CANCER DIAGNOSIS & PROGNOSIS
1: 399-409 (2021) doi: 10.21873/cdp.10053

Evaluation of Early Prognostic Factors in Patients With Pancreatic Ductal Adenocarcinoma Receiving Gemcitabine Together With Nab-paclitaxel

WATARU IZUMO[1], RYOTA HIGUCHI[1], TORU FURUKAWA[2], TAKEHISA YAZAWA[1], SHUICHIRO UEMURA[1], YUTARO MATSUNAGA[1], MASAHIRO SHIIHARA[1] and MASAKAZU YAMAMOTO[1]

[1]*Department of Surgery, Institute of Gastroenterology, Tokyo Woman's Medical University, Tokyo, Japan;*
[2]*Department of Investigative Pathology, Tohoku University Graduate School of Medicine, Sendai, Japan*

Abstract. *Background: Gemcitabine together with nab-paclitaxel (GnP) has been shown to improve outcomes in patients with pancreatic ductal adenocarcinoma (PDAC). However, the predictive markers for treatment effects remain unclear. This study aimed to identify early prognostic factors in patients with PDAC receiving GnP. Patients and Methods: We analyzed 113 patients who received GnP for PDAC and evaluated the relationship between clinical factors and outcomes. Results: The median survival time (MST) was 1.2 years. In multivariate analysis, baseline carbohydrate antigen 19-9 (CA19-9) ≥747 U/ml [hazard ratio (HR)=1.9], baseline controlling nutrition status (CONUT) score ≥5 (HR=3.7) and changing rate of CA19-9 after two GnP cycles ≥0.69 (HR=3.7) were independent risk factors for poor prognosis. When examining outcomes according to pre-chemotherapeutic measurable factors (baseline CA19-9 and CONUT), the MSTs of patients with pre-chemotherapeutic zero risk factors (pre-low-risk group, n=63) and one or more risk factors (pre-high-risk group, n=50) were 1.7 and 0.65 years (p<0.001), respectively. The MST for those with a changing rate of CA19-9 after two GnP cycles <0.69 and ≥0.69 was significantly different in both groups (2.0 and 1.2 years in the pre-low-risk group, p<0.001; 1.0 and 0.52 years in the pre-high-risk group, p<0.001). Conclusion: These results may be useful for decision-making regarding treatment strategies in patients with PDAC receiving GnP.*

Pancreatic ductal adenocarcinoma (PDAC) still has one of the worst prognoses of all cancers and is the fourth leading cause of cancer-related deaths in Japan, Europe, and the United States (1-3). Recently, PDAC has been categorized as resectable (R), borderline resectable (BR), or unresectable (UR) (4). Multidisciplinary treatment, including pre- and post-operative chemotherapy, has become the standard treatment for R-PDAC (5). Even BR- or UR-PDAC may be eligible for surgical resection if preoperative treatment is effective (6-10). New chemotherapy regimens, such as gemcitabine plus nab-paclitaxel (GnP) and FOLFIRINOX have improved the prognosis of UR-PDAC as compared to previous regimens, such as gemcitabine alone (11, 12). It has been suggested that, when positive effects are obtained using these new chemotherapy regimens, pancreatectomy may further improve the prognosis of BR- or UR-PDAC (6-10).

However, in clinical practice, not all patients with BR- or UR-PDAC have the opportunity to undergo surgery, and the optimal timing or condition of performing surgical resection remains unclear. In addition, the factors predictive of the effectiveness of chemotherapy, particularly those that can be determined before or early in chemotherapy, are unclear. If the effectiveness of chemotherapy could be predicted early, treatment methods could be changed and the prognosis of PDAC may be improved. Oncological, biological, immunological, inflammatory, and/or nutritional indicators that can be detected before surgery have been reported to be useful in predicting prognosis in patients with surgically resected PDAC (13-23). However, the relationship between these factors and prognosis has not been fully investigated in patients undergoing chemotherapy.

This article is freely accessible online.

Correspondence to: Wataru Izumo, Department of Surgery, Institute of Gastroenterology, Tokyo Woman's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo, 162-8666, Japan. Tel: +81 333538111, Fax: +81 352697507, e-mail: izumo.wataru@twmu.ac.jp

Key Words: CA19-9 antigen, chemotherapy, nutrition status, paclitaxel, risk factors.

©2021 International Institute of Anticancer Research
www.iiar-anticancer.org

Table I. *Definitions of indicators*.

Pre-chemotherapeutic indicators		Abbreviation		Formula
Neutrophil-lymphocyte ratio		NLR		Neutrophil/Lymphocyte
Platelet-lymphocyte ratio		PLR		Platelet/Lymphocyte
Prognostic nutritional index		PNI		10 × Alb + 0.005 × Lymphocyte
		Controlling nutritional status (CONUT)		
Alb (g/dl)	Alb ≥3.5	3.0≤ Alb <3.5	2.5≤ Alb <3.0	Alb <2.5
Alb score	0	2	4	6
TLC (/μl)	TLC ≥1,600	1,200≤ TLC <1,600	800≤ TLC <1,200	TLC <800
TLC score	0	1	2	3
T-cho (mg/dl)	T-cho ≥180	140≤ T-cho <180	100≤ T-cho <140	T-cho <100
T-cho score	0	1	2	3
		CONUT score = Alb score + TLC score + T-cho score		
		GPS score (GPS)		
		CRP ≤1.0 mg/dl and Alb ≥3.5 g/dl	0	
		CRP >1.0 mg/dl or Alb <3.5 g/dl	1	
		CRP >1.0 mg/dl and Alb <3.5 g/dl	2	

Alb: Serum albumin level; TLC: total lymphocyte count; T-cho: serum total cholesterol level.

Therefore, we aimed to clarify early determinable prognostic factors, including some pre-chemotherapeutic measurable indicators, to facilitate prediction of treatment effects in PDAC patients receiving GnP.

Patients and Methods

Study design. Data from 145 patients who underwent GnP chemotherapy for PDAC between 2015 and 2019 at the Department of Surgery, Institute of Gastroenterology, Tokyo Women's Medical University, Japan, were analyzed in this retrospective study. Patients with unknown examination status (n=12), serum carbohydrate antigen 19-9 (CA19-9) levels ≤37 U/ml (n=10), or pancreatectomy after GnP (n=10) were excluded. Ultimately, 113 patients who underwent GnP treatment for PDAC were analyzed retrospectively.

We evaluated the roles of clinicopathological factors in overall survival (OS). Pre-chemotherapeutic parameters included age, sex, Eastern Cooperative Oncology Group Performance Status score (24), resectability, number of metastatic sites, existence of liver metastasis, existence of pre-treatment, baseline body mass index, maximum tumor size, serum CA19-9 level, hemoglobin A1c (HbA1c) level, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), prognostic nutrition index (PNI), controlling nutritional status (CONUT) score and Glasgow prognostic score (GPS) (definitions of these indicators are shown in Table I). Intra- and post-chemotherapeutic parameters included the number of chemotherapy cycles, total amount of gemcitabine or nab-paclitaxel, occurrence of adverse events, serum CA19-9 level after two cycles of GnP, rate of change in CA19-9 after two cycles of GnP, response evaluation and post-treatment.

Multivariate analyses to predict the OS were performed with the above factors. The survival rates were further determined based only on the presence or absence of significant factors (as detected by multivariate analysis). This study was approved by the Ethics Committee of the Tokyo Women's Medical University (approval number: 3952) and performed in accordance with the Declaration of Helsinki; the requirement for informed consent was waived owing to the retrospective nature of the analysis.

Miscellaneous definitions. Pre-chemotherapeutic laboratory and imaging data were acquired within 21 days of GnP initiation and after biliary decompression, with a total bilirubin level <2.0 mg/dl and without cholangitis. Resectability was determined using pre-chemotherapy imaging studies according to the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology of 2018 (25). In patients with R-, BR-, or UR-LA PDAC, histological evidence was obtained from the primary or metastatic lesion. In a recurrent case, the primary lesion was confirmed to be PDAC based on the resected specimen. The site of recurrence or metastasis was defined as one site each for the liver, lymph nodes, peritoneum, lung, residual pancreas and bone. Recurrent or metastatic cases were defined as the presence of a tumor on the above site by imaging studies. Isolated increases in tumor marker levels alone were not considered as recurrent cases. Pancreatectomy, chemotherapy, and/or chemoradiotherapy before GnP were defined as pre-treatment. Chemotherapy and/or chemoradiotherapy after GnP were defined as post-treatment.

Chemotherapy consisted of S-1 [oral fluorouracil prodrug tegafur, oteracil potassium, and gimeracil in a molar ratio of 1:1:0.4; Taiho Pharmaceutical, Tokyo, Japan (26, 27), gemcitabine, and FOLFIRINOX. Patients who underwent pancreatectomy after GnP were excluded from the study.

Table II. *Characteristics of patients*.

		n=113
Age (median, years, range)		68 (44-83)
Gender	Male	61 (54%)
Performance status	0/1/2	98 (87%)/15 (13%)/0 (0%)
Tumor status	R/BR/UR-LA/UR-M/Recurrence	10 (9%)/18 (16%)/22 (19%)/21 (19%)/42 (37%)
Number of metastatic sites	0/1/2/3/4	51 (45%)/52 (46%)/8 (7%)/0 (0%)/2 (2%)
Synchronous liver metastasis	With	29 (26%)
Pre-treatment	With	55 (49%)
Baseline BMI (median, kg/m^2, range)		21.0 (15.2-29.1)
Baseline maximum tumor size (median, mm, range)		29 (5-76)
Baseline CA19-9 (median, U/ml, range)		328 (39-42,976)
Baseline HbA1c (median, %, range)		6.2 (4.9-9.8)
Baseline NLR (median, range)		2.3 (0.71-8.3)
Baseline PLR (median, range)		143.9 (52.3-442.5)
Baseline LMR (median, range)		4.2 (1.2-8.5)
Baseline PNI (median, range)		45.2 (33.0-57.6)
Baseline CONUT score	0/1/2/3/4/5/6/7/8	12 (11%)/20 (18%)/31 (27%)/26 (23%)/ 10 (9%)/4 (4%)/6 (5%)/2 (2%)/2 (2%)
Baseline GPS score	0/1/2	76 (67%)/27 (24%)/10 (9%)
Number of chemotherapy cycles (median, range)		8 (2-22)
Total amount of gemcitabine (median, mg. range)		20000 (3,000-61,500)
Total amount of nab-paclitaxel (median, mg, range)		2370 (390-7,660)
Adverse events	≥ Grade 3	77 (68%)
CA19-9 after two cycles (median, U/ml, range)		287 (15-25,993)
Changing rate of CA19-9 after two cycles (median, range)		0.65 (0.053-15.2)
Time to most decreased level of CA19-9 (median, days, range)		84 (28-249)
Time to re-increased level of CA19-9 (median, days, range)		119 (28-543)
Response evaluation	PD/SD/PR	25 (22%)/70 (62%)/18 (16%)
Post-treatment	With	58 (68%)

R: Resectable; BR: borderline resectable; UR-LA: unresectable-locally advanced; UR-M: unresectable-metastasis; CA19-9: carbohydrate antigen 19-9; HbA1c: hemoglobin A1c; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio; PNI: prognostic nutrition ratio; CONUT: controlling nutritional status; CAR: C-reactive protein/albumin ratio; GPS: Glasgow prognostic score; PD: progressive disease; SD: stable disease; PR: partial response.

In this study, we measured the rate of change in CA19-9 between pre-chemotherapy and after two cycles of GnP. Patients whose baseline CA19-9 was within normal limits (CA19-9 ≤37 U/ml) were excluded. As a rule, CA19-9 was measured at every cycle interval of GnP and tumor response was evaluated using dynamic computed tomography at two cycle intervals, according to Response Evaluation Criteria in Solid Tumors version 1.1 (28). Adverse events were evaluated according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 5.0 (29). When it was difficult to continue GnP because the patients' general condition deteriorated and/or it was judged that the effect of GnP was poor, patients underwent another treatment or the best supportive care after GnP. Ultimately, the decision to receive post-GnP treatment was based on the physicians' or patients' choices. OS was defined as the time from GnP treatment induction to death or the last follow-up date. The cutoff values for the baseline maximum tumor size, CA19-9, HbA1c, NLR, PLR, LMR, PNI, CONUT score, GPS score (definitions of these indicators are shown in Table I), CA19-9 after two cycles of GnP and the changing rate of CA19-9 after two cycles of GnP were determined using receiver operating characteristic (ROC) curve analysis and designated as the point at which the area under the ROC curve (AUC) was largest for predicting OS.

Statistical analysis. Univariate and multivariate analyses were performed to identify independent predictors of OS. Survival analyses were performed using the Kaplan–Meier method, log-rank test and Cox proportional hazards model. Factors showing statistical significance in univariate analysis were subjected to multivariate analysis. The Kruskal–Wallis test was used to compare the medians of three or more groups. Statistical significance was set at $p<0.05$. All analyses were performed using JMP 12.1.0, for Windows (SAS Institute Inc., Cary, NC, USA).

Results

The median survival time (MST) was 1.2 years for all patients. The 1- and 3-year OS rates of all patients were 52% and 16%, respectively. The baseline characteristics of the patients are presented in Table II, Table III, Table IV, and Table V. There was no significant difference in the baseline CA19-9 levels according to tumor status ($p=0.45$) (Table VI). The median time to the highest decrease and re-increase in CA19-9 levels was 84 and 119 days, respectively. Based on ROC analysis, the cutoff values of baseline CA19-9, COUNT score, and changing

Table III. *Details of treatment before gemcitabine together with nab-paclitaxel.*

Pre-treatment	
With	55 (49%)
Surgery plus S-1	29 (26%)
Surgery plus S-1 plus Gemcitabine	10 (9%)
Surgery alone	3 (3%)
Radiation plus S-1	4 (4%)
Radiation plus S-1 plus Gemcitabine	2 (2%)
S-1 plus gemcitabine	5 (4%)
S-1 alone	2 (2%)
Without	58 (51%)

Table IV. *Details of adverse events.*

Adverse events (Duplication)	
<Grade 3	36 (32%)
≥Grade 3	77 (68%)
Leukopenia	29 (26%)
Neutropenia	54 (48%)
Thrombocytopenia	4 (4%)
Anemia	15 (13%)
Febrile neutropenia	2 (2%)
Fatigue	5 (4%)
Peripheral neuropathy	8 (7%)
Diarrhea	0 (0%)
Another	8 (7%)

rate of CA19-9 after two cycles of GnP were 747 U/ml (AUC: 0.66), 5 (AUC: 0.70), and 0.69 (AUC: 0.73).

Overall survival rate based on all risk factors. In multivariate analyses, baseline CA19-9 ≥747 U/ml [hazard ratio (HR)=1.9], baseline CONUT score ≥5 (HR=3.7), and changing rate of CA19-9 after two treatment cycles ≥0.69 (HR=3.7) were independent risk factors for a poor prognosis (Table VII). When examining outcomes according to these prognostic factors, the 1- and 3-year OS rates of patients with a risk score of 0 (n=37), 1 (n=45), 2 (n=27), and 3 (n=4) were 94% and 39% (MST: 2.0 years), 56% and 11% (MST: 1.2 years), 0% and 0% (MST: 0.55 years), 0% and 0% (MST: 0.17 years), respectively ($p<0.001$) (Figure 1). The HRs of the risk score groups 1, 2, and 3 were 2.8, 15.9, and 201.4 times that of risk score group 0, respectively ($p<0.05$).

Table V. *Details of treatment after gemcitabine together with nab-paclitaxel.*

Post-treatment	
With	58 (68%)
Radiation plus S-1	24 (19%)
Radiation plus S-1 plus Gemcitabine	2 (1%)
Radiation plus S-1 plus FOLFIRINOX	4 (3%)
FOLFIRINOX	10 (7%)
S-1	7 (9%)
S-1 plus Gemcitabine	6 (4%)
S-1 plus FOLFIRINOX	4 (1%)
Gemcitabine	1 (3%)
Without	55 (32%)

Overall survival rate based on pre-chemotherapy-measurable risk factors. When examining outcomes according to the pre-chemotherapeutic obtainable parameters (baseline CA19-9 ≥747 U/ml and baseline CONUT score ≥5), the 1- and 3-year OS rates of patients with pre-chemotherapy-measurable risk scores (pre-risk scores) of 0 (n=63) were 79% and 27% (MST: 1.7 years); for those with pre-risk scores of 1-2, these were 20% and 4% (MST: 0.65 years), respectively ($p<0.001$) (Figure 2). The HR of the pre-risk score group 1-2 was 3.3 times that of the pre-risk score group 0 ($p<0.001$). We defined patients with pre-risk score 0 as pre-chemotherapy low-risk (pre-low-risk) group, and patients with pre-risk score 1-2 as pre-chemotherapy high-risk (pre-high-risk) group.

Overall survival rate based on pre-chemotherapeutic risk and effectiveness of GnP. We grouped the patients according to the effects of GnP. We defined patients with a changing rate of CA19-9 <0.69, after two courses of GnP, as the effective group, and patients with a changing rate of CA19-9 ≥0.69, after two courses of GnP, as the ineffective group. We analyzed the prognosis in these two categories (pre-risk and effectiveness). The 1- and 3-year OS rates of the pre-low-risk and effective group, pre-low-risk and ineffective group, pre-high-risk and effective group, and pre-high-risk and ineffective group were 94% and 39% (MST: 2.0 years), 58% and 12% (MST: 1.2 years), 48% and 10% (MST: 1.2 years), and 0% and 0% (MST: 0.52 years) ($p<0.001$), respectively (Figure 3). The HRs of the pre-low-risk and ineffective group, pre-high-risk and effective group, and pre-high-risk and ineffective group were 2.8, 2.9, and 20.3 times that of the pre-low-risk and effective groups, respectively ($p<0.05$) (Table VIII). There were no differences in the 1- and 3-year OS rates between patients in the pre-low-risk and ineffective and pre-high-risk and effective groups ($p=0.89$).

Time to most decrease and re-increase in CA19-9 levels. In patients in the pre-high-risk and ineffective group, pre-low-risk and ineffective group, pre-high-risk and effective group, and pre-low-risk and effective group, the median time to most decrease and re-increase in CA19-9 level was 61, 73, 86, and 117 days ($p=0.012$), and 41, 87, 150, and 233 days, respectively ($p<0.001$) (Table IX).

Table VI. *Relationship between baseline CA19-9 levels and tumor status.*

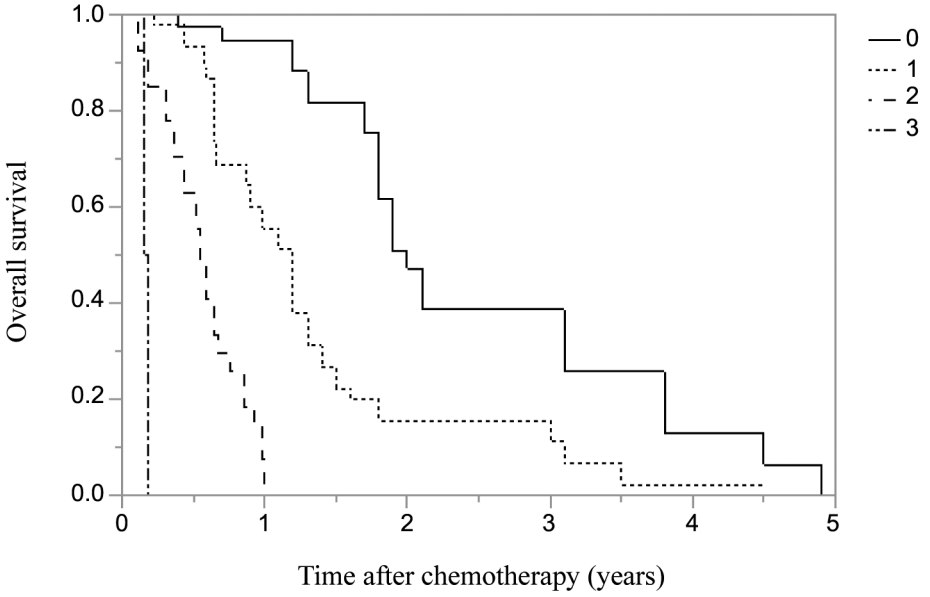
	R (n=10)	BR (n=18)	UR-LA (n=22)	UR-M (n=21)	Recurrence (n=42)	*p*-Value
Baseline CA19-9 (U/ml, range)	572 (119-2,445)	389 (57-3,272)	283 (156-3,195)	399 (104-12,127)	302 (39-42,976)	0.45

R: Resectable; BR: borderline resectable; UR-LA: unresectable-locally advanced; UR-M: unresectable-metastasis.

Table VII. *Univariate and multivariate analyses of risk factors for overall survival in patients receiving gemcitabine plus nab-paclitaxel for pancreatic ductal adenocarcinoma.*

Prognostic factors	Definition	Univariate				Multivariate	
		n	OS		*p*-Value	Hazard ratio (95% CI)	*p*-Value
			1-year	3-year			
Age (years)	<65	40	69.1	29.1	0.0018	1.0	0.36
	≥65	73	43.1	8.2		1.3 (0.74-2.3)	
Gender	Male	61	52.5	19.0	0.20		
	Female	52	51.9	12.7			
Performance status	0	98	59.2	18.3	<0.001	1.0	0.24
	1	15	6.7	0		1.6 (0.72-3.5)	
Tumor status	R	10	70.0	0	0.24		
	BR	18	76.9	25.6			
	UR-LA	22	54.6	10.4			
	UR-M	21	28.6	0			
	Recurrence	42	50.0	26.2			
Number of metastatic sites	0	51	68.7	13.9	0.26		
	≥1	62	40.6	16.6			
Liver metastasis	Without	84	65.9	20.5	<0.001	1.0	0.44
	With	29	13.8	0		1.3 (0.63-2.7)	
Pre-treatment	With	55	45.5	19.8	0.68		
	Without	58	59.1	11.7			
Baseline maximum tumor size (mm)	<32	72	62.8	25.4	0.0027	1.0	0.47
	≥32	41	34.2	0		1.2 (0.71-2.1)	
Baseline CA19-9 (U/mL)	<747	71	69.6	24.0	<0.001	1.0	0.031
	≥747	42	23.8	4.8		2.0 (1.1-3.8)	
Baseline HbA1c (%)	<6.2	52	46.9	11.6	0.62		
	≥6.2	61	56.7	19.5			
Baseline NLR	<3.5	84	57.4	15.3	0.34		
	≥3.5	29	37.9	16.1			
Baseline PLR	<136.5	41	63.9	21.4	0.20		
	≥136.5	72	45.8	13.3			
Baseline LMR	<3.2	32	46.9	14.6	0.99		
	≥3.2	81	54.5	16.2			
Baseline PNI	≥43	79	61.1	23.4	<0.001	1.0	0.16
	<43	34	32.4	0		1.7 (0.82-3.3)	
Baseline CONUT score	<5	99	59.8	18.1	<0.001	1.0	0.011
	≥5	14	0	0		3.7 (1.4-10.4)	
Baseline GPS score	0	76	63.2	17.4	0.0078	1.0	0.059
	≥1	37	27.0	11.6		1.9 (0.98-4.1)	
Neutropenia	≥Grade 3	54	72.0	19.7	<0.001	1.0	0.80
	<Grade 3	59	33.9	12.4		1.1 (0.62-1.9)	
CA19-9 after two cycles (U/ml)	<285	52	87.9	33.3	<0.001	1.0	0.094
	≥285	61	23.0	3.3		1.9 (0.89-4.2)	
Changing rate of CA19-9 after two cycles	<0.69	58	76.7	25.3	<0.001	1.0	<0.001
	≥0.69	55	27.3	5.5		4.7 (2.5-9.2)	

OS: Overall survival; CI: confidence interval; R: resectable; BR: borderline resectable; UR-LA: unresectable-locally advanced; UR-M: unresectable-metastasis; CA19-9: carbohydrate antigen 19-9; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio; PNI: prognostic nutrition ratio; CONUT: controlling nutrition status; GPS: Glasgow prognostic score; HbA1c: hemoglobin A1c.



$p<0.001$

Numbers at risk

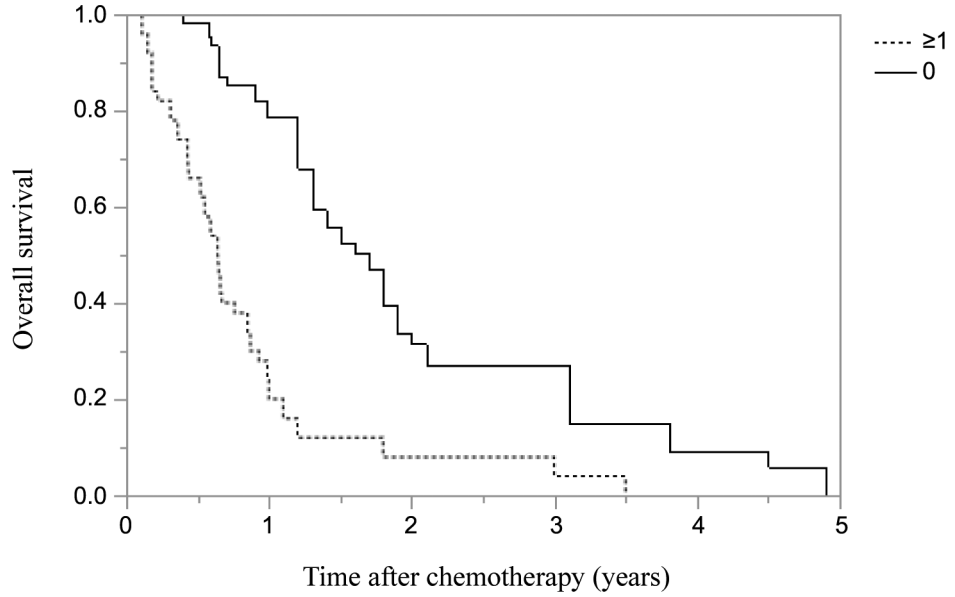
Year	0	1 year	2 years	3 years	4 years	5 years
Risk score 0	37	31	14	7	4	0
Risk score 1	45	27	9	7	3	0
Risk score 2	27	0	0	0	0	0
Risk score 3	4	0	0	0	0	0

Figure 1. *Kaplan–Meier analyses of overall survival rates in patients with pancreatic ductal adenocarcinoma receiving gemcitabine together with nab-paclitaxel, according to the all-risk score. The 1- and 3-year overall survival rates of patients with risk scores of 0, 1, 2, and 3 were as following: 94% and 39% (median survival time: 2.0 years), 56% and 11% (median survival time: 1.2 years), 0% and 0% (median survival time: 0.55 years), and 0% and 0% (median survival time: 0.17 years), respectively (p<0.001).*

Discussion

This study revealed that a baseline CA19-9 level ≥747 U/ml, baseline CONUT score ≥5, and changing rate of CA19-9 after two treatment cycles ≥0.69 were risk factors for shorter OS in patients with PDAC who were receiving GnP. In addition, we were able to predict prognosis in such patients more clearly by considering the former two pre-chemotherapeutic risk factors and the latter effectiveness factor separately. The prognosis for the pre-low-risk and ineffective groups and the pre-high-risk and effective groups were the same. We also clarified the maximum effect period and re-exacerbation period of GnP in each group. These results represent new findings that may be useful for decision-making regarding treatment strategies in patients with PDAC receiving GnP.

Although surgical resection plays an important role in PDAC treatment, it is difficult to achieve long-term survival by pancreatectomy alone. For a long time, surgical resection and adjuvant chemotherapy have been the standard treatments for PDAC (27, 30), but the results of treatments have not been satisfactory. In recent years, preoperative treatment for PDAC was reported to reduce micrometastasis, which is difficult to identify on imaging studies, and to increase the curative resection rate of locally advanced PDAC (6-10). Therefore, preoperative treatment is considered necessary to prolong the prognosis of patients with PDAC. A randomized clinical trial reported that two courses of neoadjuvant chemotherapy using



Numbers at risk

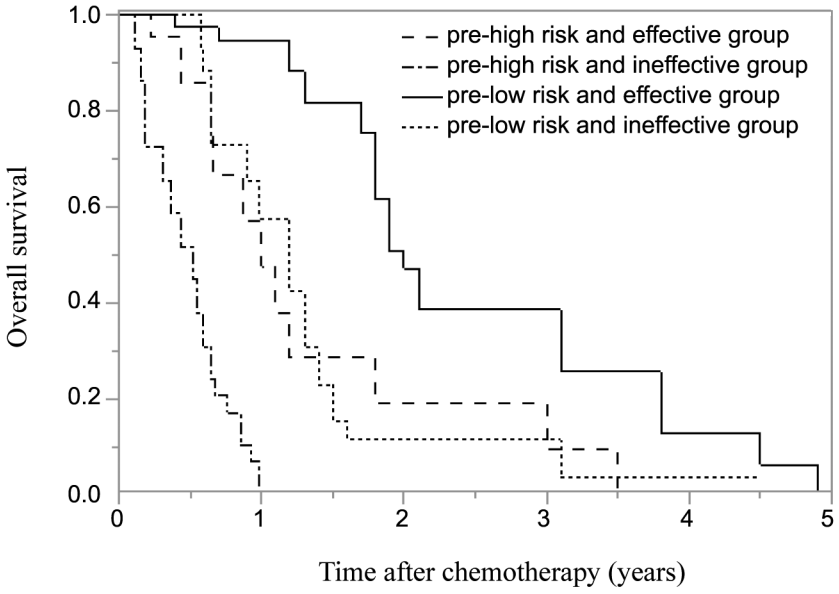
Year	0	1 year	2 years	3 years	4 years	5 years
Risk score 0	63	46	17	10	5	0
Risk score ≥ 1	50	12	6	4	0	0

Figure 2. *Kaplan–Meier analyses of overall survival rates in patients with pancreatic ductal adenocarcinoma receiving gemcitabine plus nab-paclitaxel according to pre-chemotherapy-measurable risk scores. The 1- and 3-year overall survival rates of patients with pre-chemotherapy-measurable risk scores of 0 were 79% and 27% (median survival time: 1.7 years), while for those with risk scores of 1-2, these were 20% and 4% (median survival time: 0.65 years) (p<0.001).*

gemcitabine plus S-1 improved OS in patients with R-PDAC (5); thus, it has become the standard treatment in Japan (31). Even in patients with BR- or UR-PDAC, surgical resection after neoadjuvant chemotherapy leads to a better curative resection rate and prognosis (6-10). Satoi et al. reported that UR-PDAC patients who underwent pancreatectomy after preoperative treatment for more than 8 months had a better prognosis that those who underwent pancreatectomy after preoperative treatment under 8 months (32). This can be interpreted as a good prognosis when pancreatectomy was performed on patients who had long-lasting chemotherapy, but it is possible that the chance of surgical resection had been missed in the meantime. The optimal format and duration of preoperative treatment thus remain unclear.

GnP and FOLFIRINOX were originally used for UR-PDAC (11, 12) and may also be used as preoperative treatment regimens. It has not yet been concluded which is the most effective regimen as neoadjuvant chemotherapy (33). Although FOLFIRINOX use is associated with a higher curative resection rate than GnP use, it has many adverse effects, and it has been reported that it may be difficult to complete neoadjuvant chemotherapy with this drug (6, 7). Based on this background, GnP seems to be clinically used more often. Although surgical resection should be performed in the process of maintaining the effect of chemotherapy, the appropriate selection of patients who should undergo surgical resection after GnP and the optimal timing of surgery after GnP remain unclear.

In resected PDAC, oncological factors, such as a large tumor size and elevated serum CA19-9 levels, are associated with a poor prognosis (13, 14). Furthermore, it has recently been reported that biological, oncological, immunological, inflammatory, and/or nutritional indicators, such as the NLR, PLR, LMR, PNI, CONUT and GPS, which can be measured before surgery, are good predictors of prognosis in patients



$p<0.001$

Numbers at risk

Year	0	1 year	2 years	3 years	4 years	5 years
Pre-low risk and effective group	37	31	14	7	2	0
Pre-low risk and ineffective group	26	17	4	4	3	0
Pre-high risk and effective group	21	12	6	4	0	0
Pre-high risk and ineffective group	29	0	0	0	0	0

Figure 3. *Kaplan–Meier analyses of overall survival (OS) rates in patients with pancreatic ductal adenocarcinoma receiving gemcitabine plus nab-paclitaxel (GnP) according to pre-chemotherapy risk group and changing rate of carbohydrate antigen (CA) 19-9 after two treatment cycles. The 1- and 3-year OS rates of the pre-low-risk and effective group, pre-low-risk and ineffective group, pre-high-risk and effective group, and pre-high-risk and ineffective group were 94% and 39% (median survival time: 2.0 years), 58% and 12% (median survival time: 1.2 years), 48% and 10% (median survival time: 1.2 years), and 0% and 0%, respectively (median survival time: 0.52, p<0.001).*

with resected PDAC (15-23). The lymphocyte count is a representative index of immunity, which is also regarded as a nutritional parameter, together with serum albumin and total cholesterol levels. A decreased lymphocyte count has been associated with a poor prognosis in malignant tumors (15-17), and poor nutrition status also makes it difficult to continue chemotherapy and reduces its effectiveness. The CONUT score is one of those combined biomarkers and is calculated using serum albumin concentration, total lymphocyte count, and total cholesterol concentration to assess the undernourished status of patients (34) (Table I). It has been reported that the CONUT score more strongly predicts postoperative complications and prognosis compared to other indicators in patients with resected PDAC (19, 35).

Few studies have evaluated the relationship between these indicators and prognosis in patients undergoing chemotherapy. The present study found that high CA19-9 and CONUT scores were important poor prognostic factors associated with OS among many of these indicators. The former refers to oncologically advanced tumors, while the latter to patients with a poor nutritional status. These are pre-treatment measurable factors that may also be useful when performing treatments other than GnP. This may imply that the pre-chemotherapy measurable group has a short prognosis, regardless of the treatment used. Baseline CA19-9 levels cannot be changed before treatment; however, nutritional intervention therapy can improve the CONUT score, and whether improving the CONUT score results in improved prognosis remains to be investigated.

Table VIII. *Median survival time and hazard ratio in patients with pancreatic ductal adenocarcinoma based on pre-chemotherapeutic risk and effectiveness of gemcitabine plus nab-paclitaxel.*

	Median survival time (95% CI)	Hazard ratio (95% CI)	*p*-Value
Pre-low risk and effective group (n=37)	2.0 (1.8-3.1)	1.0	
Pre-low risk and ineffective group (n=26)	1.2 (0.9-1.3)	2.8 (1.6-5.0)	<0.001*,,***
Pre-high risk and effective group (n=21)	1.0 (0.66-1.2)	2.9 (1.6-5.4)	<0.001*,**,***
Pre-high risk and ineffective group (n=29)	0.52 (0.31-0.59)	20.3 (10.2-41.7)	<0.001**,***

*p=0.89, **p<0.01, ***p<0.001.

Table IX. *Median time to highest decrease and re-increase in CA19-9 levels in patients with pancreatic ductal adenocarcinoma treated with gemcitabine plus nab-paclitaxel, based on the pre-chemotherapy risk and effectiveness.*

	All	Pre-low risk and effective group	Pre-low risk and ineffective group*	Pre-high risk and effective group	Pre-high risk and ineffective group*	*p*-Value
Time to most decrease in CA19-9 (days, range)	84 (28-249)	117 (28-249)	73 (28-158)	86 (28-221)	61 (28-103)	0.012
Time to re-increase in CA19-9 (days, range)	119 (28-543)	233 (50-543)	87 (28-403)	150 (54-254)	41 (28-179)	<0.001

*In the pre-low-risk and ineffective group and pre-high-risk and ineffective group, there were 8 (31%) and 17 (59%) patients with no improvement in CA19-9, respectively. Therefore, in the pre-high-risk and ineffective group, the values of time to most decreased CA19-9 level and time to re-increased CA19-9 level were reversed.

Previous studies have reported that the rate of change in CA19-9 levels after two courses of GnP was an early predictive marker of GnP efficacy (36, 37). A decrease in CA19-9 ≥50% or 60% after two courses of GnP led to significantly more prolonged OS than a lesser reduction in CA19-9 (36, 37). While these results are informative, the cutoff value remains controversial. In addition, in previous reports, the number of patients and examination factors in multivariate analysis were small, and no multivariate analyses included other indicators. To our knowledge, no study prior to ours performed ROC analysis to determine the cutoff value for the changing rate of CA19-9 after two cycles of GnP, or performed multivariate analysis including multiple indicators; thus, the results of this study may be considered more reliable. These results indicated that prognosis may be improved in the pre-low-risk and ineffective groups by changing the treatment.

Although progression-free survival in patients with UR-PDAC receiving GnP was reported to be 5.5 months in the MPACT trial, the time to most decrease and re-increase of the CA19-9 level were not mentioned (11). In the present study, it was clarified that there was a correlation between the effect of GnP and the period of decrease in CA19-9. This information may be useful if surgical resection is planned during the GnP treatment period.

This study has some limitations. Firstly, although there was no statistically significant difference in OS between the presence and absence of pre- and post-GnP treatments, the pre- and post-GnP treatments were not identical in all patients. In particular, concerning post-GnP treatments, a selection bias might have occurred. These variations may have skewed the outcomes during different periods of the study. Secondly, because patients with baseline CA19-9 ≤37 U/ml were excluded from this study, the results may not be generalizable to such patients. Finally, this was a retrospective study performed at a single institution, and included a limited number of participants. The biases inherent to such settings should be taken into consideration.

Conclusion

In conclusion, we were able to predict the prognosis of PDAC patients who were treated with GnP, based on pre- and intra-chemotherapeutic factors. The CA19-9 level, the CONUT score, the rate of change in CA19-9 level over two treatment cycles, and the treatment validity period may be particularly useful for predicting prognosis in this setting. Future studies should aim to determine the prospective utility of these laboratory markers and construct the best therapeutic strategy for patients with PDAC who are being treated with GnP.

Conflicts of Interest

The Authors declare that they have no competing interests.

Authors' Contributions

WI and RH contributed to conception and design. WI, RH, TF, TY, SU, YM, MS, and MY contributed to development of methodology and data acquisition. WI, RH, TF, and MY contributed to analysis and interpretation of data, writing, review, and/or revision of the manuscript. All Authors have read and approved the final manuscript.

Acknowledgements

This study was financially supported by NAKAYAMA Komei Research Fellowship Grant.

References

1 Ma J, Siegel R and Jemal A: Pancreatic cancer death rates by race among US men and women, 1970-2009. J Natl Cancer Inst *105(22)*: 1694-1700, 2013. PMID: 24203988. DOI: 10.1093/jnci/djt292

2 Malvezzi M, Bertuccio P, Levi F, La Vecchia C and Negri E: European cancer mortality predictions for the year 2014. Ann Oncol *25(8)*: 1650-1656, 2014. PMID: 24759568. DOI: 10.1093/annonc/mdu138

3 Katanoda K, Kamo K, Saika K, Matsuda T, Shibata A, Matsuda A, Nishino Y, Hattori M, Soda M, Ioka A, Sobue T and Nishimoto H: Short-term projection of cancer incidence in Japan using an age-period interaction model with spline smoothing. Jpn J Clin Oncol *44(1)*: 36-41, 2014. PMID: 24218520. DOI: 10.1093/jjco/hyt163

4 National Comprehensive Cancer Network clinical practice guidelines in oncology [internet]. Pancreatic adenocarcinoma. Version 1.2019 [updated November 8, 2018; cited 3 Mar 2019]. Available at: https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf [Last accessed on March 3, 2019]

5 Motoi F, Kosuge T, Ueno H, Yamaue H, Satoi S, Sho M, Honda G, Matsumoto I, Wada K, Furuse J, Matsuyama Y, Unno M, Study Group of Preoperative Therapy for Pancreatic Cancer (Prep) and Japanese Study Group of Adjuvant Therapy for Pancreatic cancer (JSAP): Randomized phase II/III trial of neoadjuvant chemotherapy with gemcitabine and S-1 *versus* upfront surgery for resectable pancreatic cancer (Prep-02/JSAP05). Jpn J Clin Oncol *49(2)*: 190-194, 2019. PMID: 30608598. DOI: 10.1093/jjco/hyy190

6 Tang K, Lu W, Qin W and Wu Y: Neoadjuvant therapy for patients with borderline resectable pancreatic cancer: A systematic review and meta-analysis of response and resection percentages. Pancreatology *16(1)*: 28-37, 2016. PMID: 26687001. DOI: 10.1016/j.pan.2015.11.007

7 Hackert T, Sachsenmaier M, Hinz U, Schneider L, Michalski CW, Springfeld C, Strobel O, Jäger D, Ulrich A and Büchler MW: Locally advanced pancreatic cancer: Neoadjuvant therapy with folfirinox results in resectability in 60% of the patients. Ann Surg *264(3)*: 457-463, 2016. PMID: 27355262. DOI: 10.1097/SLA.0000000000001850

8 Gillen S, Schuster T, Meyer Zum Büschenfelde C, Friess H and Kleeff J: Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. PLoS Med *7(4)*: e1000267, 2010. PMID: 20422030. DOI: 10.1371/journal.pmed.1000267

9 Jang JY, Han Y, Lee H, Kim SW, Kwon W, Lee KH, Oh DY, Chie EK, Lee JM, Heo JS, Park JO, Lim DH, Kim SH, Park SJ, Lee WJ, Koh YH, Park JS, Yoon DS, Lee IJ and Choi SH: 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 *268(2)*: 215-222, 2018. PMID: 29462005. DOI: 10.1097/SLA.0000000000002705

10 Marthey L, Sa-Cunha A, Blanc JF, Gauthier M, Cueff A, Francois E, Trouilloud I, Malka D, Bachet JB, Coriat R, Terrebonne E, De La Fouchardière C, Manfredi S, Solub D, Lécaille C, Thirot Bidault A, Carbonnel F and Taieb J: FOLFIRINOX for locally advanced pancreatic adenocarcinoma: results of an AGEO multicenter prospective observational cohort. Ann Surg Oncol *22(1)*: 295-301, 2015. PMID: 25037971. DOI: 10.1245/s10434-014-3898-9

11 Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjulandin SA, Ma WW, Saleh MN, Harris M, Reni M, Dowden S, Laheru D, Bahary N, Ramanathan RK, Tabernero J, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias J and Renschler MF: Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med *369(18)*: 1691-1703, 2013. PMID: 24131140. DOI: 10.1056/NEJMoa1304369

12 Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, Bennouna J, Bachet JB, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M, Groupe Tumeurs Digestives of Unicancer and PRODIGE Intergroup: FOLFIRINOX *versus* gemcitabine for metastatic pancreatic cancer. N Engl J Med *364(19)*: 1817-1825, 2011. PMID: 21561347. DOI: 10.1056/NEJMoa1011923

13 Matsumoto I, Murakami Y, Shinzeki M, Asari S, Goto T, Tani M, Motoi F, Uemura K, Sho M, Satoi S, Honda G, Yamaue H, Unno M, Akahori T, Kwon AH, Kurata M, Ajiki T, Fukumoto T and Ku Y: Proposed preoperative risk factors for early recurrence in patients with resectable pancreatic ductal adenocarcinoma after surgical resection: A multi-center retrospective study. Pancreatology *15(6)*: 674-680, 2015. PMID: 26467797. DOI: 10.1016/j.pan.2015.09.008

14 Izumo W, Higuchi R, Furukawa T, Yazawa T, Uemura S, Shiihara M and Yamamoto M: Evaluation of preoperative prognostic factors in patients with resectable pancreatic ductal adenocarcinoma. Scand J Gastroenterol *54(6)*: 780-786, 2019. PMID: 31180790. DOI: 10.1080/00365521.2019.1624816

15 Hasegawa S, Eguchi H, Tomokuni A, Tomimaru Y, Asaoka T, Wada H, Hama N, Kawamoto K, Kobayashi S, Marubashi S, Konnno M, Ishii H, Mori M, Doki Y and Nagano H: Pre-treatment neutrophil to lymphocyte ratio as a predictive marker for pathological response to preoperative chemoradiotherapy in pancreatic cancer. Oncol Lett *11(2)*: 1560-1566, 2016. PMID: 26893780. DOI: 10.3892/ol.2015.4057

16 Smith RA, Bosonnet L, Raraty M, Sutton R, Neoptolemos JP, Campbell F and Ghaneh P: Preoperative platelet-lymphocyte ratio is an independent significant prognostic marker in resected pancreatic ductal adenocarcinoma. Am J Surg *197(4)*: 466-472, 2009. PMID: 18639229. DOI: 10.1016/j.amjsurg.2007.12.057

17 Fujiwara Y, Misawa T, Shiba H, Shirai Y, Iwase R, Haruki K, Furukawa K, Futagawa Y and Yanaga K: Postoperative peripheral absolute blood lymphocyte-to-monocyte ratio predicts therapeutic outcome after pancreatic resection in patients with

pancreatic adenocarcinoma. Anticancer Res *34(9)*: 5163-5168, 2014. PMID: 25202109.

18 Kanda M, Fujii T, Kodera Y, Nagai S, Takeda S and Nakao A: Nutritional predictors of postoperative outcome in pancreatic cancer. Br J Surg *98(2)*: 268-274, 2011. PMID: 20960457. DOI: 10.1002/bjs.7305

19 Terasaki F, Sugiura T, Okamura Y, Ito T, Yamamoto Y, Ashida R, Ohgi K and Uesaka K: The preoperative controlling nutritional status (CONUT) score is an independent prognostic marker for pancreatic ductal adenocarcinoma. Updates Surg *73(1)*: 251-259, 2021. PMID: 32410163. DOI: 10.1007/s13304-020-00792-9

20 Jamieson NB, Mohamed M, Oien KA, Foulis AK, Dickson EJ, Imrie CW, Carter CR, McKay CJ and McMillan DC: The relationship between tumor inflammatory cell infiltrate and outcome in patients with pancreatic ductal adenocarcinoma. Ann Surg Oncol *19(11)*: 3581-3590, 2012. PMID: 22555345. DOI: 10.1245/s10434-012-2370-y

21 Pasini FS, Zilberstein B, Snitcovsky I, Roela RA, Mangone FR, Ribeiro U Jr, Nonogaki S, Brito GC, Callegari GD, Cecconello I, Alves VA, Eluf-Neto J, Chammas R and Federico MH: A gene expression profile related to immune dampening in the tumor microenvironment is associated with poor prognosis in gastric adenocarcinoma. J Gastroenterol *49(11)*: 1453-1466, 2014. PMID: 24217965. DOI: 10.1007/s00535-013-0904-0

22 Izumo W, Higuchi R, Furukawa T, Yazawa T, Uemura S, Matsunaga Y, Shiihara M and Yamamoto M: Evaluation of the significance of adjuvant chemotherapy in patients with stage IA pancreatic ductal adenocarcinoma. Pancreatology *21(3)*: 581-588, 2021. PMID: 33579600. DOI: 10.1016/j.pan.2021.01.024

23 Onodera T, Goseki N and Kosaki G: [Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients]. Nihon Geka Gakkai Zasshi *85(9)*: 1001-1005, 1984. PMID: 6438478.

24 Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET and Carbone PP: Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol *5(6)*: 649-655, 1982. PMID: 7165009.

25 National Comprehensive Cancer Network clinical practice guidelines in oncology [internet]. Pancreatic adenocarcinoma. Version 2. 2019 [updated 2018 April 9; cited 2019 May 20]. Available at: https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf [Last accessed on May 20, 2019]

26 Shirasaka T, Shimamato Y, Ohshimo H, Yamaguchi M, Kato T, Yonekura K and Fukushima M: Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. Anticancer Drugs *7(5)*: 548-557, 1996. PMID: 8862723. DOI: 10.1097/00001813-199607000-00010

27 Uesaka K, Boku N, Fukutomi A, Okamura Y, Konishi M, Matsumoto I, Kaneoka Y, Shimizu Y, Nakamori S, Sakamoto H, Morinaga S, Kainuma O, Imai K, Sata N, Hishinuma S, Ojima H, Yamaguchi R, Hirano S, Sudo T, Ohashi Y and JASPAC 01 Study Group: Adjuvant chemotherapy of S-1 *versus* gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). Lancet *388(10041)*: 248-257, 2016. PMID: 27265347. DOI: 10.1016/S0140-6736(16)30583-9

28 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer *45(2)*: 228-247, 2009. PMID: 19097774. DOI: 10.1016/j.ejca.2008.10.026

29 Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Available at: https://ctep.cancer.gov/protocol development/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf [Last accessed on August 20, 2021]

30 Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, Schramm H, Fahlke J, Zuelke C, Burkart C, Gutberlet K, Kettner E, Schmalenberg H, Weigang-Koehler K, Bechstein WO, Niedergethmann M, Schmidt-Wolf I, Roll L, Doerken B and Riess H: Adjuvant chemotherapy with gemcitabine *vs* observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA *297(3)*: 267-277, 2007. PMID: 17227978. DOI: 10.1001/jama.297.3.267

31 Japan Pancreas Society. Clinical Practice Guidelines for Pancreatic Cancer 2019. Kanehara Publishing Co., Ltd, 2019.

32 Satoi S, Yamaue H, Kato K, Takahashi S, Hirono S, Takeda S, Eguchi H, Sho M, Wada K, Shinchi H, Kwon AH, Hirano S, Kinoshita T, Nakao A, Nagano H, Nakajima Y, Sano K, Miyazaki M and Takada T: Role of adjuvant surgery for patients with initially unresectable pancreatic cancer with a long-term favorable response to non-surgical anti-cancer treatments: results of a project study for pancreatic surgery by the Japanese Society of Hepato-Biliary-Pancreatic Surgery. J Hepatobiliary Pancreat Sci *20(6)*: 590-600, 2013. PMID: 23660962. DOI: 10.1007/s00534-013-0616-0

33 Polistina F, Di Natale G, Bonciarelli G, Ambrosino G and Frego M: Neoadjuvant strategies for pancreatic cancer. World J Gastroenterol *20(28)*: 9374-9383, 2014. PMID: 25071332. DOI: 10.3748/wjg.v20.i28.9374

34 Ignacio de Ulíbarri J, González-Madroño A, de Villar NG, González P, González B, Mancha A, Rodríguez F and Fernández G: CONUT: a tool for controlling nutritional status. First validation in a hospital population. Nutr Hosp *20(1)*: 38-45, 2005. PMID: 15762418.

35 Shiihara M, Higuchi R, Izumo W, Yazawa T, Uemura S, Furukawa T and Yamamoto M: Impact of the controlling nutritional status score on severe postoperative complications of pancreaticoduodenectomy for pancreatic cancer. Langenbecks Arch Surg *406(5)*: 1491-1498, 2021. PMID: 33791827. DOI: 10.1007/s00423-021-02151-7

36 Iede K, Yamada T, Kato R, Ueda M, Tsuda Y, Nakashima S, Ohta K, Matsuyama J, Ikenaga M and Tominaga S: Predictive implications of decreased CA19-9 at 8 weeks during nab-paclitaxel plus gemcitabine for the induction of second-line chemotherapy for patients with advanced pancreatic cancer. Cancer Rep (Hoboken) *3(6)*: e1289, 2020. PMID: 32969199. DOI: 10.1002/cnr2.1289

37 Chiorean EG, Von Hoff DD, Reni M, Arena FP, Infante JR, Bathini VG, Wood TE, Mainwaring PN, Muldoon RT, Clingan PR, Kunzmann V, Ramanathan RK, Tabernero J, Goldstein D, McGovern D, Lu B and Ko A: CA19-9 decrease at 8 weeks as a predictor of overall survival in a randomized phase III trial (MPACT) of weekly nab-paclitaxel plus gemcitabine *versus* gemcitabine alone in patients with metastatic pancreatic cancer. Ann Oncol *27(4)*: 654-660, 2016. PMID: 26802160. DOI: 10.1093/annonc/mdw006

Received July 9, 2021
Revised August 7, 2021
Accepted August 23, 2021