Ann Surg Oncol (2019) 26:4498–4505
https://doi.org/10.1245/s10434-019-07735-8

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – PANCREATIC TUMORS

A Prospective, Open-Label, Multicenter Phase 2 Trial of Neoadjuvant Therapy Using Full-Dose Gemcitabine and S-1 Concurrent with Radiation for Resectable Pancreatic Ductal Adenocarcinoma

Hidetoshi Eguchi, MD[1,10], Yutaka Takeda, MD[2,10], Hidenori Takahashi, MD[3,10], Shin Nakahira, MD[4,10], Masaki Kashiwazaki, MD[5,10], Junzo Shimizu, MD[6,10], Daisuke Sakai, MD[7,10], Fumiaki Isohashi, MD[8], Hiroaki Nagano, MD[9,10], Masaki Mori, MD[1,10], and Yuichiro Doki, MD[1,10]

[1]Department of Gastroenterological Surgery, Graduate School of Medicine, Osaka University, Suita, Osaka, Japan; [2]Department of Surgery, Kansai Rosai Hospital, Amagasaki, Hyogo, Japan; [3]Department of Surgery, Osaka International Cancer Institute, Osaka, Japan; [4]Department of Surgery, Sakai City Medical Center, Osaka, Japan; [5]Department of Surgery, Osaka General Medical Center, Osaka, Japan; [6]Department of Surgery, Osaka Rosai Hospital, Osaka, Japan; [7]Department of Frontier Science for Cancer and Chemotherapy, Graduate School of Medicine, Osaka University, Osaka, Japan; [8]Department of Radiation Oncology, Graduate School of Medicine, Osaka University, Osaka, Japan; [9]Department of Gastroenterological, Breast and Endocrine Surgery, Yamaguchi University Graduate School of Medicine, Yamaguchi, Japan; [10]Clinical Study Group of Osaka University, Hepato-Biliary-Pancreatic Group, Osaka, Japan

ABSTRACT

Background. Neoadjuvant therapy reportedly shows only marginal clinical benefit in pancreatic ductal adenocarcinoma (PDAC), especially in resectable cases. However, with more effective regimens, neoadjuvant therapy may become a standard of care for resectable cases. A prospective, open-label, multicenter phases 1 and 2 trial of neoadjuvant therapy was conducted using full-dose gemcitabine and S-1 concurrently with 50.4 Gy of radiation therapy (GSRT) for resectable PDAC. This report describes the phase 2 results.

Methods. The phase 2 part of this study enrolled 57 patients with cytologically or histologically proven PDAC deemed resectable based on imaging before neoadjuvant therapy. These patients received GSRT. After reevaluation by computed tomography scan, surgical exploration was performed, followed by adjuvant therapy. According to the prescribed protocol of the clinical trial, statistical analyses included 57 phase 2 patients and 6 phase 1 patients who received the same dosage as in phase 2.

Results. This trial enrolled 63 patients (42 men and 21 women) with a median age of 70 years. Leukopenia or neutropenia of grade 3 or higher occurred for 79% of the patients, but no other severe adverse events were observed. Among the 63 patients, 54 underwent surgical resection. Intention-to-treat analysis of the 63 patients showed an excellent median survival time lasting as long as 55.3 months. The patients who completed neoadjuvant therapy, surgery, and adjuvant therapy had a 5-year survival rate of 56.6%.

Conclusions. This regimen showed outstanding clinical efficacy with acceptable tolerability for patients with resectable PDAC.

Electronic supplementary material The online version of this article (https://doi.org/10.1245/s10434-019-07735-8) contains supplementary material, which is available to authorized users.

First Received: 6 January 2019;
Published Online: 22 August 2019

H. Eguchi, MD
e-mail: heguchi@gesurg.med.osaka-u.ac.jp

Pancreatic ductal adenocarcinoma (PDAC) is among the deadliest diseases, with a 5-year survival rate of 8%.[1] Surgical resection is the only curative treatment, but only 10% of PDACs are surgically resectable, and the median survival period is 17 to 23 months, even after successful resection.[2] Because surgical resection alone is insufficient

to improve survival rates, adjuvant (postoperative) and/or neoadjuvant (preoperative) therapies are under investigation.

Compared with observation alone, adjuvant chemotherapy improves the overall survival rate and currently is widely accepted as the standard of care after resection, but the prognosis remains unsatisfactory.[3–5] Efforts to improve survival rates further involve intensive testing of nonsurgical therapies, including chemotherapy and radiation therapy before surgical resection.

An expert consensus statement divides non-metastatic PDAC into three categories: resectable, borderline resectable, and locally advanced disease.[6–8] In borderline resectable PDAC, a surgery-first strategy yields disappointing long-term survival rates, whereas several small-scale studies have demonstrated clinical benefits of neoadjuvant therapies. Thus, neoadjuvant therapy currently is the standard of care for borderline resectable PDAC.[6] However, clear evidence from randomized controlled trials is lacking. A recent single-arm phase 2 clinical trial tested neoadjuvant therapy with FOLIRINOX in 48 cases of borderline resectable PDAC and reported a favorable median overall survival time, indicating that a more effective regimen may yield improved long-term survival.[9]

The use of neoadjuvant therapies for resectable PDAC remains controversial. We and others have achieved encouraging survival rates using preoperative gemcitabine-based chemoradiotherapy for patients with potentially resectable PDAC. However, other groups have reported negative results.[10–12] Thus, to date, neoadjuvant therapy is not a standard of care for resectable PDAC, although recent systematic reviews of neoadjuvant therapies suggest a significant effect of improving long-term survival.[13–15] As described in borderline resectable PDAC, more effective regimens may yield improved long-term survival for patients with resectable PDAC.

As a fourth-generation oral fluoropyrimidine, S-1 consists of tegafur, gimeracil, and oteracil potassium in a molar ratio of 1:0.4:1. Its efficacy has been demonstrated for a variety of solid tumors, including gastric, colorectal, and pancreatic cancers,[4,16,17] and it recently was found to be superior to gemcitabine in the adjuvant setting.[4] Moreover, combination chemotherapy using gemcitabine and S-1 (GS therapy) yields a higher response rate than gemcitabine alone for locally advanced and metastatic PDAC.[18,19] Presumably, neoadjuvant therapy with more effective chemotherapeutic reagents (e.g., GS therapy) may help to improve long-term survival for patients with resectable PDAC. Furthermore, combining GS therapy with radiation therapy (GSRT) may further strengthen the antitumor effect. However, this combination has been applied only at reduced doses due to fear of adverse events.[20]

We conducted a phases 1 and 2 prospective, open-label, multicenter trial of GSRT. Our previously published results of the phase 1 component demonstrated that full-dose gemcitabine and full-dose S-1 (with 2 weeks of administration and 1 week of rest) could be combined with radiation therapy as neoadjuvant therapy for resectable PDAC.[21] In this report, we describe the results of the phase 2 component of this trial.

PATIENTS AND METHODS

Patient Eligibility

This study was a prospective, single-arm, multicenter phases 1 and 2 trial. For the phase 2 component, 57 patients were enrolled at six high-volume centers in Japan from December 2012 to May 2015. Neoadjuvant therapy was administered according to the previously described protocol.[21]

Briefly, we prospectively enrolled patients with resectable cytologically or histologically proven ductal adenocarcinoma of the pancreas. Cases were considered resectable if the pancreatic cancer had no abutment to the hepatic artery, celiac trunk, or superior mesenteric artery. Cases were considered ineligible if the pancreatic cancer showed abutment to such arteries, necessitating arterial reconstruction. However, cases were considered eligible if the tumors could be resected by distal pancreatectomy with celiac axis resection (DP-CAR, modified Appleby procedure), which relies on collateral flow from the superior mesenteric artery via the pancreatic head arcade to the liver and stomach, and thus does not require arterial reconstruction.[22] Cases also were considered resectable if the tumor showed venous abutment of the superior mesenteric vein/portal vein (SMV/PV) but the SMV/PV had suitable vessels proximal and distal to the area of vessel abutment to permit safe resection and reconstruction. The eligibility criteria were published with the results of our phase 1 study.[21]

This study was approved by the institutional review board (IRB) of Osaka University Hospital (IRB no. 09125) before patient enrollment, and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. This study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) officially accepted registries by the International Committee of Medical Journal Editors (ICMJE; registration no. UMIN000002649). All patients gave their written informed consent before undergoing any study procedure or receiving any study treatment.

Chemotherapy

The patients were administered an intravenous infusion of gemcitabine (1000 mg/m^2) on days 1, 8, 22, and 29, and S-1 was orally administered twice daily at a dose of 80 mg/m^2/day on days 1 to 5, 8 to 12, 22 to 26, and 29 to33 (Fig. 1). These dosages were based on our phase 1 trial.[21]

Gemcitabine was dissolved in saline and administered in a standard 30-min infusion. Antiemetics were not routinely used but allowed when needed. In cases with observed toxicities, chemotherapy was suspended, terminated, or reduced as appropriate. No intrapatient dose escalation was permitted.

Radiation Therapy

All the patients were treated with three-dimensional (3D) conformal radiotherapy. The total radiation dose of 50.4 Gy was delivered five times per week in daily fractions of 1.8 Gy.[21] The clinical target volume was defined as the gross tumor volume with a 5-mm margin plus the neuroplexus region and the locoregional elective lymph node region.

Evaluation of Adverse Events

The patients were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. All the patients were observed for 1 week after completion of the last radiation dose.

Surgery

If neither distant metastasis nor cancer progression requiring artery reconstruction was detected, surgical exploration was scheduled to be performed 4 to 7 weeks after the final radiation fraction. When careful inspection showed neither liver metastasis nor peritoneal implantation, a pancreatectomy was performed, together with lymphatic and connective tissue clearance. If the pancreatic tumor was fixed with the PV/SMV, it was resected together with the pancreas (en bloc resection). Pancreaticojejunostomy, cholangiojejunostomy, and jejunojejunostomy were performed after pancreaticoduodenectomy, whereas none of the anastomotic procedures were performed after caudal pancreatectomy. The entire surgical specimen was fixed in buffered formalin and sliced into 5-mm-wide sections. After hematoxylin–eosin staining, resection margins were microscopically examined. We defined R0 resection as the absence of cancer cells at the cut end of any specimen slice.

Postoperative Course

The patients with adequate performance status underwent 6 months of postoperative therapy, but the protocol did not restrict the specific reagent for adjuvant treatment. For adjuvant therapy, gemcitabine was generally used according to the CONKO-001 study,[3] whereas S-1 was used according to the protocol of the JASPAC-01 study in ASCO-GI (January 2013).[4] However, in practice, the use was determined based on the observed adverse events. Postoperative follow-up evaluation consisted of a routine physical examination and laboratory tests, including serum levels of carcinoembryonic antigen (CEA) and cancer antigen 19-9 (CA19-9). Chest x-ray and abdomen computed tomography (CT)/ultrasonography were performed every 3 months, with careful monitoring for cancer recurrence.

Statistical Analysis

According to the prescribed protocol of the clinical trial, statistical analyses included 57 phase 2 patients and 6 phase 1 patients who received the same dosage used in phase 2. All data were reported as mean ± standard deviation and/or median. Fisher's exact test was used for categorical data and the Mann–Whitney *U* test for continuous data. Data analyses were performed on an intention-

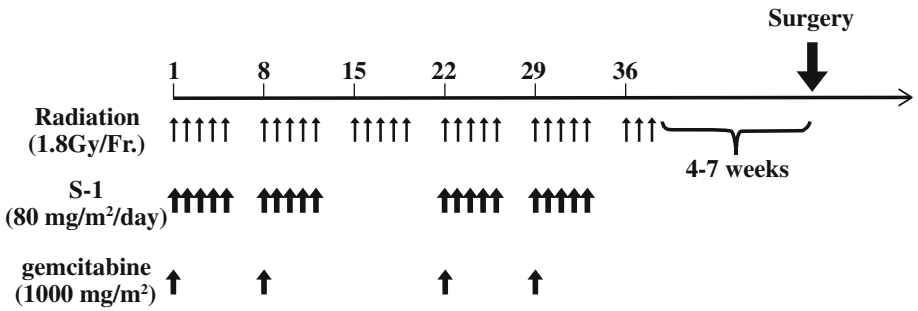

FIG. 1 The treatment schedule included preoperative radiation with 50.4 Gy (1.8 Gy/day, 5 times per week for a total of 28 fractions) administered together with concurrent 30-min intravenous infusions of gemcitabine on days 1, 8, 22, and 29 and/or with oral S-1 on days 1 to 5, 8 to 12, 22 to 26, and 29 to 33. Surgical exploration was performed 4 to 7 weeks after the final fraction of radiation

to-treat basis using the SPSS software package (SPSS Inc., Chicago, IL, USA). A *P* value lower than 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Our analysis included 63 patients, whose characteristics are listed in Table 1. The median tumor size was 24 mm (range, 10–70 mm). The median CA19-9 was 261 U/ml (range, 6–6621 U/ml), and the median CEA was 3 ng/ml (range, 0.6–168.7 ng/ml). Tumors were located in the pancreatic head in 31 patients, the body in 26 patients, and the tail in 6 patients. For all the patients, the tumor was diagnosed as resectable based on imaging before neoadjuvant therapy.

Outcomes and Adverse Events of Neoadjuvant Therapy

Table 1 shows the responses to neoadjuvant therapy and the outcomes. Among the 63 enrolled patients, 1 patient refused neoadjuvant therapy after giving informed consent, and the remaining 62 patients completed the protocol, yielding a 98% completion rate. Gemcitabine was administered four times for 44 patients (70%). Due to hematologic or non-hematologic adverse events, gemcitabine was administered three times for 12 patients (19%), twice for 5 patients (8%), and once for 1 patient (2%), whereas S-1 was administered a median of 17.5 times. The post-neoadjuvant tumor diameter was not dramatically reduced (median, 19.0 mm). The median CA19-9 level was reduced to 61 U/ml and the CEA level to 2.25 ng/ml.

During phase 2 neoadjuvant therapy, 79% of the patients experienced leukopenia of grade 3 or greater, which was the most frequently observed adverse event. Besides leukopenia and neutropenia, no adverse events exceeded grade 4 in severity (Table S1). No treatment-related deaths occurred during this study.

Perioperative Outcomes

Among the 63 patients, 54 underwent surgical resection, including pancreaticoduodenectomy for 29 patients and distal pancreatectomy for 25 patients, whereas 9 patients did not undergo resection due to distant metastases and/or peritoneal disseminations. Table 2 shows the operative procedures. Among the resected patients, the median operation time was 458 min (range, 193–714 min), and the median blood loss was 485 ml (range, 60–2010 ml).

One important issue to be analyzed was whether the strong neoadjuvant therapy was associated with an increased incidence of postoperative complications. Pancreatic fistula of grade B or higher occurred in seven patients (13%), delayed gastric emptying in five patients (9%), and surgical-site infection in four patients (7%) (Table 2). No perioperative death was observed.

TABLE 1 Patient characteristics and outcomes of gemcitabine, S-1, and radiation therapy (GSRT) *n* (%)

No. of enrolled patients	63
Median age: years (range)	70 (41–84)
Sex	
Male	42 (67)
Female	21 (33)
Performance status (0/1)	62/1
Median tumor diameter: mm (range)	24.0 (10–70)
Median pre-GSRT CA19-9 levels: U/ml (range)[a]	261.0 (6–6621)
Median pre-GSRT CEA levels: U/ml (range)	3.0 (0.6–168.7)
Primary tumor location	
Head/neck	31 (49)
Body	26 (41)
Tail	6 (10)
NCCN resectability (2016)	
Resectable	62 (98)
Borderline resectable (resectable by DP-CAR[b])	1 (2)
Unresectable	0 (0)
Completion of GSRT protocol	62 (98)
Completion of radiation	62 (98)
No. of gemcitabine administrations during GSRT	
Four times	44 (70)
Three times	12 (19)
Twice	5 (8)
Once	1 (2)
None	1 (2)
Days of S-1 administered during GSRT[c]	17.5 (0–20)
RECIST response (CR/PR/SD/PD)[d]	0/13/40/9
Median post-GSRT tumor diameter: mm (range)[d]	19.0 (8–45)
Post-GSRT CA19-9 levels: U/ml (range)[e]	61.0 (5–9000)
Post-GSRT CEA levels: U/ml (range)[d]	2.25 (0.5–15.5)
No. of patients resected	54 (86)

CA19-9 cancer antigen 19-9, *CEA* carcinoembryonic antigen, *NCCN* National Comprehensive Cancer Network, *RECIST* response evaluation criteria in solid tumors, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

[a]CA19-9 lower than 5 ($n = 2$) were excluded

[b]Distal pancreatectomy with celiac axis resection

[c]Administration twice a day was counted as 1 day, whereas administration once a day was counted as 0.5 day

[d]One patient who refused GSRT was excluded

[e]Three patients were excluded: two with CA19-9 lower than 5 before GSRT and one who refused GSRT

TABLE 2 Perioperative outcomes

Operative procedures	
PD	29
DP	25
Staging laparotomy/laparoscopy	5
No surgery	4
PV/SMV resection	16
Major arterial resection	0
Median operation time: min (range)[a]	458 (193–714)
Median blood loss: ml (range)[a]	485 (60–2010)
Postoperative complications[a,b]	
Pancreatic fistula (grade B or C)	7
Delayed gastric emptying (grade B or C)	5
Surgical-site infection	4
Intraabdominal abscess	3
Chylous ascites	3
Cholangitis	3
Serous leakage	2
Post-pancreatectomy hemorrhage (grade B or C)	1
Gastrointestinal anastomotic leak	1
Intestinal obstruction	1
Abdominal incisional hernia	1
Mortality	0

PD pancreaticoduodenectomy, *DP* distal pancreatectomy, *PV* portal vein, *SMV* superior mesenteric vein

[a]Data from 54 patients

[b]Clavien–Dindo grade 2 or more

TABLE 3 Pathologic findings and postoperative clinical course of resected patients

No. of patients resected	54
Histology	
Complete response	2
Carcinoma in situ	2
Tubular adenocarcinoma	49
Mucinous carcinoma	1
T stage (UICC)	
T0/Tis/T1/T2/T3	2/2/7/1/42
N stage (UICC)	
N0/N1	37/17
TNM stage (UICC)[a]	
0/1/2A/2B	2/7/26/17
Negative microscopic resection margin	
R0/R1[b]	54/0
Evans classification	
1/2a/2b/3/4	4/22/23/3/2
Postoperative adjuvant chemotherapy[c]	
S-1	20
Gemcitabine	18
Refused	10
Not started, judged by a doctor	4
Not started because of postoperative complications	2
Recurrence	
Liver metastasis	11
Lung metastasis	8
Liver + local recurrence	2
Local recurrence	7
Peritoneal dissemination	3

UICC Union for International Cancer Control, *TNM* tumor-node-metastasis

[a]Two patients showing complete response were excluded

[b]R0 was defined as no cancer cells at the cut end of any specimen

[c]Adjuvant therapy was started but not completed in eight patients

Pathologic Findings and Postoperative Clinical Course

Pathologic investigation of the resected specimens showed complete response in two patients and carcinoma in situ in two patients. The lymph node metastases results were negative for 37 patients (69%), with Union for International Cancer Control (UICC) pStage 0 in 2 cases, pStage 1 in 7 cases, pStage 2A in 26 cases, and pStage 2B in 17 cases. For all the resected patients, R0 resection was achieved. Table 3 shows the pathologic effects stratified by classification according to Evans et al.[23]

Postoperative adjuvant chemotherapy was administered to 38 patients, with S-1 used for 20 patients and gemcitabine for 18 patients. Only two patients did not start postoperative adjuvant chemotherapy due to postoperative complications.

Overall Survival, Recurrence-Free Survival, and Patterns of Failure

The median follow-up period was 27.2 months (range, 4.0–66.3 months). In the intention-to-treat analysis, the median survival was 55.3 months, and the 1-, 3-, and 5-year overall survival rates were 83.3%, 51.6%, and 41.2%, respectively (Fig. 2a). The median recurrence-free survival was 22.1 months, and the 1-, 3-, and 5-year recurrence-free survival rates were 76.7%, 38.3%, and 35.1%, respectively (Fig. 2b). The patients who completed neoadjuvant therapy, surgery, and adjuvant therapy showed a 5-year survival rate of 56.6% (Fig. 2c). The median recurrence-free survival period among these patients was 29.2 months, which was significantly longer than among the patients who did not complete adjuvant therapy (13.2 months) (Fig. 2d).

During the postoperative follow-up period, 31 patients experienced recurrence (Table 3). Among these patients, local recurrence was observed in only nine patients.

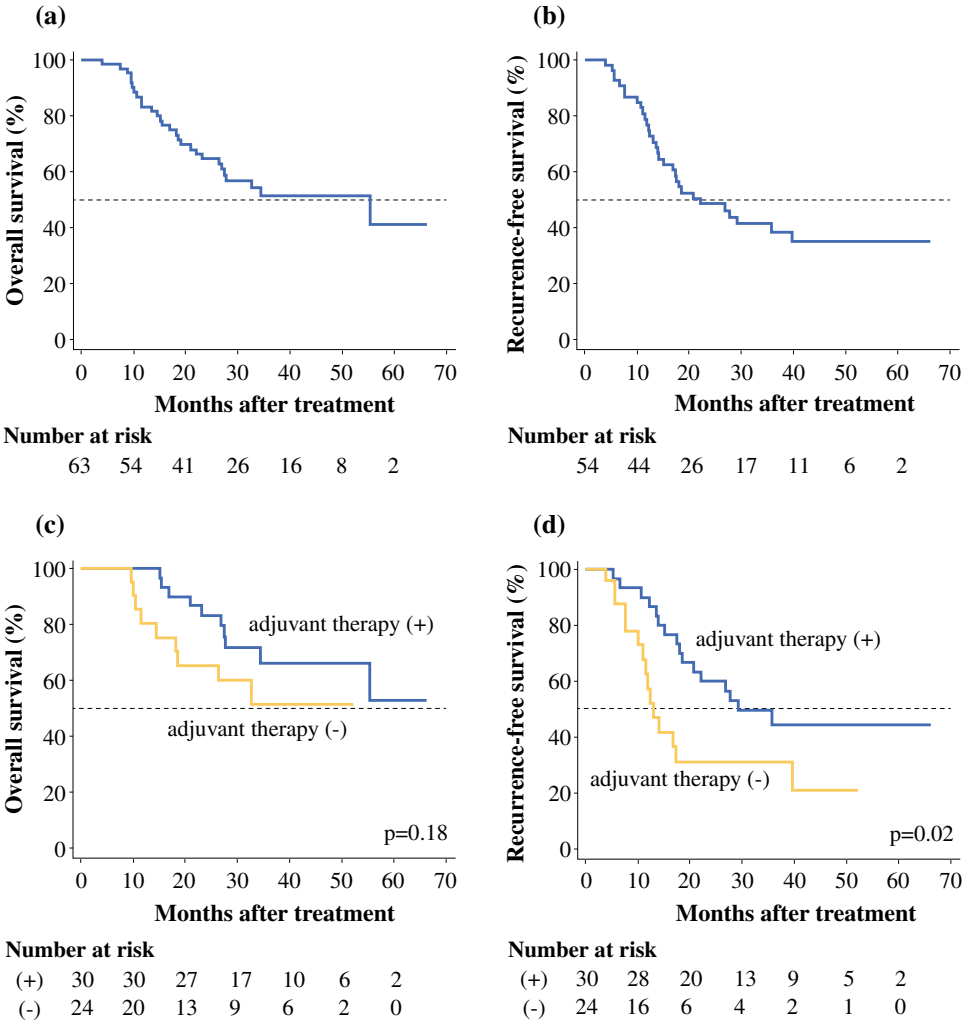

FIG. 2 Intention-to-treat analyses of **a** overall survival and **b** recurrence-free survival. Comparison of **c** overall survival and **d** recurrence-free survival between patients who underwent adjuvant therapy and those who did not

DISCUSSION

Patients with resectable PDAC who underwent resection after neoadjuvant treatment exhibited a median survival of only 23.3 months according to a meta-analysis by Gillen et al.[24] More recently, Mokdad et al.[25] reported a median survival time of 26 months for more than 2000 patients with clinical stage 1 or 2 resected PDAC and concluded that neoadjuvant therapy followed by surgery had a significant survival benefit for early-stage PDAC.

Compared with these previous studies, our results showed a strikingly better median survival time. One important reason for this improved outcome was the more robust protocol we used. The gemcitabine and S-1 trial (GEST) showed a significantly higher response rate after GS therapy than gemcitabine alone.[18] However, in the GEST study, GS therapy did not significantly improve the overall survival rates among the patients with unresectable PDAC, presumably because the patients could cross over to the GS regimen, potentially extinguishing the statistical significance of any GS therapy benefits. Our study did not include a crossover design for the regimen during neoadjuvant therapy, and we detected a clear clinical benefit of GS therapy.

Another reason for our favorable results may have been the use of full-dose radiation therapy, which might have supported our low local recurrence rates, although it remains debatable whether neoadjuvant radiation is necessary. Evans et al.[10] reported that gemcitabine concurrent with radiation therapy was associated with a median survival time of up to 34 months for resectable PDAC patients, although theirs was a single-arm study.

Lutfi et al.[26] analyzed data from the National Cancer Database and found shorter survival periods among patients who received preoperative chemoradiotherapy than among those who had received preoperative chemotherapy alone, although the patients treated with preoperative chemoradiotherapy were more likely to have node-negative resections. More recently, Cloyd et al.[27] used propensity score-adjusted analysis to compare

chemotherapy with chemoradiotherapy as preoperative therapy for resectable pancreatic ductal adenocarcinoma and showed that preoperative chemoradiotherapy was associated with less margin- and lymph node-positivity, reduced local recurrence rates, and similar overall survival rates. Because postoperative local recurrence can be experienced even by resectable patients, it may be prudent to add radiation therapy for potential improvement of locoregional control and prognosis.

An ongoing phase 3 trial is examining neoadjuvant therapy for resectable PDAC using GS therapy without radiation (PREP-05 study).[28] Future comparison between our results and those of the PREP-05 study may better elucidate the clinical benefit of neoadjuvant radiation therapy.

In addition to neoadjuvant therapy, adjuvant therapy is indispensable for improving long-term survival rates. Using S-1 as an adjuvant therapy, the JASPAC-01 trial showed outstanding long-term survival rates.[4] However, that trial postoperatively recruited patients, enrolling only patients who were successfully resected and deemed tolerant of adjuvant therapy. In contrast, our trial recruited potentially resectable patients, and we performed an intention-to-treat analysis that included unresected patients. Even with the intention-to-treat analysis, our results were favorable. Moreover, the long-term survival rates were even better among the patients who were resected and completed adjuvant therapy (Fig. 2c), indicating the clinical benefit of our protocol.

Another important question is whether our neoadjuvant therapy impaired the induction rate of adjuvant therapy. Adjuvant therapy was administered to 38 (70.3%) of 54 surgically resected patients. This rate was higher than in previously published studies, indicating that our neoadjuvant protocol did not substantially impair the adjuvant therapy induction rate.[29]

This study had several limitations. First, recently launched stronger reagents, including GA therapy (gemcitabine + nab-paclitaxel) and FOLFIRINOX, may have the potential to exert better effects when used as neoadjuvant therapy.[30,31] However, the feasibility and safety of neoadjuvant therapy with these regimens remain uncertain.[9] Moreover, the combination of such recent protocols with radiation has not been reported to date. Second, quality control of radiation therapy was lacking. Third, because this was not a randomized clinical trial, there may have been a selection bias in enrolling patients. Fourth, according to the prescribed protocol of this study, we enrolled one patient whose tumor exhibited abutment to the celiac artery but was resectable by DP-CAR. Although such a tumor may technically be resectable without arterial reconstruction, it currently is regarded as borderline resectable in the current National Comprehensive Cancer Network (NCCN) guidelines.[6]

In conclusion, neoadjuvant therapies for resectable PDAC may yield improved long-term survival, particularly when more effective chemotherapeutic reagents are used. The findings indicate that GSRT may be a candidate for improving the overall survival rate. However, randomized clinical trials are needed to confirm its clinical benefit.

CONFLICT OF INTEREST There are no conflict of interest.

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