Pretherapeutic factors predicting conversion surgery in unresectable pancreatic ductal adenocarcinoma: A retrospective study

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Abstract. Recently, conversion surgery (CS) has been reported to improve the prognosis in patients with unresectable pancreatic ductal adenocarcinoma (UR-PDAC) with a favorable response to intense chemotherapy or chemoradiotherapy. However, few pretherapeutic parameters predict the attainability of CS in patients with UR-PDAC. The present study aimed to explore the pretherapeutic predictors for the attainability of CS in patients with UR-PDAC. The present study retrospectively evaluated 130 patients with UR-PDAC treated at Gifu University Hospital (Gifu, Japan) from January 2015 to December 2021. Survival analysis was performed using the Simon and Makuch-modified Kaplan-Meier method. The hazard ratio (HR) was estimated using a time-varying Cox regression model. The association between each predictor and CS was evaluated using the univariate analysis and age-adjusted Fine-Gray sub-distribution hazard model. The bootstrap bias-corrected area under the receiver operating characteristic curve analysis for predicting CS was used to assess the cut-off values for each predictor. The cumulative incidence rate was calculated with CS as the outcome when divided into two groups based on the cut-off value of each pretherapeutic predictor. Among the 130 patients included in the analysis, only 14 (11%) underwent CS. The median survival time was significantly longer in patients who underwent CS compared with patients without CS (56.3 vs. 14.1 months; P<0.001). The age-adjusted Fine-Gray sub-distribution hazard regression showed that the total protein (TP) [HR 2.81, 95% confidence interval (CI) 1.19-6.65; P=0.018], neutrophil-to-lymphocyte ratio (NLR) (HR 0.53, 95% CI 0.31-0.90; P=0.020), and lymphocyte-to-monocyte ratio (LMR) (HR 1.28, 95% CI 1.07-1.53; P=0.006) were significantly associated with CS. Moreover, TP ≥6.8, NLR <2.84 and LMR ≥3.87 were associated with a higher cumulative incidence of CS. In conclusion, pretherapeutic TP, NLR and LMR are clinically feasible biomarkers for predicting the attainability of CS in patients with UR-PDAC.

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Introduction

Globally, pancreatic ductal adenocarcinoma (PDAC) is the seventh leading cause of cancer-related deaths among men and women (1). Unfortunately, 80-85% of patients present with unresectable PDAC (UR-PDAC) [unresectable locally advanced cancer (UR-LA) or unresectable cancer with distant metastasis (UR-M)] and have a poor prognosis (2). However, the recent implementation of intense regimens, such as FOLFIRINOX (3) and gemcitabine + nab-paclitaxel (GnP) (4), has provided better clinical response rates, and the number of patients who can expect long-term survival is increasing. Moreover, the number of long-term survival cases after such intense chemotherapy or chemoradiotherapy followed by conversion surgery (CS) has increased in recent years (5). Currently, the National Comprehensive Cancer Network Guidelines (6) suggest that CS is an option for patients with UR-LA if resectable after a successful multidisciplinary treatment. Conversely, some reports (7,8) have shown that CS may prolong the prognosis of UR-M patients, but the actual benefit of CS in patients with UR-M remains controversial.

Previous studies (9-16) have reported several prognostic factors associated with the survival time of CS or the recurrence after CS in patients with UR-PDAC. However, few pretherapeutic parameters have been reported to predict the attainability of CS in patients with UR-PDAC. Therefore, this study aimed to explore the pretherapeutic factors predicting the attainability of CS in patients with UR-PDAC. In this study, we focused on examining predictors for CS rather than

the overall survival (OS). The reason was that the association of intermediate treatment, including CS, from the start of treatment to death is too strong to ensure that baseline factors are accurate in their prediction for OS. Previous reports have shown that CS is beneficial for survival in patients with UR-PDAC. Therefore, by examining factors that predict the attainability of CS, we considered that these factors could influence the prognosis of patients with UR-PDAC.

Materials and methods

Study design. This retrospective study included patients treated at a single tertiary care center (Gifu University Hospital, Gifu, Japan) from January 2015 to December 2021, who were radiologically diagnosed with UR-PDAC according to the Classification of Pancreatic Cancer by the Japan Pancreas Society (4th English Edition) (17). We excluded patients who were lost to follow-up, underwent only the best supportive care, were not diagnosed with PDAC, and patients with UR-PDAC and other malignant tumors (Fig. 1). The participants provided informed consent by an opt-out option before enrollment in the study. The study was conducted following the human and ethical principles of the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board of the Gifu University Hospital (approval number: 2022-285).

Measures. The demographic and clinical variables included age, sex, body mass index (BMI), tumor location, tumor size, carbohydrate antigen 19-9 (CA19-9), total protein (TP), albumin, C-reactive protein, hemoglobin, neutrophil, lymphocyte, monocyte, prognostic nutritional index (18), modified Glasgow prognostic score (19), neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio. These variables were measured before the initial treatment. The tumor size was measured using pretherapeutic multidetector CT. Response Evaluation Criteria in Solid Tumors version 1.1 (20) was used for radiologic tumor response evaluation.

Outcome. In this study, the primary outcome was CS, defined as surgical resection following chemotherapy or chemoradiotherapy for patients initially diagnosed with UR-PDAC. At our institute, tumor resectability is determined case-by-case through discussions among surgeons, physicians, and radiologists. We considered surgical exploration if the eligibility criteria met after chemotherapy or chemoradiotherapy were as follows: i) Decrease or normalization of tumor markers; ii) Clinical response (stable disease/partial response/complete response) on multidetector CT; iii) Technically resectable on imaging; iv) Decreased or absent accumulation of the primary tumor on fluorine-18-fluorodeoxyglucose positron emission tomography (FGD-PET); v) In cases of UR-M, metastases shrank or disappeared on MDCT with no accumulation on FGD-PET; vi) No appearance of new metastatic sites; and vii) Fine performance status (0-1).

Statistical analysis. The patient characteristics are presented as frequencies and percentages for categorical variables, and as medians with interquartile ranges or means with standard deviations for continuous variables. When comparing the OS between patients with CS and non-CS, we treated CS as a time-varying covariate to avoid immortal time bias. The survival rate was estimated using the Simon and Makuch modified Kaplan-Meier method (21,22). The hazard ratio (HR) was estimated using a time-varying Cox regression model. The association between each pretherapeutic predictor and CS was evaluated using the univariable and age-adjusted Fine-Gray sub-distribution hazard model, considering death and disease progression as competing risks. No correction for the multiplicity of statistically significant tests was performed as the analysis was exploratory. The bootstrap bias-corrected area under the receiver operating characteristic curve (AUC-ROC) was reported as a measure of the predictive performance of the pretherapeutic predictors. In total, 10,000 bootstrap samples were generated, and the AUCs obtained from each ROC were averaged to calculate the bootstrap AUC-ROC. The cut-off values for predicting the CS obtained from ROC were determined based on the Youden Index. An appropriate cut-off value for predicting CS was calculated by averaging the thresholds obtained from each ROC from the bootstrap sample. The cumulative incidence rate was calculated with CS as the outcome when divided into two groups based on the cut-off value of each pretherapeutic predictor. Fisher's exact test was performed for categorical variables. The Mann-Whitney U test was applied for the comparison of continuous variables. All P-values are two-sided, with the significance level set at $P<0.05$. All analyses, including only data for patients with assessed pretherapeutic predictor variables, were performed using R 4.2.2 software (The R Project for Statistical Computing).

Results

Patient characteristics. This study retrospectively analyzed a total of 130 consecutive patients with UR-PDAC who were treated at our institute. Table I summarizes the patients' characteristics; 66 patients (51%) were men, with a median age of 69 years. We used multidetector CT or laparotomy to diagnose 36 patients (28%) with UR-PDAC and 94 patients (72%) with UR-M. In patients with UR-LA, the median size of the main lesion was 3.7 cm at the initial diagnosis, and the median CA19-9 level before the initial treatment was 746 U/ml. The most frequently used first-line treatment regimen was modified FOLFIRINOX (50%), followed by GnP (31%). In patients with UR-M, the median size of the main lesion was 3.4 cm at the initial diagnosis, and the median CA19-9 level before the initial treatment was 888 U/ml. The most frequently used first-line treatment regimen was modified FOLFIRINOX (62%), followed by GnP (30%).

Clinical characteristics and outcome of conversion surgery. During this study, CS was performed for six patients with UR-LA and eight patients with UR-M (Table II). The first-line treatment regimens were modified FOLFIRINOX for 12 cases and GnP for two cases. The median duration of first-line treatment was 7.4 months. Treatment responses included stable disease in four cases, partial response in nine, and complete response in one. In all cases, the preoperative CA19-9 was lower than before first-line treatment, with unresectable factors disappearing or shrinking afterwards.

Table I. Patients' characteristics.

Variable	Total (n=130)	UR-LA (n=36)	UR-M (n=94)
Male sex, n (%)	66 (51)	20 (56)	46 (49)
Median age, years (IQR)	69 (62-74)	71 (68-76)	68 (62-73)
Tumor location Ph, n (%)	56 (43)	23 (64)	33 (35)
Median tumor size at diagnosis, cm (IQR)	3.5 (2.8-4.4)	3.7 (2.9-4.1)	3.4 (2.7-4.4)
Median CA19-9, U/ml (IQR)	877 (140-5,375)	746 (169-2,426)	888 (124-7,793)
Mean TP, g/dl (SD)	6.5 (0.6)	6.6 (0.5)	6.5 (0.6)
Median albumin, g/dl (IQR)	3.8 (3.5-4.1)	4.0 (3.5-4.3)	3.8 (3.5-4.0)
Median total cholesterol, mg/dl (IQR)	177 (154-208)	172 (139-204)	178 (158-211)
Median LDH, IU/l (IQR)	186 (159-230)	179 (159-220)	189 (160-240)
Median CRP, mg/dl (IQR)	0.45 (0.14-1.56)	0.38 (0.10-1.12)	0.47 (0.15-2.31)
Mean hemoglobin, g/dl (SD)	12.1 (1.3)	12.0 (1.4)	12.1 (1.3)
Median neutrophils, cells/μl (IQR)	4,200 (2,961-5,333)	3,415 (2,773-4,975)	4,280 (3,268-5,445)
Median lymphocytes, cells/μl (IQR)	1,266 (1,000-1,528)	1,369 (1,151-1,570)	1,210 (972-1,508)
Median monocytes, cells/μl (IQR)	401 (308-513)	411 (318-532)	399 (298-512)
Median platelets, x10^4/μl (IQR)	23.1 (18.0-29.2)	20.0 (17.3-27.8)	23.4 (18.5-29.2)
Median PNI IQR	38.9 (35.7-41.8)	40.2 (35.7-43.8)	38.9 (35.7-41.3)
Modified GPS, 0/1/2	60/52/18	17/16/3	43/36/15
Median NLR (IQR)	3.10 (2.25-4.38)	2.65 (1.95-3.66)	3.42 (2.55-4.70)
Median LMR (IQR)	3.16 (2.33-4.17)	3.25 (2.37-4.08)	3.15 (2.26-4.23)
Median PLR (IQR)	178 (133-263)	156 (123-223)	189 (144-274)
First-line treatment			
mFFX/GnP/GEM/S-1/Other	76/39/11/2/2	18/11/4/1/2	58/28/7/1/0
Best response based on imaging studies			
CR/PR/SD/PD/unknown	1/45/53/29/2	0/14/14/7/1	1/31/39/22/1

UR-LA, unresectable locally advanced; UR-M, unresectable metastatic; IQR, interquartile range; Ph, pancreatic head; CA19-9, carbohydrate antigen 19-9; TP, total protein; SD, standard deviation; LDH, lactate dehydrogenase; CRP, C-reactive protein; PNI, prognostic nutritional index; GPS, Glasgow prognostic score; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio; mFFX, modified FOLFIRINOX; GnP, gemcitabine + nab-paclitaxel; GEM, gemcitabine; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

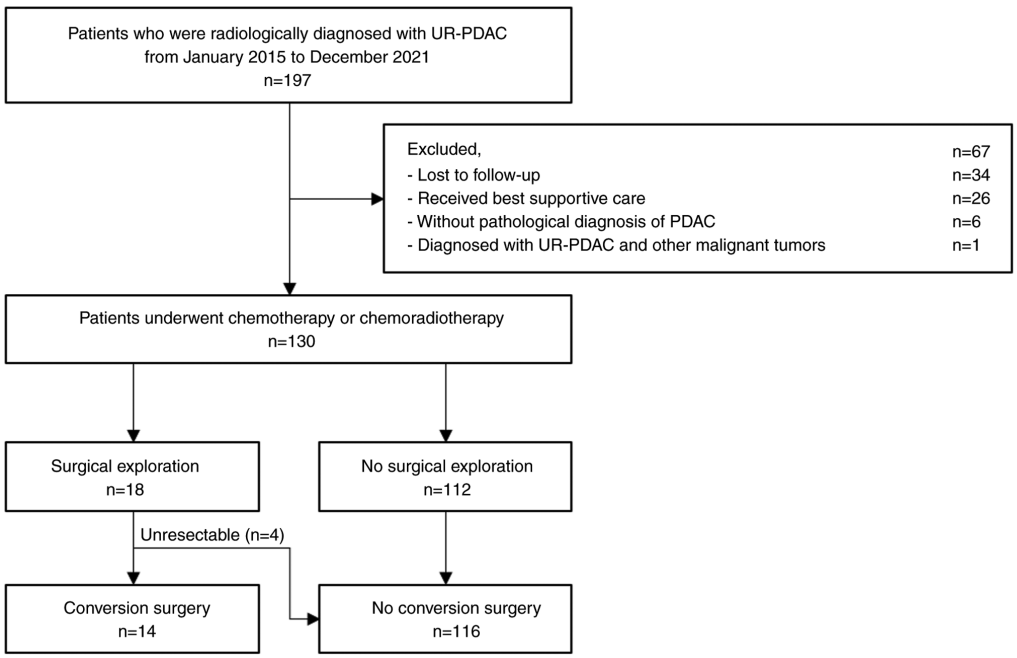

Figure 1. Flow chart of patient selection. UR-PDAC, unresectable pancreatic ductal adenocarcinoma; PDAC, pancreatic ductal adenocarcinoma.

Table II. Clinical characteristics and outcome of 14 patients who underwent conversion surgery.

No.	Age, years	Sex	Tumor location	UR status (UR factor)	First-line treatment	Duration, months	RECIST	CA19-9 before/after treatment, U/ml	UR factor after treatment	Surgery	R	Evans grade	Post-operative therapy	Recurrence site	Time to recurrence from CS, months	Prognosis, months[a]
1	72	M	Ph	LA (SMV)	mFFX	8.0	PR	1,462/43	Disappeared	PD	R0	IIb	S-1	Remnant pancreas	20	Dead (66/58)
2	73	M	Ph	LA (CHA, PHA)	mFFX	3.7	SD	354/89	Disappeared	DP-CAR	R0	IIa	None	None		Dead (45/41)
3	58	M	Ph	LA (Ao)	mFFX	6.8	PR	171/12	Shrank	PD	R0	IIb	S-1	Local	29	Alive (52/45)
4	56	F	Ph	LA (SMA, SMV)	mFFX	13.4	PR	5,451/116	Shrank	PD+PVR	R0	IV	None	Lung	14	Alive (56/43)
5	70	F	Ph	LA (CHA, PHA)	GnP	9.8	PR	228/20	Shrank	PD+ PVR+ HAR	R0	IIb	S-1	Remnant pancreas	18	Alive (50/40)
6	57	M	Ph	LA (Ao)	mFFX	6.8	PR	10,890/26	Disappeared	PD	R0	IIb	S-1	None		Alive (22/15)
7	72	M	Pt	M (eLN)	mFFX	2.8	SD	24,469/3,333	Shrank	DP	R1	IIa	mFFX	LN	50	Dead (67/64)
8	63	M	Pb	M (Per)	mFFX	4.5	SD	481/370	Disappeared	DP	R0	IIa	S-1	Lung, LN	24	Dead (35/31)
9	59	M	Pb	M (Per)	mFFX	24.0	PR	250/17	Disappeared	DP	R0	IIa	mFFX	PER	19	Dead (57/33)
10	63	F	Pb	M (Liver-Multi, Bone-Multi)	mFFX	23.3	PR	4,379/81	Disappeared	DP	R0	IIb	S-1	None		Alive (69/46)
11	79	M	Pht	M (Per)	GnP	4.6	SD	159/52	Disappeared	TP	R1	IIa	S-1	Liver	5	Dead (20/16)
12	61	F	Ph	M (Liver-Multi)	mFFX	26.0	CR	10,424/36	Disappeared	PD+Hep	R0	IV	None	None		Alive (63/37)
13	62	M	Pb	M (eLN)	mFFX	9.1	PR	96/48	Shrank	DP	R0	IIb	mFFX	None		Alive (24/15)
14	59	M	Pt	M (eLN)	mFFX	5.5	PR	13/12	Shrank	DP	R0	IV	mFFX	None		Alive (24/18)

[a]Months after initial treatment/after conversion surgery. Ph, pancreatic head; Pt, pancreatic tail; Pb, pancreatic body; Pht, pancreatic head and tail; UR, unresectable; LA, locally advanced lesion; SMV, superior mesenteric vein; CHA, common hepatic artery; PHA, proper hepatic artery; Ao, aorta; SMA, superior mesenteric artery; M, metastatic lesion; eLN, extraregional lymph node; Per, peritoneum; Multi, multiple metastatic sites; mFFX, modified FOLFIRINOX; GnP, gemcitabine + nab-paclitaxel; RECIST, response evaluation criteria in solid tumors; PR, partial response; SD, stable disease; CR, complete response; PD, pancreaticoduodenectomy; DP-CAR, distal pancreatectomy with en bloc celiac axis resection; PVR, portal vein resection; HAR, hepatic artery resection; DP, distal pancreatectomy; TP, total pancreatectomy; Hep, hepatectomy; R, residual tumor; R0, no microscopic residual on resected margin; R1, microscopic residual on resected margin; LN, lymph node; CS, conversion surgery; OS, overall survival.

Table III. Pretherapeutic predictors for the attainability of conversion surgery (univariate analysis and age-adjusted Fine-Gray sub-distribution hazard regression).

	Univariate analysis		Age-adjusted	
Variable	HR (95% CI)	P-value	HR (95% CI)	P-value
CA19-9	1.00 (1.00-1.00)	0.260	1.00 (1.00-1.00)	0.270
TP	2.59 (1.09-6.15)	0.031	2.81 (1.19-6.65)	0.018
Albumin	5.22 (0.90-30.3)	0.066	4.65 (0.75-28.8)	0.099
Total cholesterol	1.00 (0.99-1.01)	0.910	1.00 (0.99-1.01)	0.820
LDH	0.99 (0.99-1.00)	0.130	0.99 (0.99-1.00)	0.079
CRP	0.72 (0.49-1.06)	0.097	0.75 (0.54-1.04)	0.085
Hemoglobin	1.09 (0.81-1.46)	0.580	1.09 (0.80-1.47)	0.600
Neutrophil	1.00 (1.00-1.00)	0.027	1.00 (1.00-1.00)	0.029
Lymphocyte	1.00 (1.00-1.00)	0.030	1.00 (1.00-1.00)	0.017
Monocyte	1.00 (0.99-1.00)	0.310	1.00 (1.00-1.00)	0.320
Platelet	1.01 (1.00-1.01)	<0.001	1.01 (1.00-1.01)	<0.001
PNI	1.18 (1.00-1.40)	0.055	1.17 (0.98-1.39)	0.081
Modified GPS	0.68 (0.31-1.49)	0.340	0.75 (0.35-1.59)	0.450
NLR	0.53 (0.31-0.91)	0.020	0.53 (0.31-0.90)	0.020
LMR	1.27 (1.07-1.51)	0.007	1.28 (1.07-1.53)	0.006
PLR	1.00 (1.00-1.00)	0.024	1.00 (1.00-1.00)	0.022

CA19-9, carbohydrate antigen 19-9; TP, total protein; LDH, lactate dehydrogenase; CRP, C-reactive protein; PNI, prognostic nutritional index; GPS, Glasgow prognostic score; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio.

We performed pancreaticoduodenectomy for six patients, distal pancreatectomy (DP) for six, DP with en-bloc celiac axis resection for one, and total pancreatectomy for one patient. One patient initially presenting with liver metastases underwent partial hepatectomy. There were no residual cancer cells in the resected liver. R0 (no residual tumor) resection was achieved in 12 patients (86%), and 11 received postoperative chemotherapy. Recurrence was confirmed in eight patients (57%). The median OS in patients who underwent CS was estimated as 56.3 months and was significantly longer than that in all patients without CS (median OS of 14.1 months, HR 0.08, 95% CI 0.03-0.21; P<0.001) (Fig. 2A). In patients with UR-LA and UR-M, the CS group had significantly longer OS than the non-CS group (UR-LA: 64.9 vs. 12.3 months; HR 0.05, 95% CI 0.01-0.28; P=0.001 and UR-M: 56.3 vs. 14.2 months; HR 0.12, 95% CI 0.03-0.40; P=0.001, respectively) (Fig. 2B). The median OS from CS was estimated as 44.4 months in patients with UR-LA and 62.8 months in patients with UR-M.

Association between pretherapeutic parameters and the attainability of CS. Age-adjusted Fine-Gray regression showed that TP (HR 2.81; P=0.018), NLR (HR 0.53; P=0.020), and LMR (HR 1.28; P=0.006) were significant pretherapeutic markers predicting the attainability of CS (Table III). The cut-off value of each marker for CS based on the ROC curve is presented in Table IV. The optimal cut-off values for useful parameters using the bootstrap ROC curve were 6.8 (AUC=0.70), 2.84 (AUC=0.74), and 3.87 (AUC=0.72) for

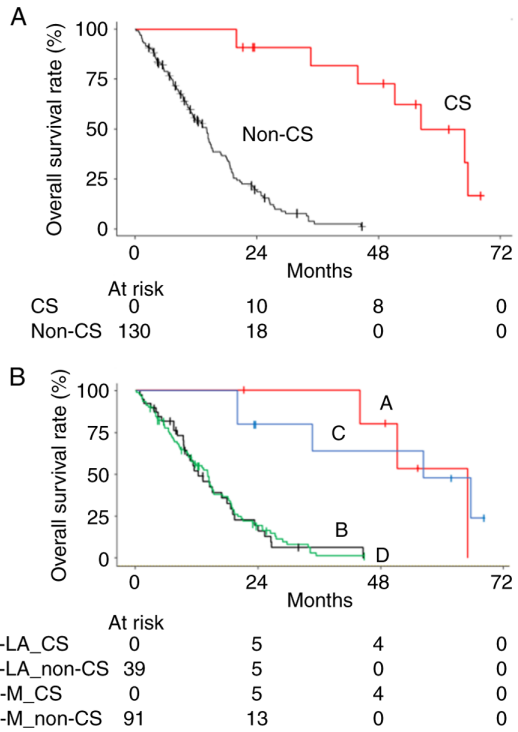

Figure 2. Simon and Makuch modified Kaplan-Meier curves. (A) OS between patients with unresectable pancreatic adenocarcinoma who underwent CS and those who did not undergo CS. (B) OS for patients who underwent CS with UR-LA (UR-LA_CS), who did not undergo CS with UR-LA (UR-LA_non-CS), who underwent CS with UR-M (UR-M_CS), and who did not undergo CS with UR-M (UR-M_non-CS). OS, overall survival; CS, conversion surgery; UR-LA, unresectable locally advanced cancer; UR-M, unresectable cancer with distant metastasis.

Table IV. Cutoff value and predictive performance for each marker based on ROC curves.

	Usual method					Bootstrap method			
Variable	AUC	95% CI	Sensitivity	Specificity	Cutoff value	AUC	Sensitivity	Specificity	Cutoff value
TP	0.70	0.54-0.86	0.86	0.50	6.6	0.70	0.76	0.66	6.8
NLR	0.74	0.61-0.87	0.86	0.55	3.08	0.74	0.83	0.65	2.84
LMR	0.72	0.59-0.86	0.64	0.77	4.12	0.72	0.77	0.70	3.87

AUC, area under the ROC curve; HR, hazard ratio; CI, confidence interval; TP, total protein; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio.

Table V. Summary of the course of treatment for each parameter.

Variable	TP <6.8 (n=85)	TP ≥6.8 (n=45)	P-value	NLR <2.84 (n=51)	NLR ≥2.84 (n=79)	P-value	LMR <3.87 (n=89)	LMR ≥3.87 (n=41)	P-value
First-line treatment			0.335			0.359			0.286
mFFX/GnP/S-1/GEM/Other	51/24/0/8/2	25/15/2/3/0		30/16/2/3/0	46/23/0/8/2		53/24/1/10/1	23/15/1/1/1	
≥Grade 3 toxicity adverse event, n (%)	75 (88.2)	37 (82.2)	0.498	44 (86.3)	68 (86.1)	0.999	77 (86.5)	35 (85.4)	0.999
Median overall treatment time, months (IQR)	11.2 (4.8-18.3)	10.8 (3.7-20.0)	0.854	13.3 (7.8-23.0)	8.5 (2.8-17.5)	0.006	8.5 (3.2-16.8)	15.8 (8.7-28.5)	<0.001

TP, total protein; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; mFFX, modified FOLFIRINOX; GnP, gemcitabine + nab-paclitaxel; GEM, gemcitabine; IQR, interquartile range.

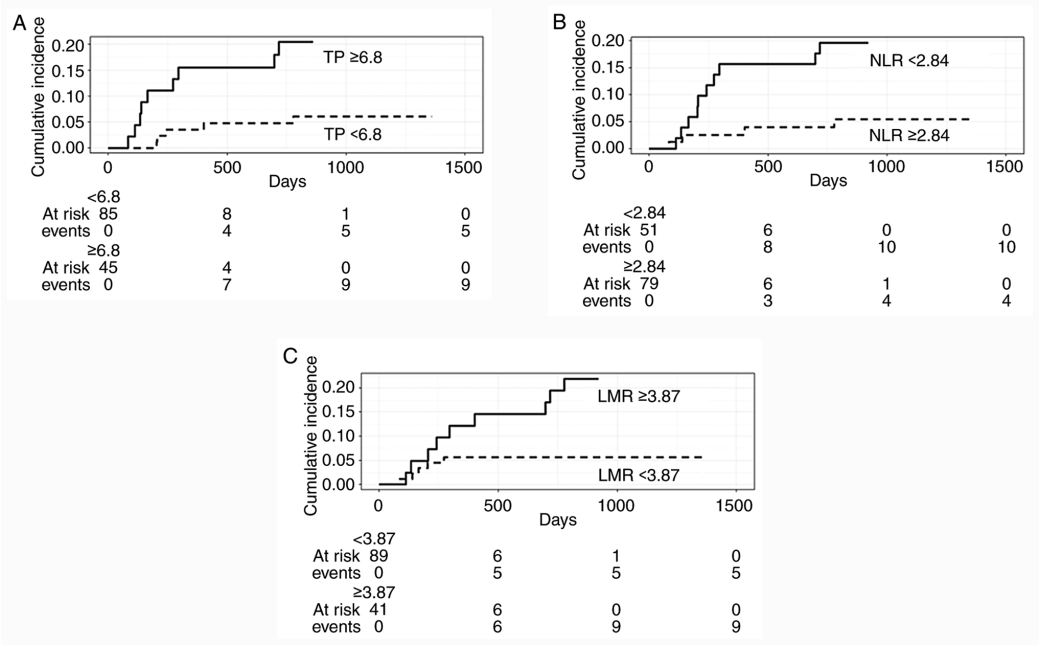

Figure 3. Cumulative incidence curve of conversion surgery, stratified by (A) total protein, (B) NLR and (C) LMR. NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio.

TP, NLR, and LMR, respectively. Fig. 3 shows the cumulative incidence of these parameters with each cut-off value using the bootstrap ROC curve. The percentage of patients who underwent CS was higher in the TP ≥6.8 (20%, 9/45), NLR <2.84 (20%, 10/51), and LMR ≥3.87 (22%, 9/41) groups compared with the TP <6.8 (6%, 5/85), NLR ≥2.84 (5%, 4/79), and LMR <3.87 (6%, 5/89) groups, respectively. In patients who underwent CS, the changes in TP, NLR, and LMR before and after first-line treatment were 0.6 (95% CI 0.28-0.86), 0.27 (95% CI-0.55-1.08), and 1.27 (95% CI 0.28-2.25), respectively. In patients who did not undergo CS, the changes in TP, NLR, and LMR between and after first-line treatment were 0.3 (95% CI 0.20-0.40), 0.31 (95% CI-0.54-1.16), and 0.25 (95% CI-0.34-0.83), respectively.

Differences in the course of treatment for each parameter. There was no difference in the first-line treatment regimens or treatment-related adverse events for each parameter (Table V). However, patients with NLR <2.84 and LMR ≥3.87 had significantly longer overall treatment time than those with NLR ≥2.84 (P=0.006) and LMR <3.87 (P<0.001), respectively.

Discussion

In this study, the median OS was significantly longer in patients who underwent CS than in all patients without CS. The study also indicated that patients who underwent CS with UR-LA and UR-M had a significant difference in the median OS compared to patients who did not undergo CS. Therefore, this study demonstrated that CS significantly impacted the prognosis of patients with UR-PDAC. We examined the factors that predict the attainability of CS based on the pretherapeutic parameters in patients with UR-PDAC. As a result, TP ≥6.8, NLR <2.84, and LMR ≥3.87 were associated with a higher cumulative incidence of CS.

The three parameters evaluated in this study were associated with nutritional status and cancer-related inflammation. TP is a predictor of postoperative prognosis in lung cancer (23) and retroperitoneal sarcoma (24). TP decreases with the progression of the disease because of malnutritional and inflammatory status, cachexia, and increased intracellular catabolism by cancer cells. Furthermore, hypoproteinemia is associated with decreased tolerance to chemotherapy (25).

NLR is a leading inflammation-related marker in various cancers and is valuable for predicting the prognosis of UR-PDAC (26-28). LMR also predicts poor outcomes in patients with UR-PDAC undergoing chemotherapy (29). Moreover, both NLR and LMR are associated with nutritional status (30,31). The features of cancer-related inflammation include the following: malignant cell proliferation and survival, inflammatory cell infiltration and production of inflammatory mediators in tumor tissues, tissue remodeling, promotion of tissue repair and angiogenesis, disruption of adaptive immune responses, and altered responses to chemotherapeutic agents (32). Therefore, TP, NLR, and LMR are important indicators of nutritional status, cancer progression, and tolerability of chemotherapy.

This study demonstrated that three pretherapeutic markers reflecting nutritional and inflammatory status were associated with the attainability of CS in patients with UR-PDAC during treatment. Moreover, patients with low NLR and high LMR had significantly longer overall treatment time than those with high NLR and low LMR, respectively. This may indicate that patients with better nutritional status and lower systemic inflammatory response were more likely to receive relatively long-term treatment because they tolerate chemotherapy better and their cancer progresses is slower. Consequently, these patients are often able to receive adequate doses of chemotherapy, potentially leading to CS. Nutrition and inflammation levels are known to affect the risk of severe toxicity during cancer chemotherapy and the overall progression of the disease. Malnutrition can impact the absorption, protein binding, hepatic metabolism, and renal elimination of drugs and their metabolites (33). In malnourished patients, a reduced concentration of plasma protein levels can heighten the toxicity risk from drugs that bind strongly to proteins, such as prednisolone, etoposide, cisplatinum, paclitaxel, and metabolites of irinotecan (34). Additionally, several studies have linked inflammation-based scores with the prognosis of several types of malignances (35). Inflammation is causally related to cancer development, through processes that involve genotoxicity, aberrant tissue repair, proliferative responses, invasion, and metastasis (36). Elevated systemic inflammation can also directly enhance cancer cell metastases in other parts of the body and accelerate the overall progression of the disease (15). While we found no significant link between these pre-treatment markers and adverse events during chemotherapy or chemoradiotherapy, assessing patients' nutritional and inflammatory status before surgery for UR-PDAC might be vital. This assessment aids in selecting appropriate treatments and identifying patients with advanced disease or those unsuitable for surgery, potentially improving patient outcomes.

Our study had some limitations. First, this was a retrospective study conducted at a single institution. Second, the number of enrolled patients, particularly those who underwent CS, was relatively small. As a result, the outcomes could not be separately evaluated between UR-LA and UR-M, although these two conditions might be different. Therefore, sufficiently large cohorts should be analyzed in future multicenter collaborative studies. Third, in this study, the criteria for surgical indications of CS were defined as described above. However, the surgical indications for CS have not been clearly defined currently. Furthermore, the efficacy of CS in patients with UR-M remains controversial. Further studies are needed to determine the efficacy and surgical indications for CS.

In conclusion, our findings suggest that pretherapeutic TP, NLR, and LMR in patients with UR-PDAC are predictive factors for the attainability of CS. These parameters may be useful to predict which patients with UR-PDAC will likely undergo CS during multidisciplinary therapy.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

TH, KM, DW, TIs, RY, MK, MF, TIw, JYT, SK, YT, NO, MS and NM conceived the study concept and study design. TH made the initial proposal for this study, collected and analyzed the data, and wrote and edited the manuscript. TH, KM, RY, MK, MF, TIw, JYT, SK, YT and NO treated and monitored the patients. TH, DW and TIs conducted the statistical analyses. KM, MS, and NM revised and supervised the study. TH, KM and NM confirm the authenticity of all the raw data. All authors read and approved the final manuscript, and agreed to be accountable for the content of this work.

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of the Gifu University Hospital (approval number: 2022-285; Gifu, Japan). Participants provided informed consent by an opt-out option before study enrollment.

Patient consent for publication

Not applicable.

Competing interests

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