based on the baseline risk score in the patients with anatomically resectable pancreatic adenocarcinoma who underwent preoperative chemoradiotherapy. (A) Rates of the curative-intent resection following preoperative chemoradiotherapy based on the risk score. (B) Overall survival curves after initial treatment based on the risk score.

than preoperative CRT for these patients. Early systemic chemotherapy employing the FOLFIRINOX regimen, combined with subsequent preoperative CRT, a strategy commonly termed total neoadjuvant therapy, has been documented to address both occult distant metatstases and positive margin risks, thereby improving outcomes for patients with borderline and locally advanced unresectable PDAC.[36] Thus, total neoadjuvant therapy may represent an optimal treatment strategy aimed at reducing early tumor relapse after surgery, even for patients diagnosed with biological BR-PDAC. Future prospective studies are warranted to develop a more effective neoadjuvant treatment strategy for this high-risk patient cohort.

The patient's conditional factors, as recommended by the IAP criteria for resectability assessment of PDAC prior to surgery, are closely related to the patient's surgical tolerance and prognosis. A preoperative ECOG-PS ≥ 2 has been reported to be independently associated with decreased OS across all tumor stages.[37] According to the IAP criteria, this score is also adopted as the cutoff point to differentiate between resectable and conditional borderline resectable PDAC. This study demonstrated that a pre-CRT ECOG-PS ≥ 1, observed in 41 patients (37.6%), was an independent predictor of poorer OS, with a significantly shorter median OS compared to those with an ECOG-PS of 0 (ECOG-PS ≥ 1 vs 0: 19.7 vs 45.3 months). Additionally, pre-CRT ECOG-PS ≥ 2 was identified as a prognostic factor significantly associated with shorter OS (ECOG-PS 0 or 1 vs ≥2: 37.5 vs 16.5 months, $P = .035$). However, only 5 (4.6%) patients had a pre-CRT ECOG-PS 2, and there were no patients with a score >2 in the present study. Therefore, we adopted an ECOG-PS ≥ 1 as the cutoff point to differentiate between resectable and conditional borderline resectable, indicating that an ECOG-PS of 0 is the optimal eligibility criterion for preoperative CRT in patients with anatomically R-PDAC. Host-related inflammatory/immunonutritional markers before surgery, as measured by indices such as the neutrophil-to-lymphocyte ratio, and PNI, have been reported as objective conditional factors adversely affecting patient prognosis.[38,39] In the present study, pre-CRT PNI was significantly associated with the rate of surgical resection after CRT, although it was not significant prognostic factor for OS. Given that the ECOG-PS is a comparatively subjective factor, further research is necessary to identify more reliable conditional factors for prognostic prediction in patients with anatomically R-PDAC. Nevertheless, our results highlight the importance of improving patient selection based on the ECOG-PS while also emphasizing the need for early prehabilitation to improve patient fitness for R-PDAC patients with the ECOG-PS ≥ 1.

In the present study, a post-CRT serum CA 19-9 level (≥111 U/mL) was found to be an independent prognostic indicator in the resection group following preoperative CRT. Normalization of post-neoadjuvant therapy CA19-9 has been closely associated

Table 3

The univariate and multivariate Cox regression analysis of perioperative factors associated with overall survival after surgery in the pancreatic adenocarcinoma patients who underwent curative-intent resection after preoperative chemoradiotherapy (n = 90).

Variable		No. of cases	MST (months)	Univariate analysis		Multivariate analysis	
				Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Gender	Male	50	37.1	1.07 (0.64–1.78)	.807		
	Female	40	42.4	1			
Age (years)		90	N/A	1.01 (0.98–1.04)	.432		
ECOG-PS	0	59	42.6	1	.176		
	≥1	31	29.6	1.43 (0.86–2.38)			
BMI (kg/m^2)		90	N/A	0.98 (0.93–1.04)	.486		
Laboratory data							
Neutrophil lymphocyte ratio		90	N/A	1.07 (0.85–1.32)	.533		
Prognostic nutrition index		90	N/A	1.00 (0.95–1.04)	.983		
Serum level of CEA before CRT (ng/mL)		90	N/A	1.01 (0.98–1.04)	.473		
Serum level of CEA after CRT (ng/mL)		90	N/A	1.02 (0.97–1.06)	.299		
Reduction rate of CEA (%)		90	N/A	1.00 (0.99–1.01)	.204		
Serum level of CA19-9 (×10^2) before CRT (U/mL)		90	N/A	1.01 (0.99–1.03)	.186		
Serum level of CA19-9 (×10^2) after CRT (U/mL)		90	N/A	1.24 (1.05–1.42)	**.013**	1.32 (1.11–1.54)	**.003**
Chemotherapeutic agent of CRT	GS-CRT	65	43.3	1.22 (0.71–2.09)	.468		
	G-CRT	25	30.3	1			
Imaging parameters							
Tumor location	Head	62	37.9	1	.996		
	Body or tail	28	34.3	1.00 (0.58–1.74)			
Tumor size before CRT (mm)		90	N/A	1.01 (0.99–1.03)	.367		
Tumor size after CRT (mm)		90	N/A	1.02 (0.99–1.04)	.235		
Reduction rate of tumor size (%)		90	N/A	0.75 (0.21–2.96)	.675		
Grade of local invasion before CRT (JPS)	cT1-T2	3	69	1	.491		
	cT3	87	37.1	1.59 (0.39–6.54)			
Bile duct invasion	No	46	42.6	1	.573		
	Yes	44	29.6	1.16 (0.70–1.91)			
Duodenal invasion	No	65	42.6	1	.239		
	Yes	25	35.9	1.41 (0.81–2.46)			
Serial side of the anterior pancreatic tissue invasion	No	26	52.9	1	.180		
	Yes	64	33.6	1.48 (0.82–2.66)			
Retropancreatic tissue invasion	No	30	49.1	1	.620		
	Yes	60	33.6	1.15 (0.67–1.98)			
Portal venous system invasion	No	31	83.2	1	**.025**	1	**.008**
	Yes	59	29.6	1.89 (1.06–3.39)		2.24 (1.19–4.21)	
Extrapancreatic nerve plexus invasion	No	72	37.9	1	.879		
	Yes	18	33.6	0.95 (0.49–1.83)			
Invasion of other organs	No	80	42.4	1	.609		
	Yes	10	33.4	1.22 (0.58–2.59)			
Grade of local invasion before CRT (UICC)	cT1 or T2	80	35.9	1	.736		
	cT3	10	42.4	0.87 (0.40–1.93)			
Lymph nodal metastasis before CRT	No	80	42.4	1	.940		
	Yes	10	29.6	0.97 (0.41–2.26)			
Surgical procedure	PD	66		1	.638		
	DP	24		0.72 (0.17–3.07)			
Operation time (minutes)		90	N/A	1.12 (0.93–1.36)	.229		
Estimated blood loss (ml)		90	N/A	1.03 (0.99–1.07)	.132		
Major postoperative complications*	No	69	42.4	1	.970		
	Yes	21	33.6	0.99 (0.56–1.76)			
Conducting adjuvant chemotherapy	Yes	78	42.4	1	.624		
	No	12	27.6	1.20 (0.59–2.44)			
Histopathological outcomes							
Pathological grade of local invasion (JPS)	pT1 or T2	38	42.4	1	.594		
	pT3	52	27.6	1.15 (0.68–1.94)			
Pathological lymph node metastasis	No	71	43.3	1	**.033**		
	Yes	19	20.7	1.95 (1.09–3.50)			
Pathological bile duct invasion	No	74	42.4	1	.133		
	Yes	16	16.4	1.64 (0.89–3.04)			
Pathological duodenal invasion	No	65	42.4	1	.125		
	Yes	25	19.6	1.55 (0.90–2.69)			
Pathological serial side of the anterior pancreatic tissue invasion	No	73	42.4	1	.752		
	Yes	17	16.8	0.90 (0.45–1.78)			
Pathological retropancreatic tissue invasion	No	66	42.4	1	.581		
	Yes	24	27	1.18 (0.66–2.12)			

(*Continued*)

Table 3

(*Continued*)

Variable		No. of cases	MST (months)	Univariate analysis		Multivariate analysis	
				Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Pathological portal venous system invasion	No	76	42.6	1	.433		
	Yes	14	18.2	1.33 (0.67–2.62)			
Extrapancreatic nerve plexus invasion	No	65	42.4	1	.258		
	Yes	25	19.6	1.69 (0.72–3.94)			
Invasion of other organs	No	65	37.9	1	.638		
	Yes	25	13.2	0.72 (0.17–3.07)			
Lymphatic invasion	No	61	42.4	1	.985		
	Yes	29	23.9	1.01 (0.58–1.75)			
Venous invasion	No	75	37.9	1	.491		
	Yes	15	30.3	0.79 (0.40–1.56)			
Perineural invasion	No	42	49.1	1	.204		
	Yes	48	30.3	1.39 (0.83–2.32)			
Degree of the residual tumor	R0	88	37.9	1	.087		
	R1	2	15.5	4.70 (1.11–20.03)			
Histological response to CRT	Grade 3 or 4	28	52.9	1	.252		
	Grade 1 or 2	62	33.6	1.41 (0.77–2.58)			

BMI = body mass index, CA = carbohydrate antigen, CEA = carcinoembryonic antigen, CRT = chemoradiotherapy, DP = distal pancreatectomy, ECOG-PS = the Eastern Cooperative Oncology Group performance status, G = gemcitabine-based, GS = gemcitabine plus S-1 based, JPS = the eighth edition of the Japan Pancreas Society classification, MST = median survival time, N/A = not applicable, PD = pancreaticoduodenectomy, UICC = the eighth edition of the International Union Against Cancer TNM classification of Malignant Tumors.

Bold values indicate that the *P*-value is statistically significant.

with lower early recurrence and longer OS after surgery in patients localized PDAC treated with neoadjuvant therapy.[40,41] In our previous study, a preoperative serum CA19-9 level was recognized as a significant predictor of early recurrence after surgery, along with reduced survival rates in localized PDAC patients treated with preoperative CRT.[41] Since elevated serum CA19-9 levels following preoperative CRT is considered to reflect systemic expansion of micrometastasis in distant sites, particularly hepatic lesions, sequential systemic chemotherapy with more potent chemotherapeutic agents (such as modified FOLFIRINOX or gemcitabine plus nab-paclitaxel) prior to surgery may be necessary for patients with R-PDAC who do not demonstrate normalization of serum CA 19-9 levels after CRT.

In addition, this study focused on the prognostic significance of anatomical factors based on pretreatment MD-CT imaging in R-PDAC patients undergoing surgical resection after preoperative CRT. The presence of cPV1, defined as tumor contact with PV/SMV <180 degrees, was identified as a critical factor that significantly correlates with decreased OS after surgery. Tumor contact with PV/SMV has been identified as an independent predictor of survival outcomes after elective resection in anatomically R-PDAC patients, suggesting that pancreatic cancer in contact with the PV/SMV may be considered BR-PDAC.[42] In the present study, R0 resection was not achieved in the 2 patients with cPV1 even after CRT, while all patients with cPV0 achieved R0 resection (rate of R0 resection for cPV0 vs cPV1: 100% vs 96.6%). Furthermore, OS after surgery was significantly worse in the patients with R1 resection compared to those with R0 resection in the R-PDAC patients featuring cPV1 (R0 vs R1: 30.3 vs 15.5 months, $P = .049$). These findings underscore the necessity of developing a more robust preoperative CRT protocol to mitigate the risk of positive surgical margins in patients with R-PDAC exhibiting clinical portal invasion.

The primary limitation of our study lies in its retrospective design and single-institution setting. Additionally, a minor limitation is the potential influence of confounding factors after surgery, including the utilization of noncontemporary chemotherapy regimens following recurrence. To better understand the prognostic value of biological and conditional factors for patients with R-PDAC undergoing neoadjuvant therapy, future multi-institutional studies are essential.

In conclusion, biological factors such as pre-CRT serum levels of CEA ≥ 6.1 ng/mL and CA19-9 ≥ 640 U/mL, in conjunction with conditional factors such as ECOG-PS ≥ 1, have been identified as independent prognostic indicators for patients with R-PDAC who undergo preoperative CRT. While preoperative CRT has demonstrated efficacy in cases lacking these risk factors, it is necessary to deliberate on treatment modalities that incorporate meticulous patient selection methodologies, such as staging laparoscopy, and the prompt initiation of potent systemic chemotherapy for individuals presenting with high-risk profiles.

Author contributions

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Methodology: Yasuhiro Murata.
Supervision: Shugo Mizuno.
Writing – original draft: Yasuhiro Murata.
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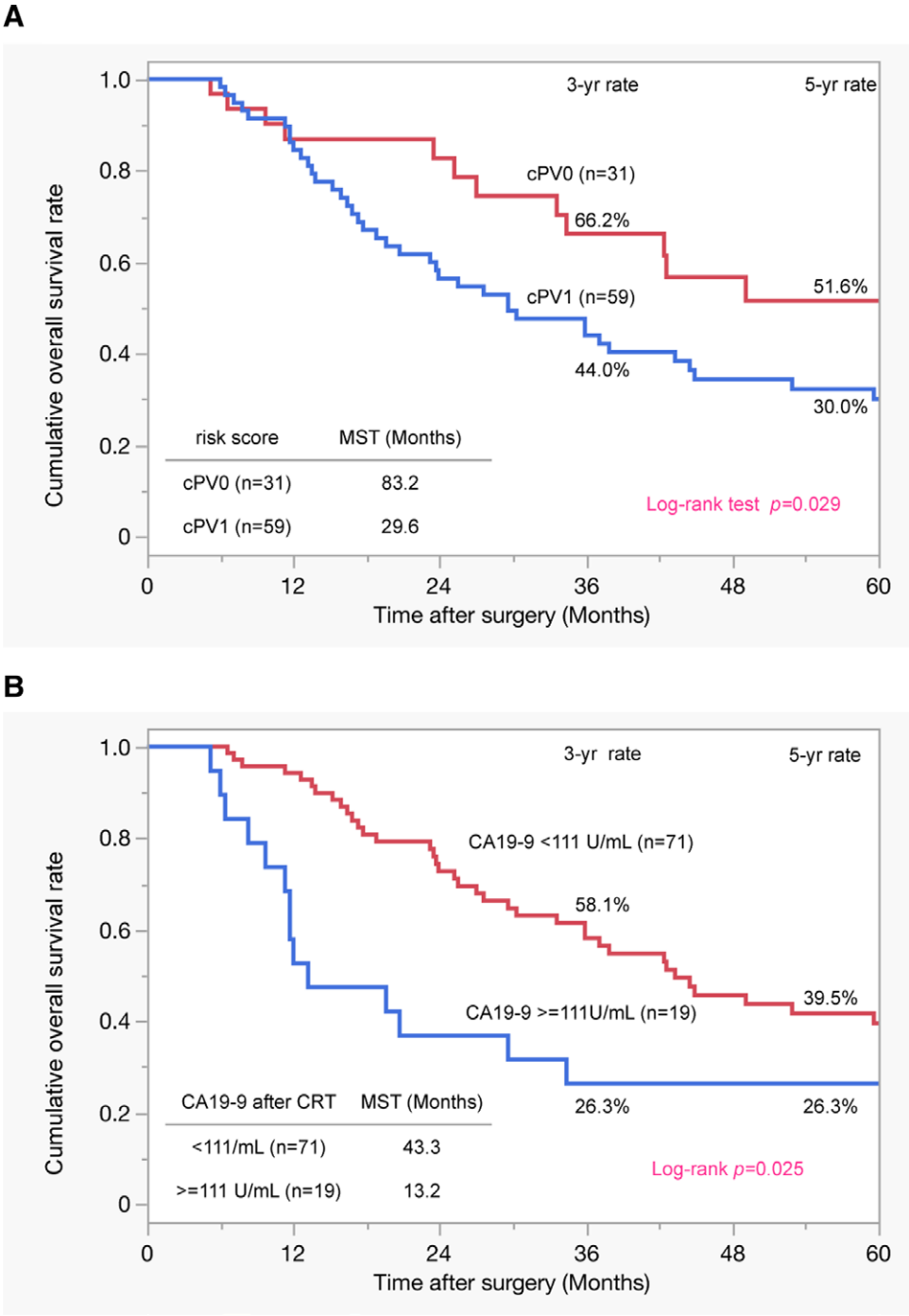

Figure 5. Comparison of the overall survival curves after surgery based on the significant preoperative prognostic factors in the patients with anatomically resectable pancreatic adenocarcinoma who underwent curative-intent resection following preoperative chemoradiotherapy. (A) cPV0 (n = 31) vs cPV1 (n = 59); (B) CA19-9 < 111 U/mL (n = 71) vs CA19-9≥111 U/mL (n = 19). CA19-9 = carbohydrate antigen 19-9, cPV1 = portal venous system invasion on imaging.

References

[1] Kolbeinsson HM, Chandana S, Wright GP, Chung M. Pancreatic cancer: A review of current treatment and novel therapies. J Invest Surg. 2023;36:2129884.

[2] Springfeld C, Ferrone CR, Katz MHG, et al. Neoadjuvant therapy for pancreatic cancer. Nat Rev Clin Oncol. 2023;20:318–37.

[3] Hajibandeh S, Hajibandeh S, Intrator C, et al. Neoadjuvant chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer: Meta-analysis and trial sequential analysis of randomized controlled trials. Ann Hepatobiliary Pancreat Surg. 2023;27:28–39.

[4] Jang JY, Han Y, Lee H, 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.

[5] Versteijne E, van Dam JL, Suker M, et al. Neoadjuvant chemoradiotherapy versus upfront surgery for resectable and borderline resectable pancreatic cancer: long-term results of the dutch randomized PREOPANC trial. J Clin Oncol. 2022;40:1220–30.

[6] Fujii T, Satoi S, Yamada S, et al. Clinical benefits of neoadjuvant chemoradiotherapy for adenocarcinoma of the pancreatic head: an observational study using inverse probability of treatment weighting. J Gastroenterol. 2017;52:81–93.

[7] Sho M, Akahori T, Tanaka T, et al. Optimal indication of neoadjuvant chemoradiotherapy for pancreatic cancer. Langenbecks Arch Surg. 2015;400:477–85.

[8] Yamane K, Anazawa T, Nagai K, et al. Neoadjuvant chemoradiotherapy using moderately hypofractionated intensity-modulated radiotherapy versus upfront surgery for resectable pancreatic cancer: a retrospective cohort study. Ann Surg Oncol. 2025;32:3603–13.
[9] Murata Y, Mizuno S, Kishiwada M, et al. Impact of histological response after neoadjuvant chemoradiotherapy on recurrence-free survival in UICC-T3 pancreatic adenocarcinoma but not in UICC-T4. Pancreas. 2012;41:130–6.
[10] Murata Y, Mizuno S, Kishiwada M, et al. Clinical significance and predictors of complete or near-complete histological response to preoperative chemoradiotherapy in patients with localized pancreatic ductal adenocarcinoma. Pancreatology. 2021;21:1482–90.
[11] Roesel R, Deantonio L, Bernardi L, et al. Neo-adjuvant treatment in primary resectable pancreatic cancer: a systematic review and PRISMA-compliant updated metanalysis of oncological outcomes. Cancers (Basel). 2023;15:4627.
[12] National Comprehensive Cancer Network. Pancreatic adenocarcinoma (Version 2.2024) https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed May 30, 2024.
[13] Conroy T, Pfeiffer P, Vilgrain V, et al. Pancreatic cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023;34:987–1002.
[14] Kato Y, Yamada S, Tashiro M, et al. Biological and conditional factors should be included when defining criteria for resectability for patients with pancreatic cancer. HPB (Oxford). 2019;21:1211–8.
[15] Lee B, Yoon YS, Kang M, et al. Validation of the anatomical and biological definitions of borderline resectable pancreatic cancer according to the 2017 international consensus for survival and recurrence in patients with pancreatic ductal adenocarcinoma undergoing upfront surgery. Ann Surg Oncol. 2023;30:3444–54.
[16] Schouten TJ, van Goor I, Dorland GA, et al. The value of biological and conditional factors for staging of patients with resectable pancreatic cancer undergoing upfront resection: a nationwide analysis. Ann Surg Oncol. 2024;31:4956–65.
[17] Huang B, Geng H, Jin Y, et al. Is it justified to assess the resectability of pancreatic cancer combined with biological and conditional factors? Transl Cancer Res. 2022;11:3458–70.
[18] Isaji S, Mizuno S, Windsor JA, et al. International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017. Pancreatology. 2018;18:2–11.
[19] Japan Pancreas Society. General Rules for the Study of Pancreatic Cancer. 8th ed. Kanehara & Co.
[20] Brierley JD, Gospodarowicz MK, Wittekind C. TNM Classification of Malignant Tumours. John Wiley & Sons; 2017.
[21] Takeuchi T, Mizuno S, Murata Y, et al. Comparative study between gemcitabine-based and gemcitabine plus S1-based preoperative chemoradiotherapy for localized pancreatic ductal adenocarcinoma, with special attention to initially locally advanced unresectable tumor. Pancreas. 2019;48:281–91.
[22] Garcea G, Ladwa N, Neal CP, Metcalfe MS, Dennison AR, Berry DP. Preoperative neutrophil-to-lymphocyte ratio (NLR) is associated with reduced disease-free survival following curative resection of pancreatic adenocarcinoma. World J Surg. 2011;35:868–72.
[23] Onodera T, Goseki N, Kosaki G. Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. Nihon Geka Gakkai Zasshi. 1984;85:1001–5.
[24] Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649–55.
[25] Mizuno S, Isaji S, Tanemura A, et al. Anterior approach to the superior mesenteric artery by using nerve plexus hanging maneuver for borderline resectable pancreatic head carcinoma. J Gastrointest Surg. 2014;18:1209–15.
[26] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205–13.
[27] Distler M, Pilarsky E, Kersting S, Grützmann R. Preoperative CEA and CA 19-9 are prognostic markers for survival after curative resection for ductal adenocarcinoma of the pancreas - a retrospective tumor marker prognostic study. Int J Surg. 2013;11:1067–72.
[28] Zhou G, Liu X, Wang X, et al. Combination of preoperative CEA and CA19-9 improves prediction outcomes in patients with resectable pancreatic adenocarcinoma: results from a large follow-up cohort. Onco Targets Ther. 2017;10:1199–206.
[29] Fujioka S, Misawa T, Okamoto T, et al. Preoperative serum carcinoembryonic antigen and carbohydrate antigen 19-9 levels for the evaluation of curability and resectability in patients with pancreatic adenocarcinoma. J Hepatobiliary Pancreat Surg. 2007;14:539–44.
[30] Kim YC, Kim HJ, Park JH, et al. Can preoperative CA19-9 and CEA levels predict the resectability of patients with pancreatic adenocarcinoma? J Gastroenterol Hepatol. 2009;24:1869–75.
[31] Yasue M, Sakamoto J, Teramukai S, et al. Prognostic values of preoperative and postoperative CEA and CA19.9 levels in pancreatic cancer. Pancreas. 1994;9:735–40.
[32] van Manen L, Groen JV, Putter H, et al. Elevated CEA and CA19-9 serum levels independently predict advanced pancreatic cancer at diagnosis. Biomarkers. 2020;25:186–93.
[33] Brockhaus M, Magnani JL, Blaszczyk M, et al. Monoclonal antibodies directed against the human Leb blood group antigen. J Biol Chem. 1981;256:13223–5.
[34] Tempero MA, Uchida E, Takasaki H, Burnett DA, Steplewski Z, Pour PM. Relationship of carbohydrate antigen 19-9 and Lewis antigens in pancreatic cancer. Cancer Res. 1987;47:5501–3.
[35] Luo G, Liu C, Guo M, et al. Potential biomarkers in lewis negative patients with pancreatic cancer. Ann Surg. 2017;265:800–5.
[36] Truty MJ, Kendrick ML, Nagorney DM, et al. Factors predicting response, perioperative outcomes, and survival following total neoadjuvant therapy for borderline/locally advanced pancreatic cancer. Ann Surg. 2021;273:341–9.
[37] Tas F, Sen F, Odabas H, Kılıc L, Keskın S, Yıldız I. Performance status of patients is the major prognostic factor at all stages of pancreatic cancer. Int J Clin Oncol. 2013;18:839–46.
[38] Ichikawa K, Mizuno S, Hayasaki A, et al. Prognostic nutritional index after chemoradiotherapy was the strongest prognostic predictor among biological and conditional factors in localized pancreatic ductal adenocarcinoma patients. Cancers (Basel). 2019;11:514.
[39] Imrie CW. Host systemic inflammatory response influences outcome in pancreatic cancer. Pancreatology. 2015;15:327–30.
[40] Aoki S, Motoi F, Murakami Y, et al. Decreased serum carbohydrate antigen 19-9 levels after neoadjuvant therapy predict a better prognosis for patients with pancreatic adenocarcinoma: a multicenter case-control study of 240 patients. BMC Cancer. 2019;19:252.
[41] Murata Y, Ogura T, Hayasaki A, et al. Predictive risk factors for early recurrence in patients with localized pancreatic ductal adenocarcinoma who underwent curative-intent resection after preoperative chemoradiotherapy. PLoS One. 2022;17:e0264573.
[42] Shirai Y, Onda S, Tanji Y, et al. Superior mesenteric vein/portal vein contact in preoperative imaging indicates biological malignancy in anatomically resectable pancreatic cancer. Surg Oncol. 2023;51:101998.