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Efficacy of Adjuvant Chemotherapy According to the Pathological Response to Neoadjuvant Chemotherapy Among Patients With Pancreatic Ductal Adenocarcinoma

SHOZO MORI, TAKU AOKI, YUHKI SAKURAOKA, TAKAYUKI SHIMIZU, TAKAMUNE YAMAGUCHI, KYUNG-HWA PARK, TAKATSUGU MATSUMOTO, TAKAYUKI SHIRAKI, YUKIHIRO ISO and KEIICHI KUBOTA

Department of Gastroenterological Surgery, Dokkyo Medical University, Tochigi, Japan

Abstract. *Background/Aim: An association between the pathological response to neoadjuvant chemotherapy (NAC) and the efficacy of adjuvant chemotherapy (AC) in patients with pancreatic ductal adenocarcinoma (PDAC) remains unknown. Patients and Methods: A total of 121 patients with PDAC who underwent a pancreatectomy between January 2013 and March 2020 were divided into two groups: an upfront surgery (UFS) group (n=42), and an NAC (gemcitabine plus S-1) group (n=79). In the NAC group, the pathological response was evaluated using the Evans classification. Results: The overall survival was significantly higher in patients with an AC relative dose intensity (RDI) ≥80% than in patients with an AC RDI <80% in the UFS, NAC-Evans IIa, and NAC-Evans IIb+III groups. However, this difference was not observed in the NAC-Evans I group. Conclusion: AC is preferable for patients with NAC-Evans IIa or IIb+III, but more effective AC regimens may be needed for NAC-Evans I patients.*

Adjuvant chemotherapy (AC) has been established as a treatment component that contributes to an improved prognosis in patients with pancreatic ductal adenocarcinoma (PDAC) who have undergone curative surgery (1-5). To further improve prognosis, neoadjuvant chemotherapy (NAC) has been developed as a promising treatment for patients with PDAC (6, 7). The use of both NAC and AC has been a recent trend in the treatment of resectable PDAC.

In various prospective phase II trials or randomized controlled trials (RCTs) of NAC with or without radiation for resectable or borderline resectable (BR) PDAC, gemcitabine or S-1 has often been chosen as one of the chemotherapeutic agents used in both NAC and AC settings (6-9). Gemcitabine and S-1 are widely known to be key agents, and their efficacies have been confirmed by RCTs (1, 2). Thus, the number of patients with PDAC who have received both NAC and AC consisting of gemcitabine or S-1 is steadily increasing in clinical settings.

NAC followed by surgery has several merits. The pathological response to NAC can be determined by examining the subsequently resected specimens; such information can be helpful in choosing AC agents. However, whether the use of AC and a high relative dose intensity (RDI) of AC are effective for patients who have exhibited a poor pathological response to NAC (NAC non-responders) remains uncertain, since the same chemotherapeutic agents are typically administered for both the NAC and AC. A relationship between the RDI of AC and prognosis has been reported for various malignancies such as gastric, colon, and pancreatic cancer (10-12), with reduced RDI being associated with worse outcomes. However, in patients with PDAC who have received NAC, this relationship remains unknown.

The aim of this study was to investigate whether the impacts of the use of AC and the RDI of AC on patient outcome differ according to differences in the pathological response to NAC in patients with PDAC who underwent curative surgery.

Patients and Methods

Patients and study design. This was a single-center, retrospective study. The study subjects were patients with PDAC who had received elective surgery at the Department of Gastroenterological Surgery, Dokkyo Medical University Hospital, between January 2013 and March 2020. Cases with Stage IV disease, those who had undergone conversion surgery for locally advanced tumors, those with R2 resections, those with para-aortic lymph node metastasis, and in-hospital deaths were excluded. This study was approved by

Correspondence to: Shozo Mori, MD, Ph.D., Department of Gastroenterological Surgery, Dokkyo Medical University, 880 Kitakobayashi, Mibu, Shimotsuga, Tochigi, 321-0293, Japan. Tel: +81 282872158, Fax: +81 282866317, e-mail: s-mori@dokkyomed.ac.jp

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the ethics committee of Dokkyo Medical University (Ethical Committee review number R-14-12J).

The resectability classification of PDAC was based on contrast-enhanced multidetector-row computed tomography (MDCT) findings according to the NCCN guidelines version 2, 2018 (13). Distant metastasis was evaluated using MDCT and/or magnetic resonance imaging and/or positron emission tomography.

Chemotherapy. NAC and/or AC were performed based on each patient's agreement and with his/her informed consent. The NAC regimen used for each patient was gemcitabine plus S-1 (GS) according to the results of previous phase II studies (NAC-GS) (14). Gemcitabine was given at a dose of 1,000 mg/m^2 on days 1 and 8 of each course. S-1 was provided orally at a dose of 40, 50, or 60 mg/m^2 twice daily according to the patient's body surface area (BSA) (<1.25 m^2, 1.25-1.5 m^2, or >1.5 m^2, respectively) for 14 consecutive days, followed by a 7-day rest. Each course was repeated every 21 days. Patients received 2 courses of GS therapy as NAC.

The AC regimen used for each patient was either gemcitabine monotherapy or S-1 monotherapy. The dosages of gemcitabine and S-1 given to the patients who received AC were based on the results of a randomized phase 3 trial for resected pancreatic cancer (1, 2). Gemcitabine was given at a dose of 1,000 mg/m^2 on days 1, 8, and 15, followed by a 1-week rest period (one cycle). This administration of gemcitabine was repeated every 4 weeks for up to six cycles. S-1 was administered orally at a dose of 40, 50, or 60 mg/m^2 twice daily according to the patient's BSA (<1.25 m^2, 1.25-1.5 m^2, or >1.5 m^2, respectively) for 28 consecutive days followed by a 14-day rest (one cycle). This administration of S-1 was repeated every 6 weeks for up to four cycles.

When adverse events associated with NAC or AC occurred, the dosages of gemcitabine and S-1 were reduced based on the degree of the adverse events or the patient's condition from 1000 mg/m^2 to 800 mg/m^2 for gemcitabine and from 120 mg to 100 mg, from 100 mg to 80 mg, or from 80 mg to 50 mg a day for S-1 (according to the patient's BSA).

NAC-GS and AC were discontinued in cases with metastasis/recurrence, severe adverse events, or at the patient's request or if the protocol treatment was difficult to continue because of a deterioration in the patient's condition. Full-dose GS therapy was started in all the patients who had received NAC. The starting dose of AC was determined by each physician based on the patient's condition prior to the initiation of AC.

The Common Terminology Criteria for Adverse Events, version 5.0, was used to evaluate treatment-related toxicities. The RDIs for gemcitabine and S-1 were calculated as the dose intensity achieved according to the standard schedule for each drug. Some patients received AC beyond the planned cycles. The adverse events and RDIs of such patients were evaluated for the period lasting until the end of the planned cycles.

Pathological reviews of the resected specimens were performed by two pathologists at our institution. Tumors were classified based on the eight edition of the American Joint Committee on Cancer staging manual for pancreatic cancer (15). The pathological response to chemotherapy was categorized according to the Evans classification as grade I (<10% tumor cell destruction), IIa (10%-50% tumor cell destruction), IIb (51%-90% tumor cell destruction), III (<10% viable-appearing tumor cells), or IV (no viable tumor cells) based on the consensus of the two pathologists (16).

Patients visited the hospital once a month for the first 12 months after surgery and at 2- to 3-month intervals thereafter. Tumor markers, including carcinoembryonic antigen and carbohydrate antigen 19-9, were examined at each visit. Patients were monitored using contrast-enhanced computed tomography of the chest and abdomen at 3-month intervals for the first 12 months and at 4-month intervals thereafter.

Statistical analysis. SPSS version 26.0 (IBM Japan, Tokyo, Japan) was used for all the statistical analyses. Continuous data were expressed as the medians with ranges and were compared using the Mann-Whitney *U*-test, while categorical data were compared using the chi-squared test or the Fisher exact test. Survival curves were calculated using the Kaplan-Meier method and were compared using the log-rank test. Multiple comparisons were performed using Bonferroni correction. Univariate and multivariate analyses were performed using the log-rank test, and the Cox proportional hazard model with forward stepwise selection was used to identify predictors of overall survival (OS). The median follow-up period was calculated as the interval between the date of surgery and the date of the last follow-up or death. Differences with a p-value <0.05 were considered statistically significant.

Results

A total of 137 patients who were scheduled for elective surgery were included. Eighty-seven (63.5%) patients received NAC and 50 (36.5%) did not [upfront surgery (UFS) group]. None of the patients missed the opportunity to undergo surgery after receiving 2 courses of NAC. In the NAC group, 8 (9.2%) patients were excluded from the study because they subsequently underwent a laparotomy only [n=7: superior mesenteric artery invasion (n=4), peritoneal dissemination (n=1), liver metastasis (n=1), para-aortic lymph node metastasis (n=1)] or because of an in-hospital death (n=1). In the UFS group, 8 (16%) patients were excluded from the study because they underwent a laparotomy only [n=7: peritoneal dissemination (n=3), liver metastasis (n=2), para-aortic lymph node metastasis (n=1), liver cirrhosis (n=1)] or because they received an R2 resection (n=1). As a result, 121 patients who underwent a pancreatectomy with or without AC were eligible for inclusion in the analysis. Seventy-nine (65.2%) patients received NAC, and 42 (34.8%) did not. Patients who received NAC were then divided into 3 groups according to the Evans classification grade (Evans): 20 patients (25.3%) were classified as NAC-Evans I, 46 patients (58.2%) were classified as NAC-Evans IIa, and 13 patients (16.5%) were classified as NAC-Evans IIb+III [11 with grade IIb (13.9%) and 2 with III (2.6%)]. AC was used in 65 (82.3%) of the 79 patients in the NAC group and in 30 (71.4%) of the 42 patients in the UFS group. The major reasons why patients did not receive AC included patient refusal (n=12) and early recurrence (n=2) in the NAC group and patient refusal (n=9) and early recurrence (n=3) in the UFS group. The study cohort of 121 patients included 69 men (57%) and 52 women

(43%) with a median age of 68 years (range=43-85 years). The median follow-up period was 17.9 months (range=2.9-81.4 months) for the entire study cohort. Patients who received AC in the NAC and UFS groups were then divided into two groups: those with an RDI of 80%-100%, and those with an RDI of <80% (Figure 1).

Clinicopathological and surgical data. The clinicopathological and surgical data for the UFS (n=42), NAC-Evans I (n=20), NAC-Evans IIa (n=46), and NAC-Evans IIb+III (n=13) subgroups are compared in Table I. Significant differences in the pretreatment serum albumin level (p=0.028), the proportion of portal vein resection (p=0.018), pN stage (p=0.014), pStage (p=0.004), lymphatic invasion (p=0.001), and venous invasion (p=0.002) were observed among the 4 groups. However, no significant inter-group differences in other clinicopathological or surgical variables were observed.

Neoadjuvant and adjuvant chemotherapy data. The NAC- and AC-related data for the UFS (n=42), NAC-Evans I (n=20), NAC-Evans IIa (n=46), and NAC-Evans IIb+III (n=13) subgroups are shown in Table II. In the NAC group, a significant difference in the NAC completion rates was observed among the 3 subgroups (p=0.041). However, no significant differences in other NAC-related variables were observed. A significant difference in the RDIs of AC was observed among the 4 groups (p=0.027). However, no significant differences in other AC-related variables were observed.

Overall survival. A comparison of OS in the UFS, NAC-Evans I, NAC-Evans IIa, and NAC-Evans IIb+III subgroups is shown in Figure 2. When data for all the patients (n=121) were examined, a significant stratification of the survival curves was observed, with a median survival time (MST) of 14.4 months for the NAC-Evans IIb+III group, 20.6 months for the NAC-Evans IIa group, 21.6 months for the UFS group, and 12.1 months for the NAC-Evans I group (p=0.004) (Figure 2A). Among the resectable patients (n=92), similar results were observed, with an MST of 14.4 months for the NAC-Evans IIb+III group, 24 months for the NAC-Evans IIa group, 22 months for the UFS group, and 12.1 months for the NAC-Evans I group (p=0.006) (Figure 2B). However, among BR or unresectable locally advanced (UR-LA) patients (n=29), survival curve stratification was not observed, with an MST of 16.1 months for the NAC-Evans IIb+III group, 13.8 months for the NAC-Evans IIa group, 17.5 months for the UFS group, and 14.6 months for the NAC-Evans I group (p=0.600) (Figure 2C).

Overall survival stratified according to AC and the RDI of AC. A comparison of OS between patients with AC and those without AC and among patients with an RDI of 80%-100%, an RDI of <80%, and those without AC are shown for the UFS (n=42), NAC-Evans I (n=20), NAC-Evans IIa (n=46), and NAC-Evans IIb+III (n=13) groups in Figure 3. The OS was significantly higher for patients with AC than for patients without AC in the UFS and NAC-Evans IIa groups (UFS: MST of 23.7 months *vs*. 8.9 months, p=0.004; NAC-Evans IIa: MST of 24 months *vs*. 10.2 months, p=0.018) (Figure 3A and E). However, a similar difference was not observed in the NAC-Evans I group (MST of 13.6 months *vs*. 6.7 months, p=0.531) (Figure 3C). In the NAC-Evans IIb+III group, the statistical analysis was not evaluable (NE) (MST of 15.2 months *vs*. 5.8 months, p=NE) (Figure 3G). Patients with an RDI of 80%-100% had a significantly better OS than patients with an RDI of <80% in the UFS, NAC-Evans IIa, and NAC-Evans IIb+III groups (UFS: MST of 28.5 months *vs*. 17.2 months, p<0.001; NAC-Evans IIa: MST of 32.7 months *vs*. 10.3 months, p=0.011; and NAC-Evans IIb+III: MST of 28.4 months *vs*. 10.4 months, p=0.004) (Figure 3B, F, and H). However, a similar difference was not observed in the NAC-Evans I group (MST of 16.8 months *vs*. 12.1 months, p=0.158) (Figure 3D).

Predictors of overall survival. The results of univariate and multivariate analyses of predictors of OS are shown in Table III. Among 20 factors, 6 [resectability status (BR or UR-LA), NAC-Evans grade II+III, pStage III, histology (moderately differentiated, poorly differentiated, others), AC (+), and AC RDI of 80%-100%] were found to be significant in univariate analyses. A multivariate analysis revealed that NAC-Evans grade II+III [hazard ratio (HR)=0.552; 95% confidence interval (CI)=0.344-0.884; p=0.013)] and an AC RDI of 80%-100% (HR=0.283; 95%CI=0.175-0.456; p<0.001) were independent predictors of OS.

Discussion

The present study demonstrated that both the use of AC with gemcitabine or S-1 and an AC RDI ≥80% conferred no survival benefit for patients with NAC-Evans I disease, who typically were not sensitive to NAC using GS (Figure 3C and D). Accordingly, the use of gemcitabine or S-1 in an adjuvant setting might not be preferable for patients classified as NAC-Evans I.

The efficacy of chemotherapy differs among individual patients because tumor sensitivity to anticancer agents varies widely (17-19). The pathological response to NAC, as confirmed by examining resected specimens, can serve as a kind of "*in vivo* chemosensitivity test". The clinical efficacy of *in vitro* chemosensitivity tests using cancer cells from resected specimens of various malignancies, such as gastric, colorectal, and pancreatic cancer, has been reported (17-19). Ariake *et al*. conducted a collagen gel droplet-embedded culture drug sensitivity test to evaluate the efficacy of 5-

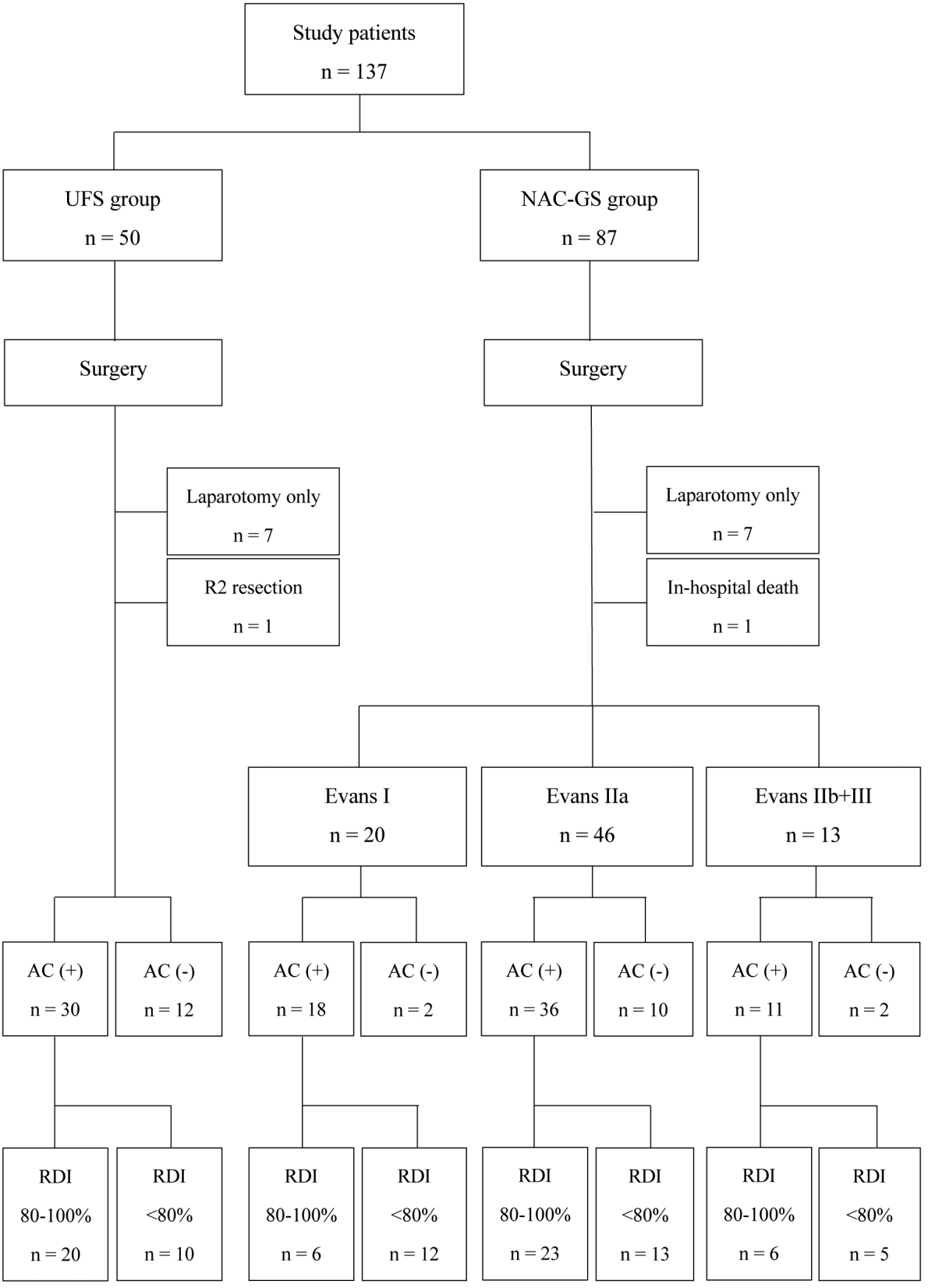


Figure 1. *Flow chart showing all the study patients with pancreatic ductal adenocarcinoma.*

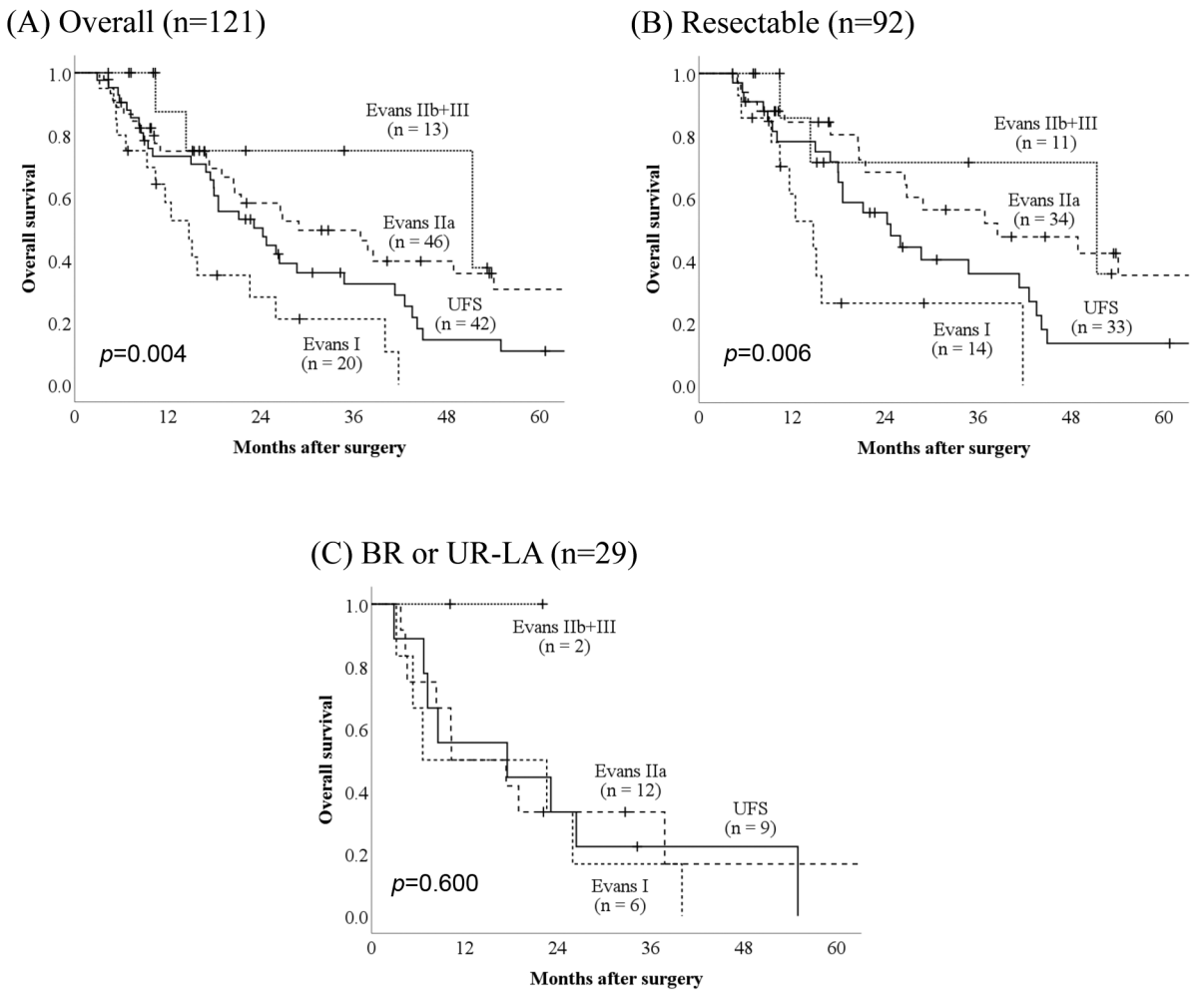


Figure 2. *Comparisons of overall survival among patients classified as UFS, NAC-Evans I, IIa, and IIb+III. (A) Overall patients (n=121). (B) Patients with resectable disease (n=92). (C) Patients with BR or UR-LA (n=29).*

fluorouracil (FU)-based S-1 adjuvant chemotherapy in 22 pancreatic cancer patients and demonstrated that 5-FU-sensitive patients had a better recurrence-free survival outcome than 5-FU-resistant patients (19). Furthermore, the sensitivity to 5-FU was an independent predictor of recurrence. Assessments of the pathological response to NAC seem to be similar to *in vitro* chemosensitivity tests, since both methods examine the chemosensitivity of cancer cells. The results of the present study suggest that the pathological response to NAC could be useful for the selection of anticancer agents in adjuvant settings.

The use of AC led to improved survival in the UFS and NAC-Evans IIa groups (Figure 3A and E). On the other hand, a statistical analysis was not performed for the NAC-Evans IIb+III group because the number of patients was too small (Figure 3G). An RDI ≥80% was associated with improved survival, compared with an RDI <80%, in the NAC-Evans IIa, NAC-Evans IIb+III, and UFS groups (Figure 3B, F, and H). A multivariate analysis identified NAC-Evans II+III and an AC RDI ≥80% as independent predictors of an improved OS (Table III). Yabusaki *et al*. reported that patients with pancreatic cancer who were treated with gemcitabine, S-1, or gemcitabine plus S-1 and who had an AC RDI of ≥80% had a significantly better OS than patients with an RDI of <80% (12). These results indicate that gemcitabine or S-1 can be used for AC in patients with NAC-Evans IIa or IIb+III disease who are sensitive to NAC. Efforts to maintain an RDI of ≥80% with careful adjustments of the doses and schedule of AC and the management of adverse events are thus indispensable for improving prognosis. To the best of our knowledge, this is the first report to demonstrate an association between the RDI of AC and the outcome of patients with PDAC who received NAC.

Table I. *Clinicopathological and surgical data (n=121).*

Variables*	UFS	NAC-GS			*p*-Value
	(n=42)	Evans I (n=20)	Evans IIa (n=46)	Evans IIb+III (n=13)	
Age (years)	69 (46-85)	65 (52-84)	65 (43-82)	70 (47-83)	0.165
Male	29 (69)	10 (50)	24 (52)	6 (46)	0.267
BMI (kg/m^2)	21.4 (16.1-31.8)	22.7 (17.4-29.2)	20.9 (15.6-28.9)	24.1 (19.2-30.3)	0.100
Albumin (g/dl)	3.5 (2-4.7)	3.8 (2.1-4.5)	3.9 (2.9-4.8)	3.8 (3.1-4.6)	**0.028**
CEA (ng/ml)	3.7 (0.7-18.8)	5.2 (1-163)	2.6 (0.8-40.4)	2.3 (0.8-14.9)	0.104
CA19-9 (U/ml)	270.5 (2-12,000)	656.5 (2-12,000)	87.5 (2-12,000)	308 (2-3480)	0.156
Tumor location					0.911
Head	27 (64)	14 (70)	28 (61)	8 (62)	
Body-tail	15 (36)	6 (30)	18 (39)	5 (38)	
Resectability status					0.646
Resectable	33 (79)	14 (70)	34 (74)	11 (84)	
BR-PV	7 (17)	3 (15)	8 (17)	1 (8)	
BR-A	2 (4)	3 (15)	2 (4)	1 (8)	
UR-LA	0	0	2 (4)	0	
Type of operation					0.172
PD	26 (62)	13 (65)	28 (61)	7 (54)	
DP	10 (24)	3 (15)	17 (37)	5 (38)	
TP	6 (14)	4 (20)	1 (2)	1 (8)	
Portal vein resection					**0.018**
(–)	30 (71)	9 (45)	35 (76)	12 (92)	
(+)	12 (29)	11 (55)	11 (24)	1 (8)	
Operative time (min)	484 (195-730)	541 (354-738)	475 (208-734)	500 (242-837)	0.283
Blood loss (ml)	713 (164-3,417)	834 (217-2,607)	642 (50-3,579)	717 (234-2,275)	0.363
Morbidity**					0.891
0, I, II	32 (76)	15 (75)	32 (70)	10 (77)	
III, IV	10 (24)	5 (25)	14 (30)	3 (23)	
Hospital stay (days)	28 (11-90)	24 (12-79)	22 (11-153)	17 (10-47)	0.204
pT stage					0.478
T1	6 (14)	4 (20)	13 (28)	5 (38)	
T2	27 (64)	10 (50)	26 (57)	6 (46)	
T3	7 (17)	3 (15)	4 (9)	2 (16)	
T4	2 (5)	3 (15)	3 (6)	0	
pN stage					**0.014**
N0	12 (29)	6 (30)	23 (50)	8 (62)	
N1	19 (45)	8 (40)	21 (46)	5 (38)	
N2	11 (26)	6 (30)	2 (4)	0	
pStage					**0.004**
IA	1 (2)	1 (5)	11 (24)	4 (31)	
IB	8 (19)	4 (20)	11 (24)	2 (15)	
IIA	1 (2)	0	1 (2)	2 (15)	
IIB	19 (45)	7 (35)	18 (39)	5 (38)	
III	13 (31)	8 (40)	5 (11)	0	
Cytology***					0.648
(–)	17 (89)	15 (100)	27 (90)	10 (91)	
(+)	2 (11)	0	3 (10)	1 (9)	
Histology****					0.394
Well	14 (33)	7 (35)	19 (41)	5 (38)	
Moderately	26 (62)	8 (40)	22 (48)	7 (54)	
Poorly	1 (2)	4 (20)	4 (9)	0	
Others	1 (2)	1 (5)	1 (2)	0	
Lymphatic invasion					**0.001**
(–)	6 (14)	2 (10)	19 (41)	7 (54)	
(+)	36 (86)	18 (90)	27 (59)	6 (46)	
Venous invasion					**0.002**
(–)	5 (12)	0	6 (13)	6 (46)	
(+)	37 (88)	20 (100)	40 (87)	7 (54)	

Table I. *Continued*

Table I. *Continued*

Variables*	UFS (n=42)	NAC-GS Evans I (n=20)	NAC-GS Evans IIa (n=46)	NAC-GS Evans IIb+III (n=13)	*p*-Value
Perineural invasion					0.672
(–)	6 (14)	2 (10)	5 (11)	3 (23)	
(+)	36 (86)	18 (90)	41 (89)	10 (77)	
Surgical margin					0.052
R0	35 (83)	17 (85)	45 (98)	13 (100)	
R1	7 (17)	3 (15)	1 (2)	0	

BMI: Body mass index; BR-A: borderline resectable-artery; BR-PV: borderline resectable-portal vein; CA19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; DP: distal pancreatectomy; NAC-GS: neoadjuvant chemotherapy-gemcitabine plus S-1; PD: pancreaticoduodenectomy; TP: total pancreatectomy; UFS: upfront surgery; UR-LA: unresectable-locally advanced. *Data are expressed as median (range) or as *n* (%); **Clavien-Dindo classification grade; ***Intra-operative peritoneal washing cytology was not performed in 46 patients; ****n=1, missing data (Evans IIb+III). Bold values indicate statistical significance.

Table II. *Neoadjuvant and adjuvant chemotherapy data (n=121).*

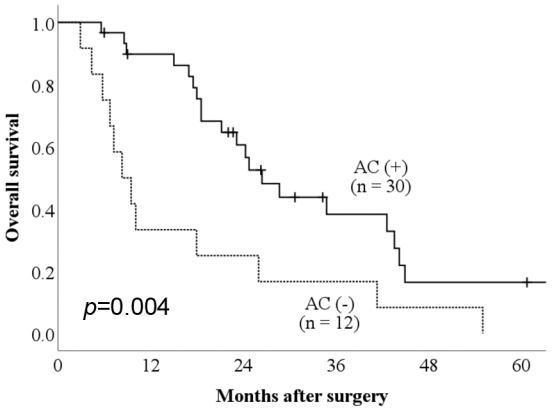
Variables*	UFS (n=42)	NAC-GS Evans I (n=20)	NAC-GS Evans IIa (n=46)	NAC-GS Evans IIb+III (n=13)	*p*-Value
NAC-related					
RDI (%)		87.5 (46.4-100)	90.8 (35-100)	95 (47.5-100)	0.584
Completion		8 (40)	26 (57)	11 (85)	**0.041**
Days until surgery		47 (35-74)	47 (16-84)	50 (42-75)	0.256
CEA after NAC (ng/ml)		4.7 (0.9-97.5)	2.9 (0.7-47.1)	2.6 (0.9-9.6)	0.316
CA19-9 after NAC (U/ml)		168 (2-11,300)	50 (2-12,000)	54 (2-346)	0.187
Reduction rate of CEA (%)		11 (-164-94)	-15 (-625-98)	0 (-184-78)	0.440
Reduction rate of CA19-9 (%)		59 (-60-96)	38 (-5404-92)	54 (0-96)	0.200
AC					0.376
(–)	12 (29)	2 (10)	10 (22)	2 (15)	
(+)	30 (71)	18 (90)	36 (78)	11 (85)	
AC agents					0.884
S-1	27 (90)	16 (89)	34 (94)	10 (91)	
Gemcitabine	3 (10)	2 (11)	2 (6)	1 (9)	
AC-related					
RDI (%)	80 (20-100)	50 (6.3-100)	80 (5.4-100)	85 (40-100)	**0.036**
Completion	21 (70)	7 (39)	22 (61)	7 (64)	0.197
Days until AC	56 (26-220)	66 (32-148)	59 (21-225)	50 (30-145)	0.352

AC: Adjuvant chemotherapy; CA19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; NAC-GS: neoadjuvant chemotherapy-gemcitabine plus S-1; RDI: relative dose intensity; UFS: upfront surgery. *Data are expressed as median (range) or as *n* (%). Bold values indicate statistical significance.

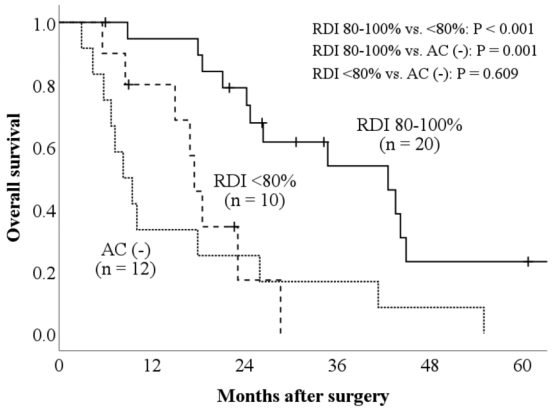
From the viewpoint of tumor sensitivity to anticancer agents, switching to other regimens with different drug characteristics, such as fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) or gemcitabine plus nab-paclitaxel (GN) therapy, may be advisable in adjuvant settings, especially for patients with NAC-Evans I disease. Conroy *et al*. demonstrated that AC using a modified FOLFIRINOX regimen led to a significantly longer survival period than AC with gemcitabine among 493 patients with resected pancreatic cancer in a randomized phase 3 trial (median OS: 54.4 months *vs*. 35 months, $p=0.003$) (4). Tempero *et al*. revealed that AC using GN contributed to an improved survival, compared with AC using gemcitabine, in 866 surgically resected pancreatic cancer patients in a

UFS group (n=42)

(A)

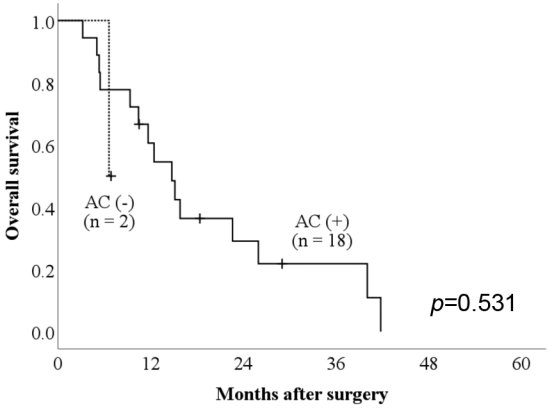


(B)

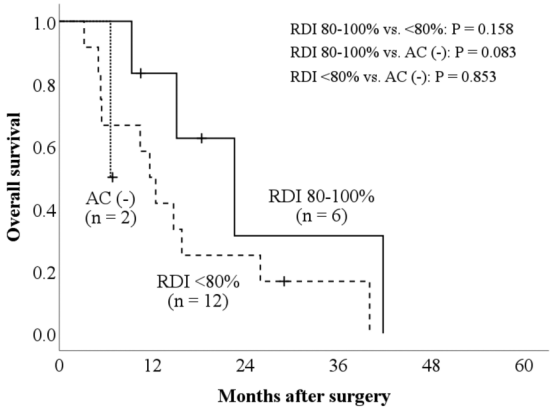


NAC-Evans I group (n=20)

(C)

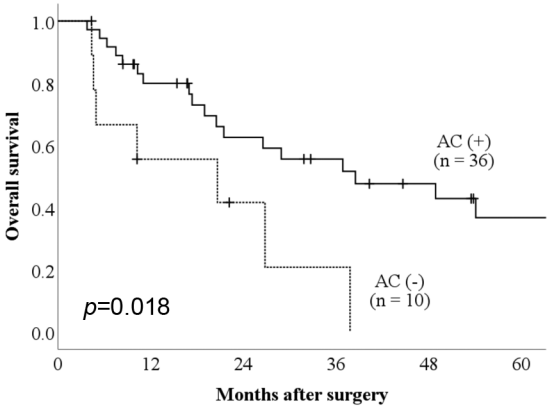


(D)



NAC-Evans IIa group (n=46)

(E)



(F)

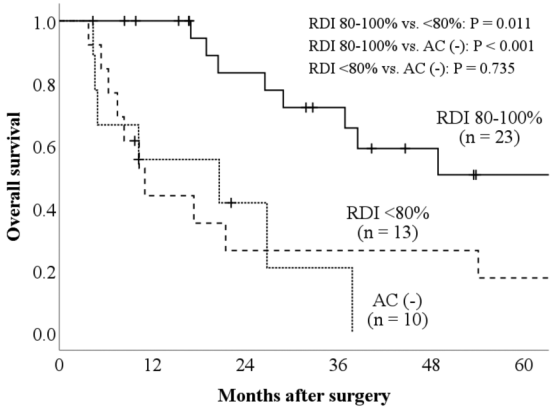


Figure 3. *Continued*

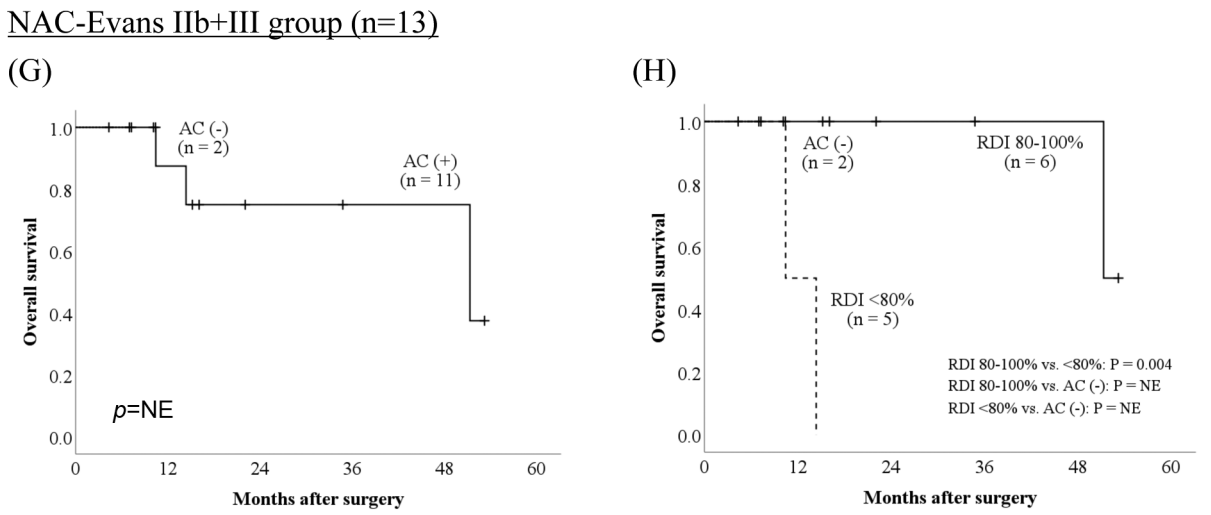


Figure 3. *Comparisons of overall survival between patients with AC and those without AC and among patients with an RDI of 80%-100%, patients with an RDI <80%, and those without AC are shown for the UFS (n=42) (A, B), NAC-Evans I (n=20) (C, D), NAC-Evans IIa (n=46) (E, F), and NAC-Evans IIb+III (n=13) (G, H) groups.*

Table III. *Univariate and multivariate analyses of predictors of overall survival (n=121).*

		Uni*	Multi**		
Variables	n	*p*-Value	HR	95%CI	*p*-Value
Age ≥70 years	54	0.181			
Male	69	0.914			
BMI <20 kg/m^2	38	0.187			
CEA >5 ng/ml	44	0.518			
CA19-9 >37 U/ml	87	0.266			
Resectability status (BR or UR-LA)	29	**0.017**	–	–	–
NAC (+)	79	0.276			
NAC-Evans grade II+III	59	**0.004**	0.552	0.344-0.884	**0.013**
Surgical procedure (PD)	74	0.199			
Operation time ≥480 min	65	0.644			
Blood loss ≥1,000 ml	30	0.566			
Clavien-Dindo grade III, IV	32	0.337			
pStage III	26	**0.002**	–	–	–
Histology (moderately, poorly, others)	75	**0.031**	–	–	–
Lymphatic invasion (+)	87	0.103			
Venous invasion (+)	104	0.349			
Neural invasion (+)	105	0.767			
Resection margin (+)	11	0.538			
AC (+)	95	**<0.001**	–	–	–
AC RDI of 80%-100%	55	**<0.001**	0.283	0.175-0.456	**<0.001**

AC: Adjuvant chemotherapy; BMI: body mass index; BR: borderline resectable; CA19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; CI: confidence interval; HR: hazard ratio; NAC: neoadjuvant chemotherapy; PD: pancreaticoduodenectomy; RDI: relative dose intensity; UR-LA: unresectable-locally advanced. *Log-rank test; **Cox proportional hazard model with forward stepwise selection. Bold values indicate statistical significance.

randomized phase 3 trial (median OS: 40.5 months *vs*. 36.2 months, *p*=0.045) (5).

Overall, the survival curves were clearly stratified according to the pathological response to NAC, with NAC-Evans IIb+III patients having the longest survival period followed by NAC-Evans IIa patients, UFS patients, and NAC-Evans I patients (Figure 2A). Stratification of the survival curves was also observed for patients with

resectable PDAC, but not for patients with BR or UR-LA PDAC (Figure 2B and C). The results of an RCT using NAC-GS demonstrated that the superiority of NAC-GS to UFS with respect to OS was only evident for patients with resectable or BR-PV PDAC (20). The usefulness of NAC-GS for patients with BR-A or UR-LA PDAC remains uncertain. Possible reasons for these results include: 1) the biological behavior of the tumor, such as its invasiveness and aggressiveness, might influence the pathological response to NAC, or 2) a good pathological response to NAC might enable tumor downstaging.

The RDI of AC was significantly lower in patients classified as NAC-Evans I because of the frequent and early development of tumor recurrence, compared with the other groups (Table II). Although significantly lower NAC completion rates were observed in patients with NAC-Evans I, the RDI of NAC was similar among patients classified as NAC-Evans I, IIa, and IIb+III (Table II). Accordingly, the associations among the RDI, the completion rate of NAC, and the pathological response to NAC remain uncertain.

Our study has some limitations. First, this was a single-center, retrospective study that analyzed data for only a small number of Japanese patients with PDAC during a 7-year period. Within this study period, the indications for NAC were not uniform. Second, a selection bias might have existed in this series, since various factors including pre-, intra-, and post-operative variables and the patients' age and general conditions could have influenced the selection of NAC and AC. Third, decisions regarding the starting doses and the discontinuation of AC varied among the physicians. Therefore, further prospective studies with larger numbers of patients are necessary to reach definitive conclusions.

In conclusion, a pathological response to NAC influences the efficacy of AC and is associated with an improved prognosis. In particular, AC is preferable for patients with NAC-Evans IIa or IIb+III disease, while more effective AC regimens may be advisable for patients with NAC-Evans I disease.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Study concept and design: S.M.; drafting of the manuscript: S.M.; data collection: S.M., Y.S., T.S., T.Y., K.P., T.M., T.S., and Y.I.; critical revision of the manuscript: T.A.; study supervision: K.K.

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