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Neoadjuvant Chemotherapy With Gemcitabine and S-1 Versus Upfront Surgery for Resectable Pancreatic Cancer

Results of the Randomized Phase II/III Prep-02/JSAP05 Trial

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Objective: This randomized phase II/III study evaluated the superiority of neoadjuvant therapy with gemcitabine plus S-1 over upfront surgery for patients with resectable pancreatic ductal adenocarcinoma (PDAC).

Background: PDAC is a leading cause of cancer mortality that urgently requires better treatment.

Methods: Patients with resectable PDAC (without arterial abutment) were randomly assigned to upfront surgery or neoadjuvant chemotherapy with gemcitabine (1000 mg/m^2 days 1 and 8) and S-1 (40–60 mg orally twice daily, days 1–14 every 3 wk for 2 cycles). Phase II and III primary endpoints were resection rate and overall survival, respectively. UMIN Clinical Trials Registry number: UMIN000009634.

Results: Patients (n = 364) were enrolled and randomly allocated to upfront surgery (UPS; n = 182) or neoadjuvant gemcitabine plus S-1 (NAC-GS; n = 182). Patient demographics and tumor characteristics were balanced between groups. Median overall survival in the UPS and NAC-GS groups was 26.6 (95% CI: 21.5, 31.5) and 37.0 (95% CI: 28.6, 43.3) months, respectively. The hazard ratio for mortality in the NAC-GS group compared with the UPS group was 0.73 (95% CI: 0.56, 0.95; $P = 0.018$). Median relapse-free survival in the UPS and NAC-GS groups was 11.3 (95% CI: 9.41, 13.5) and 14.3 (95% CI: 11.7, 17.0) months, respectively. The hazard ratio for relapse in the NAC-GS group compared with the UPS group was 0.77 (95% CI: 0.61, 0.98; $P = 0.030$).

Conclusions: The Prep-02/JSAP05 trial results showed that neoadjuvant chemotherapy with gemcitabine plus S-1 significantly extends survival compared with upfront surgery in patients with resectable PDAC.

Key Words: resectable pancreatic cancer, neoadjuvant chemotherapy, randomized controlled trial, gemcitabine and S-1

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Pancreatic ductal adenocarcinoma (PDAC) has the poorest outcome among malignant tumors, and improved treatments are urgently needed. In Japan, PDAC is the fourth leading cause of death, with the Japanese National Cancer Center reporting 37,677 pancreatic cancer deaths in 2020,[1] and the number continues to increase. In the United States, PDAC is the third most common cause of cancer death.[2]

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Upfront surgery followed by adjuvant chemotherapy is the current standard of care for resectable PDAC, but the 5-year survival rate is only 20% for patients who undergo complete resection followed by gemcitabine adjuvant therapy.[3] In 2016, the Japan Adjuvant Study Group of Pancreatic Cancer (JASPAC-01) study revealed the significant superiority of S1-adjuvant therapy over gemcitabine adjuvant therapy, reporting a median overall survival (OS) of 46.5 months for patients treated with the S1-adjuvant.[4] In 2018, Conroy and colleagues reported findings from a multicenter international randomized phase III trial, the PRODIGE 24/CCTG PA.6 trial, comparing the effects of gemcitabine and mFOLFIRINOX adjuvant therapy after pancreatic cancer resection. They revealed a significantly longer median OS of 54.4 months for mFOLFIRINOX and recommended it as the new standard of care following pancreatic resection.[5]

Postoperative adjuvant chemotherapy with mFOLFIRINOX is linked to a high occurrence of adverse events; however, and is thus suitable for only a subset of patients in excellent general condition. Due to the limitations of adjuvant chemotherapy, neoadjuvant chemotherapy is attracting increasing attention, particularly for patients with borderline resectable PDAC.[6]

In 2010, we established the Study Group of Preoperative therapy for Pancreatic cancer (Prep Group) and have been evaluating preoperative treatments for pancreatic cancer. In our first phase II multicenter prospective clinical study (Prep-01), neoadjuvant chemotherapy with gemcitabine and S-1 was administered for a total of 6 weeks before surgery.[7] Over a 2-year period, from September 2010 to September 2012, 104 patients (including those with resectable and borderline resectable PDAC) were eligible for the study; among these, 101 patients were analyzed, excluding 3 patients who did not meet the eligibility criteria. The overall 2-year survival rate (including nonresected cases) was 55.9%, with the on-protocol group (resected cases with both neoadjuvant and adjuvant chemotherapy) achieving a 2-year survival rate of 74.6%. Although phase II trials demonstrated the usefulness of neoadjuvant therapy, randomized controlled trials are required to reveal whether the treatment prolongs survival.

Here we report the results of a randomized phase II/III trial evaluating whether neoadjuvant gemcitabine plus S-1 (GS) chemotherapy improves the prognosis compared with upfront surgery in patients with resectable PDAC.

METHODS

Study Design

The study design was described previously[8] and is only briefly described here. The primary objective of this randomized, open-label, multicenter, phase II/III study was to confirm the superiority of neoadjuvant therapy with GS over the standard strategy of upfront surgery in patients with resectable PDAC. Led by the Study Group of Preoperative Therapy for Pancreatic Cancer (PREP) and the Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer (JSAP), PREP-02/JSAP05, the study involved 67 specialized centers as of December 20, 2012. The trial was completed in accordance with the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research Involving Human Subjects of the Ministry of Health, Labor, and Welfare of Japan. The protocol was approved by the Institutional Protocol Review Boards of Tohoku University (affiliation of the principal investigator) and the other participating institutions.

Endpoints

In phase II, the primary endpoint was the resection rate, with adverse events as the secondary endpoint. In phase III, the primary endpoint was OS, and secondary endpoints included resection rate, adverse events, recurrence-free survival, and patterns of recurrence for resected cases, residual tumor status, nodal metastasis, tumor marker kinetics, dose intensity, and radiologic and histologic responses in the experimental arm. The OS was calculated from the day of randomization to death from any cause, with censoring at the last documented date the patient was known to be alive.

Inclusion and Exclusion Criteria

The inclusion criteria for the study were as follows: (1) histologically or cytologically confirmed treatment-naïve PDAC; (2) localized tumor with no distant metastasis to the liver, peritoneum, lung, etc.; (3) R0/R1 resectable tumor without involvement of the hepatic, celiac, or superior mesenteric arteries; (4) candidate for curative resection; (5) Eastern Cooperative Oncology Group performance status of 0 or 1; (6) preserved organ function with the following laboratory values: white blood cell count $\geq 3000/mm^3$ and $< 12{,}000/mm^3$, neutrophils $\geq 2000/mm^3$, platelet count $\geq 100{,}000/mm^3$, hemoglobin ≥ 9.0 g/dL, serum total bilirubin ≤ 2.0 mg/dL, aspartate aminotransferase ≤ 150 IU/L, alanine aminotransferase ≤ 150 IU/L, creatinine ≤ 1.2 mg/dL, creatinine clearance ≥ 50 mL/min; (7) adequate oral intake; (8) age 20–79 years; and (9) written, informed consent to participate in the study. Exclusion criteria included the following: (1) pulmonary fibrosis or interstitial pneumonia; (2) severe diarrhea; (3) active infection; (4) regular use of flucytosine, phenytoin, or warfarin; (5) pregnancy, breastfeeding, or desire to preserve fertility; (6) synchronous malignancy except for carcinoma in situ or intramucosal tumor after adequate curative treatment; (7) metachronous malignancy unless relapse-free survival (RFS) ≥ 3 y; and (8) patients deemed unsuitable for the study by the primary care physician.

Registration and Randomization

Eligible patients were centrally registered and randomly assigned to treatment by the nonprofit organization Japan Clinical Research Support Unit, Tokyo, Japan. Using a 1:1 ratio, patients were allocated to either neoadjuvant GS (NAC-GS) or upfront surgery (UPS). Randomization was conducted at the data center using a modified minimization method, ensuring balance across institutions and serum CA19-9 levels (< 37, 37–370, > 370 U/mL).

Central Review

A blinded central review of the baseline contrast-enhanced CT scans was conducted by an experienced radiologist to classify patients as having either resectable or borderline resectable (without arterial contact) disease for subgroup analysis. In addition, a thorough review of baseline CT scans confirmed that no cases exhibited distant metastasis or locally advanced disease.

Neoadjuvant Chemotherapy

Patients in the NAC-GS group received chemotherapy comprising intravenous gemcitabine at 1000 mg/m^2 on days 1 and 8, along with oral S-1 orally, with doses based on body surface area (BSA): 40 mg for BSA < 1.25 m^2, 50 mg for BSA 1.25–1.50 m^2, and 60 mg for BSA > 1.50 m^2;

administered twice daily on days 1 to 14 of a 21-day cycle. For patients with a creatinine clearance of 50 to 60 mL/min, the S-1 dose was reduced by 20 mg/d. Neoadjuvant treatment was given for 2 cycles, and treatment was discontinued in cases of unacceptable toxicity, such as grade 4 toxicity, based on the Common Toxicity Criteria (version 3.0). For patients experiencing Grade 3 hematologic toxicity or grade 2 nonhematologic toxicity, both gemcitabine and S-1 were paused until recovery. If grade 4 hematologic or grade 3 nonhematologic toxicity occurred, the doses of gemcitabine and S-1 were reduced by 200 mg/m^2/d and 20 mg/d, respectively, when treatment resumed.

Surgery

Patients in the UPS group underwent primary surgery with curative intent within 8 weeks of enrollment. Those in the NAC-GS group underwent surgery from 2 to 4 weeks (up to a maximum of 6 wk) after their final dose of oral S-1. In both groups, pancreatectomy with regional lymph node dissection was performed with curative intent, tailored to the tumor's location and extent in each patient.

Adjuvant Chemotherapy

Patients in both groups were strongly advised to begin S-1 adjuvant therapy within 10 weeks after curative surgery and to continue the therapy for 6 months as postoperative treatment.

Statistical Analyses

The sample size calculation assumed that the 2-year survival probability is 35% for the UPS group and 50% for the NAC-GS group, as reported previously.[7] To detect a 15% improvement in 2-year OS with NAC-GS compared with UPS, with 80% power and a 2-sided alpha level of 5%, the required sample size was set at 360 patients, allowing for 210 events. The planned accrual period was 3 years, with a 2-year follow-up for the primary analysis. Statistical analysis was performed with SAS software (version 9.2; SAS Institute, Cary, NC). This clinical trial was registered with the UMIN Clinical Trials Registry (UMIN000009634).

RESULTS

Between January 2013 and January 2016, 364 patients were enrolled and randomly allocated to UPS (n = 182) or NAC-GS (n = 182). After randomization, three patients allocated to UPS were deemed ineligible: 1 case in which consent was not obtained, and 2 cases with no malignancy. As a result, the full intention-to-treat analysis set included 361 patients (UPS, n = 179; NAC-GS, n = 182; Fig. 1). The baseline characteristics are shown in Table 1. Patient demographics and tumor characteristics were evenly distributed between the 2 groups. We analyzed the phase II results using the data of 84 cases in October 2013. The resection rates were 82% (36/44, UPS) and 93% (39/44, NAC-GS). As the prespecified criteria were met and there was no significant reduction in the resection rate in the NAC-GS group, we proceeded to phase III based on the recommendation from the Independent Data and Safety Monitoring Committee.

In September 2018, 2 years and 9 months after the final enrollment, > 210 events were recorded in the total cohort (with group masking). Therefore, we concluded the data collection and finalized the data set.

In the UPS group, 2 patients did not undergo surgery due to liver metastases that were not detected at the time of enrollment. Surgery was performed on 177 patients; however, 21 patients were deemed unresectable during surgery due to distant metastases. In addition, 20 patients underwent pancreatectomy but were classified as having noncurative resections owing to R2 resection, distant metastases (including extraregional lymph nodes), or positive peritoneal cytology. In the NAC-GS group, 10 patients did not receive neoadjuvant therapy. Of these, 7 patients withdrew consent, and 3 patients were unable to start chemotherapy within the protocol-defined timeframe. After neoadjuvant treatment, 11 patients did not undergo surgery, including 8 who were ineligible due to distant metastases. Among 161 patients who proceeded to surgery, 4 were found to have distant metastases during surgery and were deemed unresectable, while 15 underwent noncurative resections (Fig. 1).

Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/SLA/F467, shows adverse events in the NAC-GS group. All but 10 patients who did not start neoadjuvant therapy (n = 172) experienced some grade of adverse events, with grade 3 adverse events occurring in 48.8% and grade 4 occurring in 23.8%. The grade 3 adverse events frequently (> 5%) observed in patients receiving NAC-GS were neutropenia, leukopenia, skin rash, appetite loss, febrile neutropenia, and stomatitis. Grade 4 neutropenia was observed in 22.7%, but no grade 4 febrile neutropenia or nonmyeloid adverse events were reported.

In the intention-to-treat analysis, the median OS was 26.6 months (95% CI: 21.5, 31.5) in the UPS group and 37.0 months (95% CI: 28.6, 43.3) in the NAC-GS group. The hazard ratio (HR) for mortality in the NAC-GS group compared with the UPS group was 0.73 (95% CI: 0.56, 0.95, $P = 0.018$; Fig. 2A). The OS rate at 1, 2, and 3 years was 75.9%, 52.8%, and 36.6%, respectively, in the UPS group compared with 87.1%, 63.7%, and 50.2%, respectively, in the NAC-GS group.

Median RFS was 11.3 months (95% CI: 9.4, 13.5) in the UPS group and 14.3 (95% CI: 11.7, 17.0) in the NAC-GS group. The HR for relapse in the NAC-GS group compared with the UPS group was 0.77 (95% CI: 0.61, 0.98, $P = 0.030$; Fig. 2B). The estimated RFS at 1, 2, and 3 years was 47.6%, 27.1%, and 20.0%, respectively, in the UPS group, and 56.6%, 36.1%, and 27.5%, respectively, in the NAC-GS group.

Subgroup analysis revealed an estimated HR > 1.0 for tumor-stage 2, but the number of patients in the subgroup was small (Fig. 3). The groups were stratified based on resectability criteria as determined by central review [ie, resectable (R) and borderline resectable-PV], and the subgroups were analyzed. Both subgroups had better outcomes in the NAC-GS group.

No significant differences in operative time, blood loss, operation method, intraoperative washing cytology, or morbidity were detected between groups. A significant trend toward fewer vascular combined resections and more R0 resections was noted in the NAC-GS group. No operative deaths occurred in either group.

Regarding the histopathologic results of the operative specimens,[9] the number of lymph node-positive cases (pN1) was significantly lower (59.2%) in the NAC-GS group than in the UPS group (81.4%). Based on the Japanese Pancreas Society[10] and Evans grading systems[11] for PDAC, the response to chemotherapy was higher in histopathologic specimens from the NAC-GS group.

S-1 adjuvant therapy was equivalently administered in both groups. The completion rate of 4 cycles of S-1 chemotherapy and the mean dose intensity were 63.3%

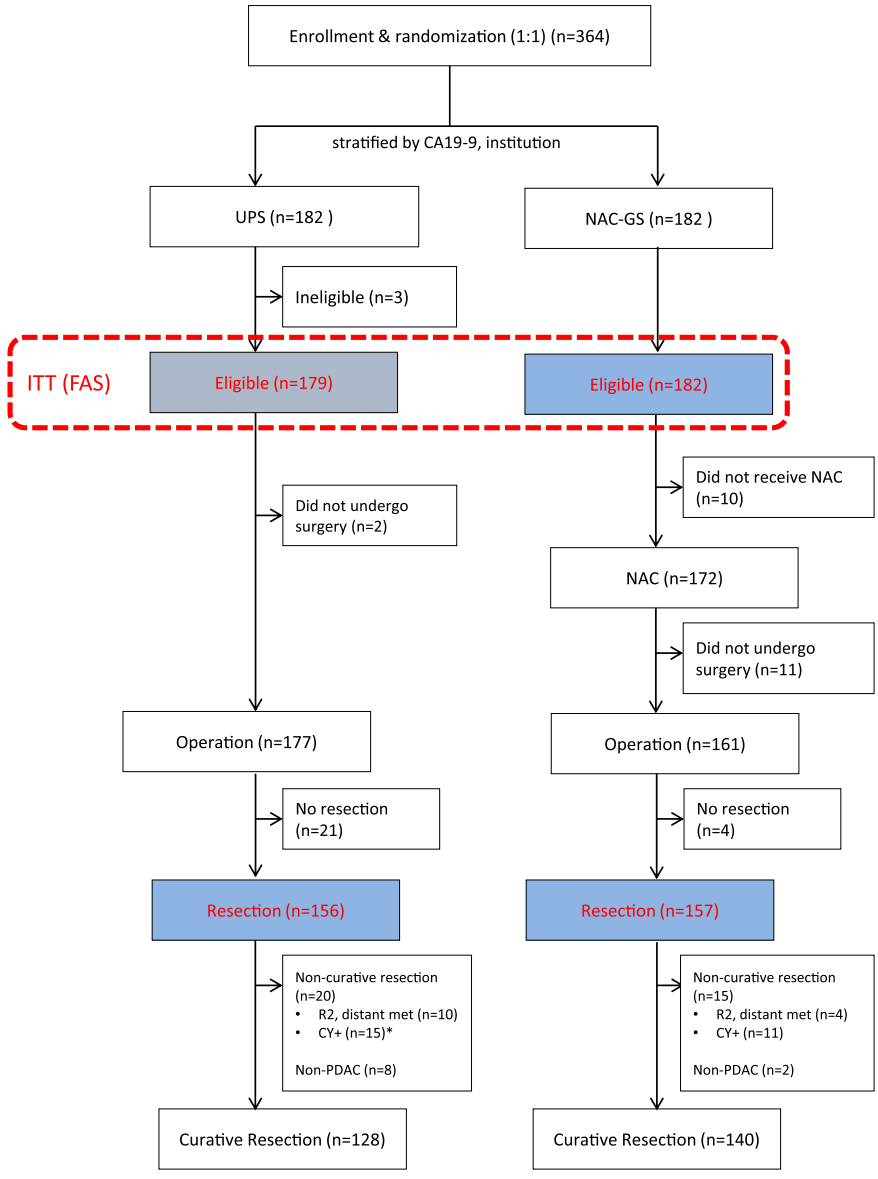


FIGURE 1. CONSORT diagram of the PREP-02/JSAP05 trial. FAS indicates full analysis set; ITT, intention to treat; *, duplicated values.

and 79.3%, respectively, in the UPS group, and 62.1% and 77.6%, respectively, in the NAC-GS group.

Recurrence was detected in 117 (65.4%) of 179 patients in the UPS group and 110 (60.4%) of 182 patients in the NAC-GS group (Table 2). The liver was the most frequent site of recurrence in both groups, with the NAC-GS group having significantly lower recurrence in the liver than the UPS group (30.0% vs 47.9%, $P < 0.01$).

DISCUSSION

This randomized phase II/III trial provides compelling evidence supporting the use of neoadjuvant chemotherapy with GS for patients with resectable PDAC. As the first phase III trial to demonstrate a significant improvement in OS and RFS for patients receiving neoadjuvant therapy compared with those undergoing upfront surgery, it marks a pivotal advancement. Neoadjuvant GS achieved a more favorable pathologic response and a lower incidence of postoperative liver metastases while maintaining manageable toxicity levels. These factors likely contributed to the significant survival benefit observed in this trial.

Even after surgical resection for PDAC, patients often develop early liver metastasis, peritoneal dissemination, and lymph node recurrence, suggesting the presence of preoperative micrometastases of cancer cells in the liver, peritoneum, and lymph nodes. For this reason, adjuvant therapy in the early postoperative period is frequently deemed necessary.[12,13] Postoperative adjuvant therapy leads to better outcomes, with a median survival time of 54.4 months for mFOLFIRINOX[5] and 46.5 months for S-1.[4] It is important to note, however, that patients enrolled in these clinical studies typically represent a select population, as they recover in better general condition postoperatively and

TABLE 1. Baseline Demographics and Clinicopathologic Characteristics of Included Patients

Variables	UPS (n = 179)	NAC-GS (n = 182)	*P*
Sex, n (%)	—	—	1.00
Male	95 (53.1)	96 (52.7)	
Female	84 (46.9)	86 (47.3)	—
Age (mean)	66.0 ± 7.9	67.3 ± 8.2	0.27
< 65, n (%)	71 (39.7)	61 (33.5)	—
≧65, n (%)	108 (60.3)	121 (66.5)	——
CA19-9, n (%)	—	—	0.43
< 37	53 (29.6)	44 (24.2)	—
37≦ < 370	75 (41.9)	87 (47.8)	—
370≦	51 (28.5)	51 (28.0)	—
Performance status, n (%)	—	—	0.42
0	169 (94.4)	176 (96.7)	—
1	10 (5.6)	6 (3.3)	—
Location, n (%)	—	—	0.83
Head	129 (72.1)	134 (73.6)	
Body/tail	50 (27.9)	48 (26.4)	
Max size (cm, median)	2.4	2.5	0.37
cT stage, n (%)	—	—	0.38
cT1	28 (15.6)	24 (13.2)	—
cT2	19 (10.6)	28 (15.4)	—
cT3	132 (73.7)	130 (71.4)	—
cN stage, n (%)	—	—	1.00
cN0	140 (78.2)	143 (78.6)	—
cN1	39 (21.8)	39 (21.4)	—
cM stage, n (%)	—	—	—
cM0	179 (100)	182 (100)	—
cM1	0	0	—
	n = 156	**n = 157**	—
Operation from Randomization (d)	17.7 ± 9.2	64.4 ± 12.6	< 0.01
Operation time (min)	462.5 ± 158.0	448.4 ± 163.1	0.35
Bleeding (mL)	959.1 ± 917.1	1079.3 ± 1777.8	0.86
Operation method, n (%)	—	—	0.80
	Pan-creati-coduo-		
denectomy	109 (69.9)	114 (72.6)	—
Distal Pancreatectomy	42 (26.9)	37 (23.6)	
Total Pancreatectomy	5 (3.2)	6 (3.8)	——
Combined resection, n (%)	——		0.08
Portal	61 (39.1)	58 (36.9)	—
Arterial	5 (3.2)	0	—
Intraperitoneal washing cytology, n (%)	—	—	1.00
Positive	8 (5.1)	9 (5.7)	—
Negative	144 (92.3)	145 (92.4)	
Not exam	4 (2.6)	3 (1.9)	—
Residual tumor, n (%)	—	—	0.23
R0	134 (85.9)	143 (91.1)	—
R1	18 (11.5)	13 (8.3)	—
R2	4 (2.6)	1 (0.6)	—
Reoperation	4 (2.6)	0	0.12
Morbidity	77 (49.4)	72 (45.9)	0.61
Mortality	0	0	—
pT, n (%)	—	—	0.33
pT0	0	1 (0.6)	—
pT1	8 (5.1)	16 (10.2)	—
pT2	3 (1.9)	5 (6.4)	—
pT3	122 (78.2)	110 (70.1)	—
pT4	22 (14.1)	24 (15.3)	—
pN, n (%)	—	—	< 0.01
pN0	29 (18.6)	63 (40.1)	—
pN1	127 (81.4)	93 (59.2)	—
pM, n (%)	—	—	0.69
pM0	139 (89.1)	143 (91.1)	—
pM1	17 (10.9)	14 (8.9)	—
	n = 106	**n = 111**	—
Treatment effect (JPS), n (%)	—	—	< 0.01
1a (> 90%)	86 (81.1)	40 (36.0)	—
1b (50-90%)	17 (16.0)	55 (49.5)	—
2 (10-50%)	3 (2.8)	13 (11.7)	—
3 (< 10%)	0	3 (2.7)	—
4 (0%)	0	0	—
Treatment effect (Evans), n (%)	—	—	< 0.01
I	86 (81.1)	41 (36.9)	—
IIa	17 (16.0)	54 (48.6)	—
IIb	3 (2.8)	13 (11.7)	—
III	0	3 (2.7)	—
IV	0	0	—
	n = 128	**n = 140**	—
Initiation of adjuvant chemotherapy, n (%)	108 (84.4)	119 (85.0)	0.89
Completion of adjuvant chemotherapy, n (%)	81 (63.3)	87 (62.1)	0.84
Relative dose intensity (%)	—	—	0.59
Mean	79.3	77.6	—
Median	97.3	87.5	—

JPS indicates Japan Pancreas Society; NAC-GS, neoadjuvant chemotherapy with gemcitabine plus S-1; UPS, upfront surgery.

can begin adjuvant chemotherapy early without postoperative complications. This likely contributes to the high survival rates observed. In real-world clinical practice, liver metastasis or peritoneal dissemination may be discovered during laparotomy when surgery is planned, or postoperative pathologic examination shows positive peritoneal cytology or para-aortic lymph node metastases. In addition, postoperative complications can delay recovery, leading some patients to forgo adjuvant chemotherapy. As a result, relying solely on adjuvant therapy alone may limit the potential for improving outcomes in PDAC.

In recent years, neoadjuvant therapy has gradually gained attention as a complementary treatment to adjuvant therapy.[14,15] Neoadjuvant therapy has several advantages, including (1) cancer treatment can be started immediately after diagnosis, (2) drug intensity can be very high because the patient is preoperative and in good general condition, (3) potential downstaging by neoadjuvant treatment can reduce the extent of resection and resected organs, (4) treatment results can be improved by eliminating micrometastases, and (5) postoperative adjuvant chemotherapy can be more effectively tailored based on the response to preoperative treatment.

On the other hand, neoadjuvant therapy also has major disadvantages, such as (1) the risk of tumor progression during treatment, which may result in a lost opportunity for resection; (2) treatment may be difficult to continue due to adverse events; (3) increased risk of intraoperative and postoperative complications and mortality; (4) potential for overtreatment; and (5) the necessity of a definitive histologic or cytologic diagnosis before initiating therapy.

In a retrospective study comparing thousands of patients receiving preoperative treatment with those undergoing upfront surgery, data from the United States National Cancer

Database showed a significantly better prognosis for the preoperative treatment group.[16] The level of evidence is limited, however, due to inherent biases associated with the retrospective design of the study. Neoadjuvant therapy has advantages and disadvantages, and intention-to-treat analysis should be performed in randomized controlled trials to clarify the benefit of neoadjuvant therapy in resectable PDAC. No randomized controlled trials on neoadjuvant therapy for resectable pancreatic cancer have demonstrated its superiority over upfront surgery. The PREOPANC-1 trial compared the effects of neoadjuvant chemoradiotherapy (CRT) with gemcitabine and upfront surgery for resectable and borderline resectable pancreatic cancer.[6] This trial showed that patients with borderline resectable pancreatic cancer who underwent neoadjuvant therapy had a better prognosis than those who underwent upfront surgery. Patients with resectable pancreatic cancer did not experience a survival benefit from neoadjuvant CRT, however, compared with those who underwent upfront surgery. Interestingly, this trial, along with several recent RCTs, reported resection rates of 61% to 63% following neoadjuvant therapy with CRT,[6,17–19] which was ~10% lower than that of upfront surgery. In contrast, the current trial using GS as a neoadjuvant therapy revealed no decrease in the resection rate (86.2% vs. 87.1%) and a significantly reduced incidence of postoperative hepatic recurrence compared with upfront surgery. In this regard, patients with resectable PDAC can benefit from neoadjuvant chemotherapy due to its systemic nature. The results of the NORPACT-1 trial comparing neoadjuvant FOLFIRINOX and upfront surgery for resectable pancreatic head cancer were recently reported.[20] In this phase II RCT, neoadjuvant FOLFIRINOX showed no survival benefit compared with upfront surgery. That trial revealed a relatively lower completion rate for neoadjuvant therapy with FOLFIRINOX (60%) and adjuvant therapy with mFOLFIRINOX (25%–43%). Furthermore, neoadjuvant FOLFIRINOX therapy was associated with a higher incidence of adverse events compared with GS therapy, resulting in delayed recovery from intensive pancreatectomies and reduced tolerance for subsequent postoperative adjuvant therapy. These factors may influence survival outcomes in the neoadjuvant group.

A significant difference in treatment strategy between the present study and prior RCTs is the allocation of adjuvant chemotherapy. While prior studies adjusted the duration of adjuvant chemotherapy to align the total treatment period before and after surgery, our study retained the duration of adjuvant chemotherapy and aimed to evaluate the additional efficacy of neoadjuvant therapy. To demonstrate the additional benefit of neoadjuvant therapy over the standard adjuvant chemotherapy approach for resectable PDAC, it is crucial to show that the completion rate of adjuvant chemotherapy is not diminished compared with upfront surgery followed by adjuvant chemotherapy strategy. This study demonstrated that adjuvant chemotherapy was administered at comparable rates between the UPS group and the NAC-GS group. As anticipated, a certain number of patients could not initiate adjuvant chemotherapy following curative resection. In the NAC-GS group, however, these patients received some chemotherapy before surgery. In addition, this study standardized the adjuvant chemotherapy regimen to S-1, the standard therapeutic agent in Japan,[4] thereby avoiding inconsistencies in treatment due to mixed regimens, which is a notable strength of this study. Furthermore, no mortality was observed in either group in this prospective study. This finding not only confirms that NAC-GS does not negatively impact perioperative outcomes but also suggests that its high safety profile contributed to the study's anticipated results. A potential drawback of neoadjuvant therapy is the risk of losing the opportunity for surgical resection. In this study, eight patients did not undergo surgery following the introduction of NAC-GS due to disease progression. The number of patients unable to achieve curative resection due to distant metastases identified after enrollment, however, was lower in the NAC-GS group than in the UPS group. This suggests that rather than representing a loss of surgical opportunity, these outcomes

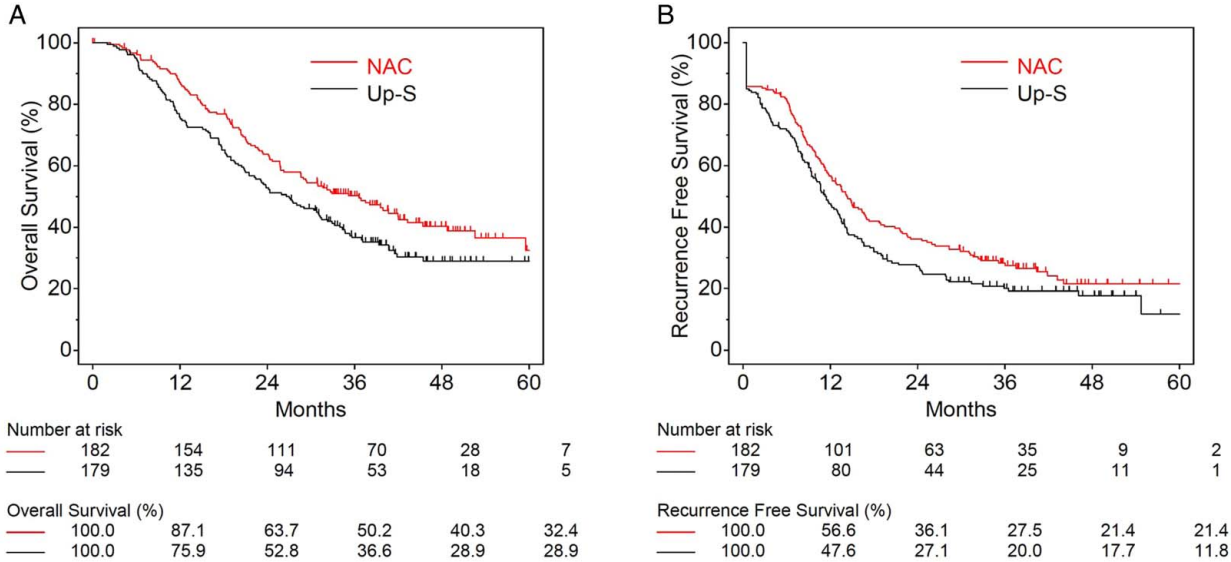
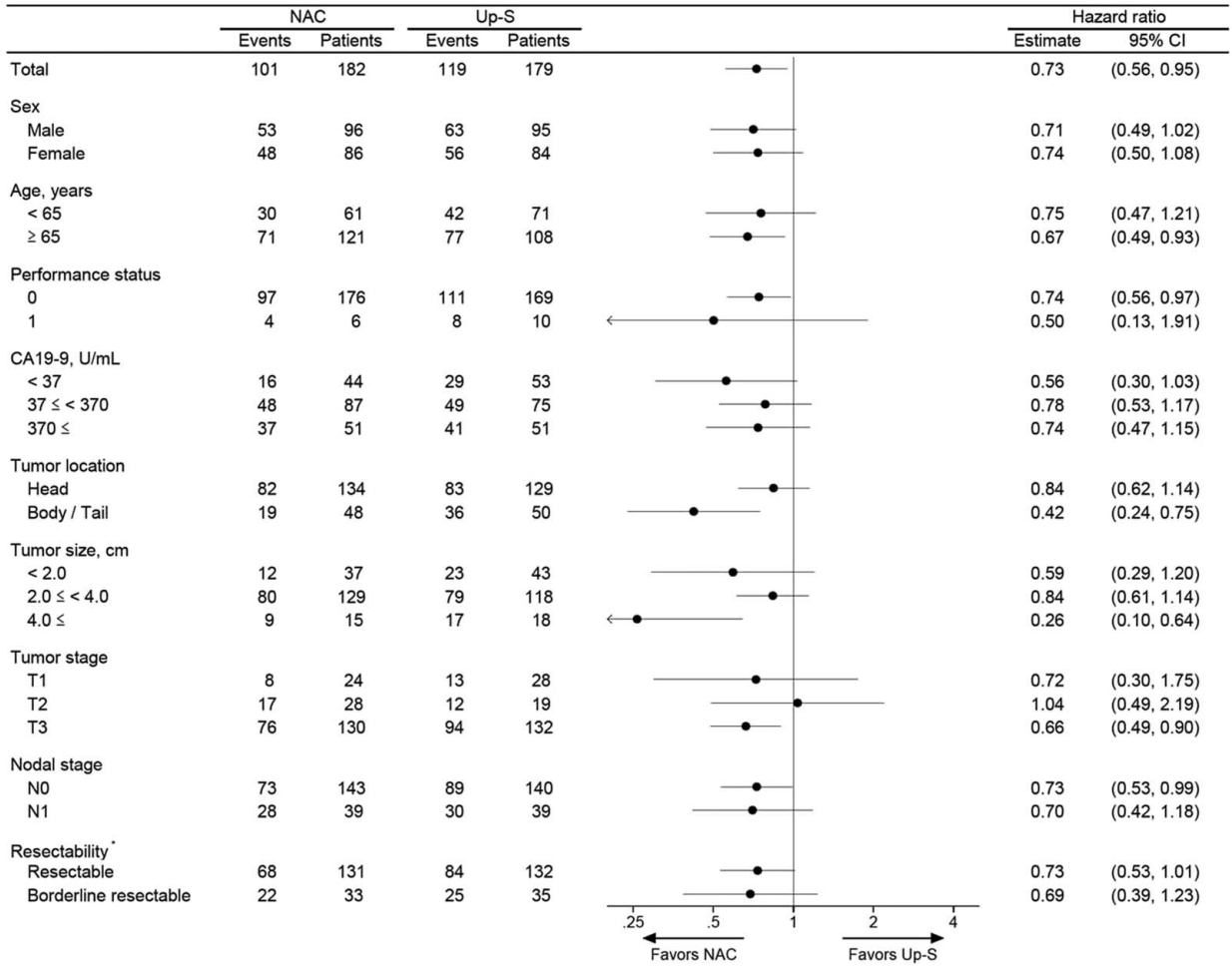


FIGURE 2. Kaplan-Meier survival curves. A, Overall survival. Median overall survival was 26.6 months (95% CI: 21.5, 31.5) in the UPS group and 37.0 months (95% CI: 28.6, 43.3) in the NAC-GS group. The hazard ratio for mortality in the NAC-GS group compared with the UPS group was 0.73 (95% CI: 0.56, 0.95, $P = 0.018$). B, Relapse-free survival. Median relapse-free survival was 11.3 months (95% CI: 9.4, 13.5) in the UPS group and 14.3 (95% CI: 11.7, 17.0) in the NAC-GS group. The hazard ratio for relapse in the NAC-GS group compared with the UPS group was 0.77 (95% CI: 0.61, 0.98, $P = 0.030$).



* 30 patients (NAC: 18, Up-S: 12) were not evaluable.

FIGURE 3. Subset analysis of overall survival using the Cox regression model.

may more appropriately be interpreted as the avoidance of futile surgical interventions.

A limitation of this study is that only Japanese patients were included. In addition, the regimen differed from the recent regimens for mFOLFIRINOX or gemcitabine and nanoparticle albumin bound-paclitaxel, and the optimal duration of neoadjuvant therapy is unknown.

We are confident that the development of more effective regimens and clarification of the optimal treatment duration will further enhance future outcomes.

The Prep-02/JSAP-05 study demonstrated significant survival benefits of neoadjuvant chemotherapy with NAC-GS. The neoadjuvant therapy was generally safe, although some grade 3 or 4 adverse events of leukopenia or neutropenia occurred. The NAC-GS group had fewer lymph node metastases and less liver recurrence, which may have contributed to the improved prognosis. Although the optimal regimen and duration of neoadjuvant therapy have yet to be established, the doublet regimen of gemcitabine and S-1 could be a new standard therapy for patients with resectable PDAC.

TABLE 2. Recurrence

	UPS (n = 179), n (%)	NAC-GS (n = 182), n (%)	*P*
Total	117 (65.4)	110 (60.4)	
Recurrence site			
Local	27 (23.1)	30 (27.3)	0.56
Liver	56 (47.9)	33 (30.0)	< 0.01
Distal lymph node	27 (23.1)	18 (16.7)	0.27
Lung	15 (12.8)	20 (18.2)	0.35
Bone	0	0	-
Peritoneal dissemination	16 (13.7)	23 (20.9)	0.20
Others	12 (10.3)	8 (7.3)	0.58

NAC-GS indicates neoadjuvant chemotherapy with gemcitabine plus S-1; UPS, upfront surgery.

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