

# Clinical Significance of Neoadjuvant Chemotherapy With Gemcitabine Plus S-1 for Resectable Pancreatic Ductal Adenocarcinoma

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**Abstract.** *Background/Aim:* Little is known about the efficacy of neoadjuvant chemotherapy (NAC) with gemcitabine plus S-1 (GS) for patients with resectable pancreatic ductal adenocarcinoma (R-PDAC). The aim of this study was to investigate differences in the long-term outcome of patients with R-PDAC undergoing pancreatectomy with and without NAC-GS to clarify the clinical significance of NAC-GS. *Patients and Methods:* A total of 77 patients with R-PDAC who were scheduled for pancreatectomy between January 2012 and December 2017 were enrolled. Of these patients, 39 received NAC-GS (GS group) and 38 had upfront surgery (UFS group). *Results:* Among the 77 patients, one patient in each group did not undergo pancreatectomy due to intraoperative non-curative factors. Median tumor size and the number of lymph nodes with metastasis were significantly lower in the GS group than in the UFS group ( $p=0.002$  and  $p=0.017$ ). However, the 5-year overall survival rate was similar in the two groups (26.1% versus 21.5%,  $p=0.930$ ). *Conclusion:* NAC-GS may not be recommended for patients with R-PDAC since it does not seem to offer any survival benefits.

Pancreatic ductal adenocarcinoma (PDAC) is an almost invariably fatal abdominal neoplasm with a 5-year overall survival (OS) rate of only 9% (1). Although only surgical resection can offer curative treatment for patients with PDAC, the 5-year survival rate following surgery is extremely poor,

ranging from 6% to 30% (2-4), due to a high rate of cancer recurrence. In addition, surgical resection can be offered to only 15-20% of patients with PDAC at initial diagnosis (5, 6), because of the presence of distant metastases or tumor invasion to peripheral vessels including the common hepatic artery (CHA), superior mesenteric artery (SMA), and portal vein (PV). Therefore, improvement of resectability is mandatory for increasing the chance of cure.

A classification of PDAC resectability was introduced by the National Comprehensive Cancer Network (NCCN) guidelines, and is since being used worldwide (7). PDAC has been classified into three categories: i) resectable (R), ii) borderline resectable (BR), or iii) unresectable (UR), based on residual tumor status evaluated by contrast-enhanced multidetector-row computed tomography (MDCT). Although a better R0 resection rate can be achieved in patients with R-PDAC compared to patients with BR- or UR-PDAC, the 5-year OS remains unsatisfactory (8-10).

Gemcitabine and S-1 are known to be key drugs for improving the survival of patients with PDAC (11, 12). Therapy using a combination of gemcitabine plus S-1 (GS) was employed as standard for patients with advanced PDAC in Japan until the clinical introduction of fluorouracil/leucovorin plus irinotecan plus oxaliplatin (FOLFIRINOX) or gemcitabine plus nab-paclitaxel (GN) therapy (13-15). A randomized phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer (GEST study) has been conducted in Japan and Taiwan (13, 16). Although the superiority of GS to gemcitabine was not proved in terms of OS, the objective response rate and the median tumor shrinkage ratio were higher in the GS group compared to the gemcitabine and S-1 groups (29.3% versus 13.3% and 21.0%, respectively, and 20.9% versus 7.0% and 7.9%, respectively). The GS combination was advantageous in terms of tumor shrinkage, possibly allowing BR and UR cases to become resectable. These results indicate that GS may be a favorable regimen for neoadjuvant

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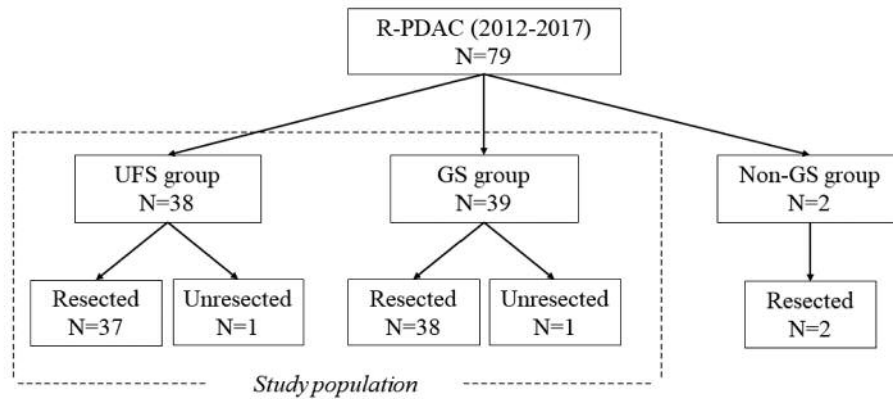


Figure 1. Flow chart of treatment course for patients with resectable pancreatic ductal adenocarcinoma (R-PDAC) from 2012 to 2017.

chemotherapy (NAC), and a clinical trial of NAC-GS for patients with R- and BR- PDAC has been conducted (17, 18). The results of this trial have suggested that, with sufficient tolerability and safety, NAC-GS may improve both survival and the R0 resection rate. However, the clinical significance of NAC-GS for patients with R-PDAC has remained unclear, as only a few studies have addressed this issue. Therefore, the aim of the present study was to investigate differences in the long-term outcome of patients with R-PDAC undergoing pancreatectomy with and without NAC-GS to clarify the clinical significance of NAC-GS.

## Patients and Methods

A total of 131 patients with a clinical diagnosis of PDAC who were scheduled for elective surgery at the Department of Gastroenterological Surgery, Dokkyo Medical University Hospital, between January 2012 and December 2017 were retrospectively reviewed. Among these patients, those with R-PDAC without distant metastasis were included in this study. The diagnosis of R-PDAC was based on the findings of contrast-enhanced MDCT, according to the NCCN guidelines version 2, 2018 (7). R-PDAC was defined as both absence of tumor contact with the celiac artery (CA), SMA, or CHA and absence of tumor contact with the superior mesenteric vein (SMV) or PV, or  $\leq 180$  contact without vein contour irregularity. Distant metastasis was evaluated by MDCT and/or magnetic resonance imaging, and/or positron emission tomography. Among the patients with R-PDAC, those who underwent NAC followed by surgery were categorized as the GS group, and those who had undergone surgery without NAC as initial treatment were categorized as the upfront surgery (UFS) group. This study was approved by the ethics committee of Dokkyo Medical University (Ethical committee review number R-15-8J).

Pancreatoduodenectomy, distal pancreatectomy, or total pancreatectomy with regional lymph node dissection was performed, according to the tumor location. PV or SMV resection to achieve curative resection was undertaken if tumor invasion was recognized or suspected during surgery. When distant metastases to areas, such

as the liver, extra-regional lymph nodes (LN) or peritoneum, or tumor invasion to the CHA or CA were found during surgery, these were judged as inoperable cases. Postoperative complications were classified according to the Clavien-Dindo classification (19).

Pathological features of the resected specimens were classified according to the seventh edition of the Japanese Rules for Pancreatic Cancer and the eighth edition of the American Joint Committee on Cancer (AJCC) staging manual for pancreatic cancer (20, 21).

LN ratio was determined by dividing the number of LNs with metastasis by the total number of LNs dissected.

**GS group.** The dosage of gemcitabine and S-1 given to the patients who received NAC was based on the results of a phase II studies of GS therapy (17, 22). Gemcitabine was given at a dose of 1000 mg/m<sup>2</sup> on days 1 and 8 of each course. S-1 was provided orally at a dose of 40, 50, or 60 mg/m<sup>2</sup> twice daily according to body surface area (less than 1.25 m<sup>2</sup>, 1.25-1.5 m<sup>2</sup>, or over 1.5 m<sup>2</sup>) for the first 14 consecutive days followed by a 7-day rest. Each course was repeated every 21 days. Patients received two courses of GS therapy. The Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 was used for the evaluation of treatment-related toxicities (23). Relative dose intensity (RDI) for gemcitabine and S-1 was calculated as the dose intensity achieved according to the standard schedule for each drug. Average RDI was calculated as the average of each RDI for gemcitabine and S-1. The Response Evaluation Criteria in Solid Tumors (RECIST) were utilized for evaluation of the response rate (24). The pathological response to the chemotherapy was categorized according to Evans' classification (25).

**Statistical analysis.** SPSS version 25.0 (IBM Japan, Tokyo, Japan) was used for all statistical analyses. Continuous data were expressed as medians with ranges and compared using the Mann-Whitney *U*-test, while categorical data were compared using the chi-squared test or Fisher's test. Survival curves were calculated using the Kaplan-Meier method and were compared using the log-rank test. Uni- and multivariate analyses were performed using the log-rank test, and the Cox proportional hazards forward stepwise model was used to identify risk factors for OS. Differences at  $p < 0.05$  were considered statistically significant.

Table I. Preoperative clinical outcomes of patients with resectable pancreatic ductal adenocarcinoma who underwent surgery.

Characteristics	UFS group (n=38)	GS group (n=39)	p-Value
Age (years)	67 (46-82)	65 (43-80)	0.359
Gender (male/female)	27/11	23/16	0.267
Location (head/body-tail)	26/12	23/16	0.389
Tumor size (mm)	25.4 (10-66)	23.1 (10.2-42)*	0.273
Biliary drainage (+)	21 (55%)	18 (46%)	0.424
CEA (ng/ml)	3.2 (1-40.3)	2.5 (1-40.3)*	0.783
CA19-9 (U/l)	260.5 (2-12000)	159 (2-2730)*	0.330
Dupan-2 (U/ml)†	81 (25-3000)	162 (25-4000)*	0.518
Span-1 (U/ml)‡	41 (1-2170)	38 (1.3-270)*	0.315
Elastase-1 (ng/dl)§	334 (50-3528)	161 (25-3910)*	0.332

Data are expressed as median (range). \*Measurement before GS therapy. †Missing data (n=3). ‡Missing data (n=3). §Missing data (n=7). CA19-9: Carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; Dupan-2: pancreatic cancer associated antigen; GS: gemcitabine plus S-1; Span-1: S-pancreas-1; UFS: upfront surgery.

Table II. Surgical outcomes of patients with resectable pancreatic ductal adenocarcinoma who underwent pancreatectomy.

Characteristics	UFS group (n=37)	GS group (n=38)	p-Value
Type of surgery (PD/DP/TP)	25/10/2	22/16/0	0.168
Portal vein resection (+)	4 (11%)	6 (16%)	0.385
Operation time (min)	453 (254-661)	479 (208-685)	0.660
Blood loss (ml)	599 (50-1781)	623 (50-3579)	0.282
Complications (C-D grade 0-II/III-V)	25/12	23/15	0.525
In-hospital death	1 (2.7%)	0	0.493
Postoperative hospital stay (days)	28 (11-49)	25 (11-153)	0.844
Adjuvant chemotherapy (+)	31 (84%)	35 (92%)	0.226

Data are expressed as median (range). C-D: Clavien-Dindo classification; DP: distal pancreatectomy; GS: gemcitabine plus S-1; PD: pancreatoduodenectomy; TP: total pancreatectomy; UFS: upfront surgery.

## Results

**Preoperative patient characteristics.** Seventy-nine patients (60.3%) with R-PDAC were treated during the same period (2012-2017). A flow chart of the treatment course for patients with R-PDAC is shown in Figure 1. Thirty-eight patients underwent surgery without NAC (UFS group) and 39 patients initially received the GS regimen (GS group). The remaining 2 patients who received other regimens, including GS 1 course followed by the GN 1 course were excluded from the study. In the UFS group, 37 (97.4%)

Table III. Comparison of clinical data before and after GS therapy.

Variables	GS group (n=39)
Reduction rate (%)	
CEA	-15.4 (-145.5-71.1)
CA19-9	39.9 (-108.2-94)
Dupan-2	36.2 (-41.7-84.9)
Span-1	40.7 (-100-82.5)
Elastase-1	29.2 (-220-98.6)
Tumor size	19 (-16-46.5)
Radiographic response (CR/PR/SD/PD)	0/6/33/0
ARDI (%)	90.8 (39.3-100)
Body weight loss (kg)	1.9 (-3-15.1)

Data are expressed as median (range). ARDI: Average relative dose intensity; CA19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; CR: complete response; Dupan-2: pancreatic cancer-associated antigen; GS: gemcitabine plus S-1; NAC: neoadjuvant chemotherapy; PD: progressive disease; PR: partial response; SD: stable disease; Span-1: S-pancreas-1.

patients underwent pancreatectomy and 1 patient did not because of liver metastasis. In the GS group, 38 patients (97.4%) underwent pancreatectomy and 1 patient did not because of para-aortic LN metastasis.

Table I shows the preoperative clinical data for the UFS and GS groups. There were no significant inter-group differences in terms of age, gender, tumor location, tumor size, biliary drainage, and levels of serum tumor markers, such as carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), pancreatic cancer-associated antigen (Dupan-2), S-pancreas-1 (Span-1), and elastase-1.

**Surgical outcomes.** Surgical outcomes in the UFS and GS patients who underwent pancreatectomy are listed in Table II. There were no significant inter-group differences in the type of surgery, PV resection, operation time, blood loss, postoperative complications, in-hospital deaths, postoperative hospital stays, and adjuvant chemotherapy (AC). AC, such as gemcitabine (n=12), S-1 (n=52), and other (n=2) had been used in 9, 20, and 2 UFS group patients and in 3, 32, and 0 GS group patients, respectively.

**Tumor response to NAC.** Table III shows the changes in clinical parameters following GS therapy relative to those before the therapy. The degrees of reduction in the levels of tumor markers were -15.4% (-145.5-71.1) for CEA, 39.9% (-108.2-94) for CA19-9, 36.2% (-41.7-84.9) for Dupan-2, 40.7% (-100-82.5) for Span-1, and 29.2% (-220-98.6) for elastase-1. Four of the tumor markers, with the exception of CEA, decreased from the baseline following GS therapy. The degree of reduction in tumor size was 19% (-16-46.5). None of the patients showed a complete response (CR) or

Table IV. Adverse events of gemcitabine plus S-1 therapy (n=39).

Adverse event	Grade				Total n (%)	Grade 3/4, n (%)
	1	2	3	4		
<b>Hematological</b>						
Neutropenia	2	6	13	5	26 (66.7)	18 (46.2)
Thrombocytopenia	10	6	2	3	21 (53.8)	5 (12.8)
Anemia	10	8	3	0	21 (53.8)	3 (7.7)
Febrile neutropenia	0	0	2	2	4 (10.3)	4 (10.3)
<b>Non-hematological</b>						
Rash	5	7	4	0	16 (41)	4 (10.3)
AST increase	10	2	3	0	15 (38.5)	3 (7.7)
ALT increase	11	1	3	0	15 (38.5)	3 (7.7)
Mucositis	4	2	3	0	9 (23.1)	3 (7.7)
Anorexia	3	0	1	0	4 (10.3)	1 (2.6)
Nausea	3	1	0	0	4 (10.3)	0
Cholangitis	0	0	3	0	3 (7.7)	3 (7.7)
Diarrhea	1	0	1	0	2 (5.1)	1 (2.6)
Fever	2	0	0	0	2 (5.1)	0
Creatinine increase	2	0	0	0	2 (5.1)	0
Vomiting	0	0	1	0	1 (2.6)	1 (2.6)
Sepsis	0	0	1	0	1 (2.6)	1 (2.6)
Duodenal ulcer	0	0	1	0	1 (2.6)	1 (2.6)
Constipation	1	0	0	0	1 (2.6)	0
Eye pain	1	0	0	0	1 (2.6)	0
Alopecia	0	1	0	0	1 (2.6)	0
Dyspepsia	0	1	0	0	1 (2.6)	0
Malaise	1	0	0	0	1 (2.6)	0

AST: Aspartate aminotransferase; ALT: alanine aminotransferase.

progressive disease (PD), 6 patients showed a partial response (PR), and 33 patients showed stable disease (SD). The median relative dose intensity (RDI) of gemcitabine and S-1 was 100% (40-100) and 100% (28.6-100), respectively. The average RDI was 90.8% (39.3-100). Patients lost 1.9 kg in body weight (-3-15.1) during the GS therapy.

The maximum tumor size measured by preoperative CT was well correlated with the resected specimen (Spearman correlation coefficient,  $R^2=0.616$ ,  $p=0.01$ , data not shown).

**Toxicity and adverse events.** The GS-related toxicities are shown in Table IV. All of the 39 patients were assessable for adverse events. Among them, 14 (35.9%) completed two planned courses of GS therapy without any dose reduction and 11 (28.2%) completed the course with dose down. However, 14 (35.9%) could not complete the two courses. Hematological toxicities, such as neutropenia, thrombocytopenia, and anemia were common, occurring in 66.7%, 53.8%, and 53.8% of the patients, respectively. The most common non-hematological toxicities were rash and increased levels of aspartate aminotransferase and alanine aminotransferase (41%, 38.5%, and 38.5%, respectively). The most common grade 3/4 adverse event was neutropenia (46.2%).

Table V. Pathological outcomes of patients with resectable pancreatic ductal adenocarcinoma who underwent pancreatectomy.

Characteristics	UFS group (n=37)	GS group (n=38)	p-Value
Tumor size (mm)	25 (15-90)	22 (15-50)	0.002
T (T1/T2/T3)*	4/27/6	12/24/2	0.046
LN metastasis (+)	29 (78%)	18 (47%)	0.006
Number of dissected LNs	20 (6-49)	17 (3-69)	0.454
Number of LNs with metastasis	1 (0-11)	1 (0-12)	0.017
LN ratio	0.122 (0-0.563)	0.033 (0-0.706)	0.014
Stage (Ia/Ib/IIa/IIb/III)*	0/7/1/19/10	9/12/0/12/6	0.012
<b>Histology</b>			
(wel/mod/por/other)	10/23/1/3	15/16/5/2	0.164
Lymphatic invasion (+)	33 (89%)	27 (71%)	0.050
Venous invasion (+)	35 (95%)	34 (89%)	0.414
Neuronal invasion (+)	29 (78%)	35 (92%)	0.093
Portal vein invasion** (+)	6 (16%)	2 (5%)	0.122
Residual tumor (R1)	6 (16%)	2 (5%)	0.122
<b>Pathological response<sup>†</sup></b>			
(I/IIa/IIb/III)	n.a.	9/24/4/1	n.a.

Data are expressed as median (range). \*AJCC 8th edition. <sup>†</sup>Evans' classification. \*\*Invasion to portal vein or superior mesenteric vein or splenic vein. GS: Gemcitabine plus S-1; LNs: lymph nodes; Mod: moderately; Por: poorly; SF: surgery first; Wel: well.

**Pathological outcomes.** Pathological outcomes in the SF and GS groups are summarized in Table V. The maximum tumor size was significantly less in the GS group compared to the SF group ( $p=0.002$ ). The numbers of dissected LNs were similar in the two groups. However, the number of LNs with metastasis and the LN ratio were significantly lower in the GS group compared to the SF group ( $p=0.017$  and  $p=0.014$ ). Lymphatic invasion occurred less commonly in the GS group compared to the SF group ( $p=0.050$ ). However, the degrees of differentiation, venous invasion, neural invasion, PV invasion, and residual tumor status were similar in the two groups. Histological response evaluation according to Evans' classification revealed grade I, IIa, IIb, and III in 9 (23.7%), 24 (63.2%), 4 (10.5%), and 1 (2.6%) of the 38 patients, respectively.

**Overall survival and relapse-free survival.** The median follow-up period was 24.2 months (0.6-84.2) for the 75 patients who underwent pancreatectomy. The 5-year OS and relapse-free survival (RFS) rates in the SF and GS groups were 21.5% and 12.8%, and 26.1% and 8%, respectively ( $p=0.930$  and  $p=0.764$ , respectively) (Figure 2A and B). The median OS and RFS periods in the SF and GS groups were 24.3 months and 15.6 months, and 21.5 months and 12.7 months, respectively. Recurrence was observed in 30 patients (81.1%) in the SF group and 27 patients (71.1%) in the GS group ( $p=0.309$ ).

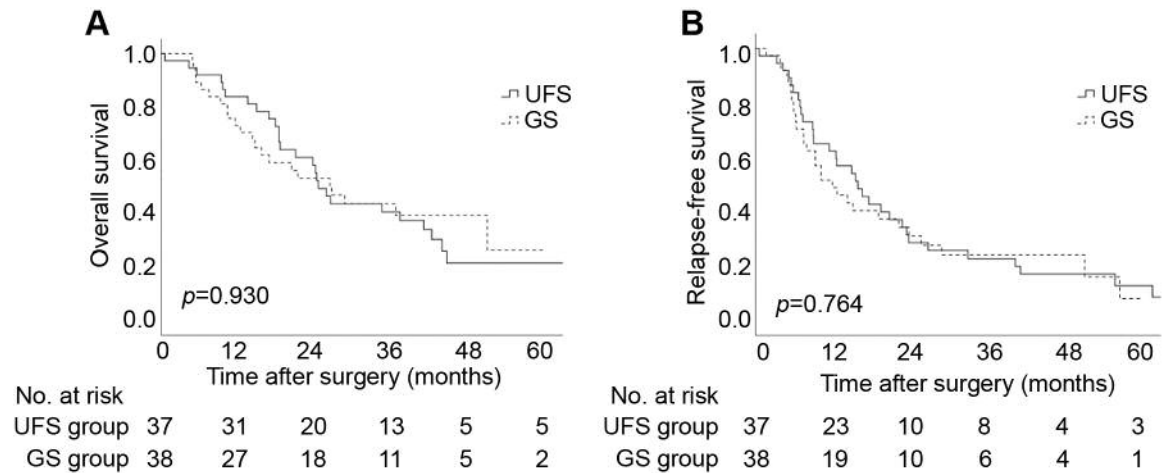


Figure 2. (A) Overall survival (OS) and (B) relapse-free survival (RFS) in the upfront surgery (UFS) ( $n=37$ ) and gemcitabine plus S-1 (GS) ( $n=38$ ) groups. There were no significant differences in OS and RFS between the two groups.

Table VI. Uni- and multivariate analyses of risk factors for survival ( $n=75$ ).

Variables	n	Univariate	Multivariate		
		p-Value*	HR	95% CI	p-Value**
Male	49	0.685			
Age $\geq 75$ years	15	0.048	–	–	–
CEA $>5$ ng/ml	22	0.670			
CA19-9 $>37$ U/ml	54	0.996			
Operation time $\geq 480$ min	28	0.982			
Blood loss $\geq 1000$ ml	14	0.878			
Blood transfusion (+)	18	0.016	–	–	–
T3, 4	8	0.002	2.900	1.308-6.428	0.009
LN metastasis (+)	47	0.257			
LN ratio $>0.1$	31	0.009	2.040	1.147-3.628	0.015
Histology (mod, por, or others)	50	0.273			
Lymphatic invasion (+)	60	0.134			
Venous invasion (+)	69	0.569			
Perineural invasion (+)	64	0.624			
Portal vein invasion (+)	8	0.179			
Residual tumor (R1)	8	0.224			
Adjuvant chemotherapy (–)	9	0.002	3.569	1.636-7.783	0.001

\*Log-rank test. \*\*Cox proportional hazards model. CA19-9: Carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; CI: confidence interval; HR: hazard ratio; LN: lymph node; Mod: moderately; Por: poorly.

**Risk factors for survival.** Table VI shows the results of uni- and multivariate analyses of risk factors for OS. Five of 17 factors were found to be significant by univariate analysis: i) age  $>75$  years, ii) blood transfusion (+), iii) T3, 4, iv) LN ratio  $>0.1$ , and v) AC (–). Multivariate analysis revealed that T3, 4 [hazard ratio (HR)=2.900, 95% Confidence Interval (CI)=1.308-6.428,  $p=0.009$ ], LN ratio  $>0.1$  (HR=2.040, 95%CI=1.147-3.628,  $p=0.015$ ), and AC (–) (HR=3.569, 95%CI=1.636-7.783,  $p=0.001$ ) were independent risk factor for poor OS.

## Discussion

NAC offers several advantages over upfront surgery, including early delivery of anti-cancer drugs for control of micro-metastasis, high tolerability of multi-agent regimens, and a higher R0 resection rate, that may lead to a better prognosis. Various regimens including GS, GN, or FOLFIRINOX as NAC have been studied and reported to improve postoperative survival (17, 18, 26-28). However,

most of these studies were intended for patients with BR- or UR-PDAC, for whom an increase in the R1 resection rate was considered potentially feasible. The issue of whether the use of NAC is actually beneficial for patients with R-PDAC has remained unclear. Therefore, we prospectively investigated the clinical significance of NAC-GS only for patients with R-PDAC, classified on the basis of the NCCN guidelines, who were scheduled for surgery.

NAC has two potential risks. First, its toxicities may impact perioperative morbidity and mortality. In this study, the most common hematological and non-hematological toxicities were neutropenia (66.7%) and rash (41%), being grade 3/4 in 46.2% and 10.3% of the patients, respectively. There was no NAC-GS-related mortality. All patients who suffered adverse events recovered and were scheduled for surgery. Comparable results have been reported previously in a phase II trial (17). No increase in operation time, blood loss, morbidity, or mortality was observed following NAC-GS treatment in our case, therefore, its use appears to be feasible and safe for patients with R-PDAC. Second, R-PDAC may progress and become unresectable during the course of NAC. Motoi *et al.*, have reported that 6 (3.2%) of 185 patients with R-PDAC who received NAC with various regimens (mainly gemcitabine monotherapy) could not undergo surgery due to tumor progression (29). In the present study, however, R-PDAC did not become unresectable in any of the patients who received NAC-GS and planned surgery was performed as scheduled. Accordingly, NAC-GS may be useful for control of tumor progression in the short term.

NAC-GS decreased the levels of tumor markers such as CA19-9, Dupan-2, Span-1, and elastase-1, except for CEA. Because 28 (71.8%) of 39 patients had a normal level of CEA before NAC-GS, only a slight change from the baseline level of CEA was observed following NAC-GS. Therefore, NAC-GS might not decrease the median level of CEA. Thirty-seven (94.9%) of the 39 patients showed tumor shrinkage after NAC-GS, with a median reduction rate of 19%. Although the number of dissected LNs was roughly equivalent between the UFS and GS groups, the number of LNs with metastasis and the LN ratio were significantly lower in the GS group compared to the UFS group. In 594 propensity score-matched patients with borderline resectable pancreatic cancer, Nagakawa *et al.*, (30) have also demonstrated that neoadjuvant therapy is beneficial for reducing the number of LNs with metastasis. Thus, NAC could be expected to reduce the incidence of LN metastasis, as previous studies have already reported (27, 29). The proportion of patients with pathological stage I was significantly higher in the GS group compared to the UFS group, suggesting that the use of NAC-GS contributes to tumor down-staging in patients with R-PDAC.

In terms of long-term outcome, the 5-year OS and RFS rates did not differ significantly between the UFS and GS groups. It has been suggested that the CA19-9 response to NAC is associated with postoperative survival (31). However, the response of tumor markers, including CEA, CA19-9, Dupan-2, Span-1 and elastase-1 to NAC had no impact on postoperative survival in the present study. Xia *et al.*, (32) have reported that there is no correlation between the degree of radiologic response based on RECIST and the degree of pathological response according to Evans' classification in patients with BR-PDAC. Furthermore, in terms of pathological response, patients with Evans' grade IIB-IV showed improved OS relative to patients with Evans' grade I-IIa. The present study demonstrated a survival advantage for patients with Evans' grade IIA-III compared to patients with Evans' grade I. However, before the initiation of NAC-GS, it may be difficult to predict patients who would potentially benefit from it in terms of pathological response.

Two possible reasons why NAC-GS had no impact on postoperative survival in patients with R-PDAC can be suggested, despite the fact that NAC-GS contributed to tumor down-staging. First, there may have been some difference in residual tumor status between the UFS and GS groups. Among patients with BR-PDAC, Masui *et al.*, (18) have reported that the frequency of R0 resection is significantly higher in those who receive NAC-GS than in those who do not (87% versus 53%,  $p=0.002$ ). It has been reported that the rate of R0 resection in upfront surgery for BR-PDAC patients ranges from 53% to 77% (18, 26, 29, 30). The R0 resection rate is lower in patients with BR-PDAC compared to patients with R-PDAC due to the possible invasion of peripheral vessels and tissues. Conversely, the down-staging effects of NAC are more likely to improve the R0 resection rate, thus help prolong survival. However, in patients with R-PDAC, surgical resection without NAC can achieve a higher R0 resection rate, ranging from 81.3% to 90.2% (9, 29, 33). Therefore, it may be unlikely that NAC can further improve the R0 resection rate. In a systematic review and meta-analysis of prospective studies, Zhan *et al.*, (33) have demonstrated that NAC has not been proven to be beneficial, and should be considered with caution in patients with R-PDAC. In addition, AC may have a strong impact on postoperative survival. Surgical resection followed by AC, including gemcitabine or S-1, is the only treatment strategy currently available offering a chance of cure (11, 12, 24). In the present study cohort, multivariate analysis revealed that the use of AC was the most powerful prognostic factor. While there were no significant differences between the UFS and GS groups in the number of patients who received AC and the period until initiation of AC after surgery. The use of NAC-GS did not affect the initiation of AC. Since Uesaka *et al.*, (12) have demonstrated the superiority of S-1 to gemcitabine for patients undergoing PDAC resection in a

phase III trial, S-1 is often chosen for AC in Japan. In terms of postoperative survival, AC may be superior to NAC for patients with R-PDAC. Because parameters of surgical invasiveness, such as operation time, blood loss, and concomitant vascular resection are milder in patients with R-PDAC compared to patients with BR- or UR-PDAC (28, 29), it may be more feasible to initiate AC without dose reduction.

Multivariate analysis in the present study showed that a LN ratio of  $>0.1$  was associated with poor survival. Pawlik *et al.*, (34) have demonstrated that a high LN ratio portends poor tumor biology and, as expected, poorer overall survival. Although NAC-GS was useful for reducing the LN ratio, patients who retain a high LN ratio might have tumors with a higher malignant potential.

Our study had several limitations that need to be pointed out. This was a single-center retrospective study that analyzed data for only a small number of patients with R-PDAC during a 6-year period. Therefore, further prospective studies with larger numbers of patients will be required in order to reach definitive conclusions. At present, a randomized phase II/III trial of NAC with GS *versus* upfront surgery for resectable pancreatic cancer has begun, and the results of that study are awaited (35).

In conclusion, although the use of NAC-GS contributes to tumor down-staging, NAC-GS may not be recommended for the treatment of patients with R-PDAC because any survival benefits have yet to be demonstrated.

## Conflicts of Interest

The authors have no conflicts of interest to declare.

## Authors' Contributions

All Authors contributed to the design and implementation of the study, to the analysis of the results, and to the writing and final approval of the manuscript.

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