Table 5 Peri-operative outcome in resecteable group

Group	Surgery first	Neoadjuvant	*P*-value
Resection, *n*	375	171	–
PD, *n* (%)	236 (62.9)	111 (64.9)	0.66
DP, *n* (%)	126 (33.6)	52 (30.4)	0.46
TP, *n* (%)	12 (3.2)	7 (4.1)	0.60
PV resection, *n* (%)	71 (18.9)	37 (21.6)	0.46
Arterial resection, *n* (%)	4 (1.1)	4 (2.3)	0.27
Operative time (ml), median (range)	404 (141–829)	470 (157–1,021)	0.0001
Blood loss (ml), median (range)	872 (50–16,422)	1,088 (55–12,925)	0.0059
Blood transfusion (U), median (range)	2 (0–52)	2 (0–16)	0.65
Postoperative hospital stay (day), median (range)	31 (7–167)	36 (8–115)	0.0020
Morbidity, *n* (%)	194 (51.7)	102 (59.7)	0.084
POPF (all grade), *n* (%)	90 (24.0)	35 (20.5)	0.36
POPF (grade B/C), *n* (%)	43 (11.5)	20 (11.7)	0.94
DGE	40 (10.7)	27 (15.8)	0.10
Hemorrhage	16 (4.3)	7 (4.1)	0.93
Abscess	38 (10.1)	19 (11.1)	0.73
Wound infection	30 (8.0)	17 (9.9)	0.46
Leakage[a]	5 (1.3)	6 (3.5)	0.11
Pneumonitis	8 (2.1)	3 (1.8)	>0.99
Thrombosis	3 (0.8)	2 (1.2)	0.65
Cardiac disease	4 (1.0)	0 (0.0)	0.31
Brain	0 (0.0)	1 (0.6)	0.31
Fluid collection/	16 (4.3)	4 (2.3)	0.33
Hepatic disorder	4 (1.1)	4 (2.3)	0.27
Catheter infection	3 (0.8)	2 (1.2)	0.65
Ileus	4 (1.1)	1 (0.6)	>0.99
Cholangitis	4 (1.1)	0 (0.0)	0.31
Diarrhea/enteritis	10 (2.7)	6 (3.5)	0.59
DIC	2 (0.5)	1 (0.6)	>0.99
UTI	1 (0.3)	1 (0.6)	0.53
Renal disorder	2 (0.5)	0 (0.0)	>0.99
Anaphylaxis	1 (0.3)	1 (0.6)	0.53
Sepsis	1 (0.3)	0 (0.0)	>0.99
Splenic infarction	1 (0.3)	1 (0.6)	0.53
Peptic ulcer	1 (0.3)	0 (0.0)	>0.99
Herpes Zoster	2 (0.5)	0 (0.0)	>0.99
Portal vein trouble	1 (0.3)	0 (0.0)	>0.99
Severe complication (Grade IIIa–V), *n* (%)	58 (15.8)	23 (13.9)	0.59
Reoperation	9 (2.4)	7 (4.1)	0.29
Mortality, *n* (%)	6 (1.6)	1 (0.6)	0.44

[a] Leakage includes anastomosis insufficiency except for pancreatic fistula

neoadjuvant therapy in patients with pancreatic cancer. Adjuvant chemotherapy with gemcitabine is a standard therapy following resection for pancreatic cancer and significantly enhances recurrence-free and overall survival compared with surgery alone, with a median overall survival of almost 2 years after surgery [3–5]. However, this approach of surgery followed by adjuvant therapy cannot be offered to a significant proportion of patients with pancreatic cancer because of risks of surgical morbidity and the presence of unresectable disease at laparotomy. In contrast, almost all patients can receive neoadjuvant therapy before surgery [17, 18].

A major concern in treating these patients with neoadjuvant therapy is the risks of operative morbidity and

Table 6 Peri-operative outcome in borderline group

Group	Surgery first	Neoadjuvant	*P*-value
Resection, *n*	156	158	–
PD, *n* (%)	95 (60.9)	121 (76.6)	0.0026
DP, *n* (%)	51 (32.7)	31 (19.6)	0.0081
TP, *n* (%)	9 (5.8)	6 (3.8)	0.44
PV resection, *n* (%)	84 (53.9)	112 (70.9)	0.0018
Arterial resection, *n* (%)	13 (8.3)	10 (6.3)	0.50
Operative time (ml), median (range)	496 (161–1,221)	567 (190–1,160)	0.0005
Blood loss (ml), median (range)	1,137 (20–16,201)	1,400 (60–8,422)	0.16
Blood transfusion (U), median (range)	4 (0–54)	4 (0–18)	0.51
Postoperative hospital stay (day), median (range)	30 (7–397)	31 (8–124)	0.50
Morbidity, *n* (%)	93 (50.0)	82 (40.4)	0.057
POPF (all grade), *n* (%)	34 (18.3)	16 (7.9)	0.0022
POPF (gradeB/C), *n* (%)	19 (10.2)	8 (3.9)	0.015
DGE	24 (12.9)	20 (9.9)	0.34
Hemorrhage	3 (1.6)	4 (2.0)	0.55
Abscess	16 (8.6)	17 (6.4)	0.41
Wound infection	18 (9.7)	20 (9.9)	0.95
Leak[a]	8 (4.3)	3 (1.5)	0.13
Pneumonitis	2 (1.1)	4 (2.0)	0.69
Thrombosis	1 (0.5)	1 (0.5)	1.0
Cardiac disease	0 (0.0)	2 (1.0)	0.50
Brain	2 (1.1)	1 (0.5)	0.61
Fluid collection/	5 (2.7)	17 (8.4)	0.016
Hepatic disorder	3 (1.6)	5 (2.5)	0.73
Catheter infection	1 (0.5)	2 (1.0)	0.53
Ileus	1 (0.5)	0 (0.0)	0.48
Cholangitis	2 (1.1)	2 (1.0)	0.65
Diarrhea/enteritis	4 (2.2)	9 (4.4)	0.26
DIC	0 (0.0)	0 (0.0)	–
UTI	0 (0.0)	0 (0.0)	–
Renal disorder	0 (0.0)	0 (0.0)	–
Anaphylaxis	0 (0.0)	0 (0.0)	–
Splenic infarction	0 (0.0)	0 (0.0)	–
Peptic ulcer	1 (0.5)	1 (0.5)	1.0
Herpes Zoster	0 (0.0)	0 (0.0)	–
Portal vein trouble	1 (0.5)	1 (0.5)	1.0
Severe complication (Grade IIIa–V), *n* (%)	22 (14.5)	21 (13.7)	0.85
Reoperation	6 (3.9)	6 (3.8)	0.98
Mortality, *n* (%)	2 (1.3)	7 (4.4)	0.17

[a] Leakage includes anastomosis insufficiency except for pancreatic fistula

mortality. Although several small prospective studies have demonstrated the feasibility of this approach [10, 11, 19], this has not been confirmed because of the small sample sizes. Several nationwide surveys [20, 21] and systematic reviews and meta-analyses [22, 23] indicated that this strategy was feasible in larger numbers of patients, but could not quantify the data. Only one systematic review showed the rate of surgical morbidity and mortality after neoadjuvant therapy [24]. We found that neoadjuvant treatment did not significantly increase perioperative mortality and morbidity rates, including pancreatic fistula and delayed gastric emptying, indicating that neoadjuvant treatment was a feasible strategy in patients with pancreatic cancer. Neoadjuvant therapy, however, resulted in significantly longer operation times and postoperative hospital stay, as well as higher rates of grade 3/4 hematological toxicities. Nevertheless, these preoperative toxicities were manageable, with <0.5% of patients becoming ineligible for surgery.

Table 7 Peri-operative outcome in resecteable group: (**a**) Resectable and (**b**) Borderline

		Surgery first	Neoadjuvant	*P*-value
(a) Resectable				
T	0	1 (0.3)	2 (1.2)	0.033
	1	33 (8.8)	28 (16.5)	
	2	35 (9.3)	13 (7.7)	
	3	304 (81.1)	124 (72.9)	
	4	2 (0.5)	3 (1.8)	
N	0	168 (44.8)	118 (69.4)	<0.0001
	1	207 (55.2)	52 (30.6)	
M	0	354 (94.4)	160 (94.1)	0.895
	1	21 (5.6)	10 (5.9)	
Stage	0	0 (0)	2 (0.4)	<0.0001
	IA	28 (7.5)	24 (14.1)	
	IB	28 (7.5)	10 (5.9)	
	IIA	110 (29.3)	81 (47.7)	
	IIB	186 (49.6)	40 (23.5)	
	III	2 (0.5)	3 (1.7)	
	IV	21 (5.6)	10 (5.9)	
(b) Borderline				
T	0	2 (1.3)	1 (0.6)	0.042
	1	2 (1.3)	12 (7.6)	
	2	4 (2.6)	9 (5.7)	
	3	140 (90.3)	129 (82.2)	
	4	7 (4.5)	6 (3.8)	
N	0	39 (25.2)	88 (55.7)	<0.0001
	1	116 (74.8)	70 (44.3)	
M	0	132 (85.2)	143 (90.5)	0.895
	1	23 (14.8)	15 (9.5)	
Stage	0	0 (0.0)	1 (0.6)	<0.0001
	IA	1 (0.7)	10 (6.3)	
	IB	2 (1.3)	5 (3.2)	
	IIA	32 (20.7)	64 (40.5)	
	IIB	91 (58.7)	58 (36.7)	
	III	6 (3.9)	5 (3.2)	
	IV	23 (14.8)	15 (9.5)	

Another concern associated with the neoadjuvant strategy is a possible decrease in tumor resectability due to tumor progression during preoperative treatment. A meta-analysis showed that, of patients with resectable tumors, 73.6% to 82.9% remained resectable after neoadjuvant therapy [17, 24], findings similar to those in patients scheduled for primary resection and adjuvant therapy. We found that neoadjuvant therapy did not decrease tumor resectability, both in patients with resectable and borderline resectable pancreatic cancers. Intention-to-treat analysis showed that, in resectable tumors, the curability (R0 resection rate) was improved after neoadjuvant treatment. Radiologically, 90% of patients who received neoadjuvant therapy showed lack of tumor progression or tumor shrinkage, with only 10% showing tumor progression, suggesting that neoadjuvant treatment increased the likelihood of curative resection. These advantages of neoadjuvant therapy, however, were not observed in patients with borderline resectable disease, and resectability and R0 resectability were similar in the neoadjuvant and surgery-first groups. The incidence of nodal involvement was significantly lower in the neoadjuvant than in the surgery-first group. Neoadjuvant therapy has been reported to reduce the number of lymph node metastases [25, 26], suggesting that the main effect of neoadjuvant therapy is to reduce peripancreatic lymph node positivity rather than the size of primary tumors. Since nodal involvement is one of the most significant predictors of patient survival [27, 28], neoadjuvant therapy may have a survival benefit following resection of pancreatic cancer.

Although the number of patients receiving neoadjuvant therapy is the largest to date, questionnaire surveys have limitations. Data were collected from the various treatment centers retrospectively, not prospectively. In addition, there was significant inter-center heterogeneity in eligibility criteria for neoadjuvant treatment, neoadjuvant regimens, radiologic and intraoperative indications for resection, and postoperative therapy regimens. This heterogeneity may have introduced selection biases, preventing definite conclusions. Prospectively designed trials with adequate numbers of patients are required to determine the feasibility and efficacy of neoadjuvant treatment in patients with pancreatic cancer. This survey analyzing the effects of neoadjuvant treatment on resectablity and perioperative outcomes in patients with pancreatic cancer could not determine the impact of treatment on survival. However, several studies have reported that neoadjuvant therapy had survival benefits in patients with resectable or borderline resectable pancreatic cancer [11, 17, 21, 22, 24]. These suggest the need for prospective randomized studies to clarify the effects on survival of neoadjuvant therapy compared with the standard surgery-first strategy, in patients with pancreatic cancer [12, 18]. In conclusion neoadjuvant therapy may not increase the mortality and morbidity rates, and may be able to increase the chance for curative resection especially against resectable tumor.

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ORIGINAL ARTICLE – PANCREATIC TUMORS

Neoadjuvant Chemotherapy with Gemcitabine and S-1 for Resectable and Borderline Pancreatic Ductal Adenocarcinoma: Results from a Prospective Multi-institutional Phase 2 Trial

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ABSTRACT

Background. Surgical resection is the only curative strategy for pancreatic ductal adenocarcinoma (PDAC), but recurrence rates are high even after purported curative resection. First-line treatment with gemcitabine and S-1 (GS) is associated with promising antitumor activity with a high response rate. The aim of this study was to assess the feasibility and efficacy of GS in the neoadjuvant setting.

Methods. In a multi-institutional single-arm phase 2 study, neoadjuvant chemotherapy (NAC) with gemcitabine and S-1, repeated every 21 days, was administered for two cycles (NAC-GS) to patients with resectable and borderline PDAC. The primary end point was the 2-year survival rate. Secondary end points were feasibility, resection rate, pathological effect, recurrence-free survival, and tumor marker status.

Results. Of 36 patients enrolled, 35 were eligible for this clinical trial conducted between 2008 and 2010. The most common toxicity was neutropenia in response to 90 % of the relative dose intensity. Responses to NAC included radiological tumor shrinkage (69 %) and decreases in CA19-9 levels (89 %). R0 resection was performed for 87 % in resection, and the morbidity rate (40 %) was acceptable. The 2-year survival rate of the total cohort was 45.7 %. Patients who underwent resection without metastases after NAC-GS ($n = 27$) had an increased median overall survival (34.7 months) compared with those who did not undergo resection ($P = 0.0017$).

Conclusions. NAC-GS was well tolerated and safe when used in a multi-institutional setting. The R0 resection rate and the 2-year survival rate analysis are encouraging for patients with resectable and borderline PDAC.

Pancreatic ductal adenocarcinoma (PDAC) is associated with poor prognosis and an overall 5-year survival rate of <5 %.[1–3] It is the fourth leading cause of cancer deaths in the United States and Japan.[2,4] A minority of patients present with resectable disease at the time of diagnosis.[4] Surgery is the most effective treatment and the only chance for cure of nonmetastatic PDAC, but recurrence rates are high even after R0 resection.[5,6] The ESPAC-1 trial revealed a significant survival benefit for adjuvant chemotherapy.[7] The CONKO-001 and Japanese trials suggested that adjuvant treatment with gemcitabine offered

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a good chance for prolonged disease-free survival in patients undergoing curative resection of PDAC.[8,9]

Curative resection followed by adjuvant therapy is now the standard treatment for resectable PDAC. However, this strategy is still associated with a 2-year survival of <50 %.[7–10] Neoadjuvant therapy allows for the delivery of chemotherapy and/or radiotherapy to a vascularized primary tumor, provides early treatment of micrometastatic disease, and facilitates the evaluation of biomarkers and surrogate measures of response that can be exploited in the postoperative period.[11] Moreover, a larger proportion of patients may receive an active systemic treatment in the neoadjuvant setting compared with the adjuvant setting, which is associated with surgical complications and delayed recovery after surgery.[12] A population-based study demonstrated improved overall survival in patients with PDAC who underwent neoadjuvant therapy followed by resection compared with a similar cohort who underwent surgery-first resection and adjuvant therapy.[13] Several studies reported that neoadjuvant chemotherapy (NAC) with gemcitabine and platinum agents was safe and associated with a high resection rate and an encouraging survival rate.[14–16] These data suggest that NAC is feasible and effective for patients with resectable PDAC and warrant further investigation.

S-1 (TS-1, Taiho Pharmaceutical) is an oral fluoropyrimidine derivative in which tegafur (the prodrug of 5-fluorouracil, 5-FU), has been combined with two 5-FU-modulating substances: 5-chloro-2,4-dihydroxypyridine and potassium oxonate.[17] S-1 monotherapy is associated with antitumor activity in chemonaive patients or in patients with gemcitabine-refractory metastatic PDAC.[18,19] The combination of S1 and gemcitabine (GS) for the first-line treatment of unresectable PDAC was associated with promising antitumor activity and acceptable toxicity.[20–23] On the basis of encouraging results in patients with unresectable PDAC, Miyagi HBPCOG initiated a multi-institutional phase 2 trial to evaluate the feasibility and efficacy of NAC-GS for PDAC (UMIN-CTR, #000001504).

PATIENTS AND METHODS

Eligibility Criteria and Patient Evaluation

This multi-institutional phase 2 cooperative group study was open to patients with PDAC. Between November 2008 and April 2010, a total of 36 patients from nine participating institutions from northeastern Japan were enrolled onto this trial.

Inclusion criteria were as follows: (1) newly diagnosed PDAC; (2) age ≥ 18 years; (3) Eastern Cooperative Oncology Group performance status of 0–1; (4) complete history and physical examination, and staging evaluation requiring multidetector-row computed tomography (MD-CT); (5) no distant metastases; (6) tumor considered as potentially or borderline resectable; (7) no previous antitumor treatment except for biliary drainage; and (8) adequate hematologic, hepatic, renal, and cardiopulmonary functions. Tumor with encasement of the portomesenteric vein and/or abutment of major arteries (hepatic or mesenteric artery) within 180° was defined as borderline. This study was approved by the institutional review board of Tohoku University and each participating institution. Written informed consent was obtained from all patients before the initiation of therapy.

Treatment Regimen and Dose Intensity

Gemcitabine was provided at a dose of 1,000 mg/m^2 on days 1 and 8 of each cycle. S-1 was administered orally at a dose of 40 mg/m^2 twice daily for the first 14 consecutive days followed by a 7-day rest. Each cycle was repeated every 21 days. Patients received two cycles of this regimen. During the preoperative treatment, patients underwent an interim medical history, physical examination, and laboratory studies. Toxicity of the treatment was evaluated by the Common Toxicity Criteria (CTCAE, version 3.0). After completion of two cycles of GS, surgery was planned to occur at 1–6 weeks, and all patients underwent restaging studies with MD-CT to exclude disease progression and to assess resectability. Relative dose intensity for each individual drug was calculated and defined as the dose intensity achieved relative to the standard schedule of each drug.

Resectability and Surgery

After NAC, patients with disease that demonstrated potentially or borderline resectability without newly detected distant metastases were referred for R0-directed pancreatectomy. After exploration and confirmation of resectability, subtotal-stomach-preserving pancreatoduodenectomy (SSPPD) for neoplasm in the head lesion or distal pancreatectomy (DP) for neoplasm in the body or tail was performed. A subtotal-stomach-preserving total pancreatectomy (SSPTP) was performed for the neoplasm extending from the head to body. When the tumor was not separable from the superior mesenteric artery or aorta, the case was considered to be unresectable. For neoplasm infiltrating the portal vein, en-bloc vascular resection was performed. For neoplasm in the body or tail involving the common hepatic artery, en-bloc celiac axis resection (DP-CAR) was performed.[24]

Assessment of Treatment Responses and Surgical Outcomes

Radiographic responses were determined by a comparison of pretreatment MD-CT and preoperative scans.

Response evaluation criteria in solid tumors (RECIST) were used to assess the type of response.[25,26] Serum tumor marker response was determined by a comparison of pretreatment and preoperative levels of carbohydrate antigen 19-9 (CA19-9) values. In the case of biliary obstruction, pretreatment bilirubin level was recorded as total bilirubin level <3.0 mg/dL after biliary drainage. Level of tumor marker was also measured within 2 months after operation to evaluate for normalization.

Information regarding surgery after the completion of the protocol included the type of operation, duration of the operation, estimated blood loss, complications, and 30-day mortality rate. Designated pathologists at each institution examined resected specimens, and their review included the size of the primary tumor, resection margins, and lymph node status. Tumor grade and stage were reported according to the American Joint Committee on Cancer staging manual.[27] Pathological response by the chemotherapy was evaluated by central review according to the classification reported by Evans et al.[28]

Survival

Patient follow-up was performed by MD-CT every 2 months and serum tumor marker level every month after resection. Patients not undergoing operation or resection were followed at the treating institutions or by their primary physicians.

Statistical Analysis

In this single-arm phase 2 trial, the primary end point was the 2-year survival rate. The study was designed to detect an increase in the 2-year survival rate from 25 % expected NAC to 45 %, with a one-sided alpha of 5 % and a power of 80 %. Secondary end points were the resectability, histological and tumor marker response, and disease-free survival. Both the 2-year survival rate and the disease-free survival were estimated according to the Kaplan–Meier method. Variables were compared by Student's *t* test by JMP software, version 10.0.

RESULTS

Patient Characteristics

Of the 36 patients enrolled, 35 were eligible for participation in this clinical trial. One ineligible patient had distant metastases that were discovered after study enrollment (Fig. 1). Feasibility of NAC was assessed in 35 patients, and patient demographics are shown in Table 1. The treating surgeon determined the initial assessment of resectability, with subsequent confirmation by the central reviewer (FM). Among all eligible cases, 19 patients (54 %) were considered to have resectable disease and 16 patients (46 %) were considered to have borderline disease according to our criteria, which were similar to those of the National Comprehensive Cancer Network guidelines.[29]

Dose Intensity and Toxicity

Of 35 eligible patients, 30 (86 %) received two planned cycles of NAC. Five patients required termination of NAC, including two patients who were limited to 0.5 cycles as a result of grade 3 skin rash and three patients who were limited to 1.5 cycles as a result of gastritis or cholangitis. Dose reduction was required in three patients because of grade 4 neutropenia. Mean relative dose intensity of gemcitabine and S-1 was 92.2 and 96.5 %, respectively.

All eligible patients were assessable for adverse events. NAC-related toxicities are listed in Table 2. Four patients developed grade 3 skin rash, and NAC was terminated early in two of these patients. Other grade 3 nonhematological toxicities included cholangitis and gastritis, which required treatment interruption. The most common

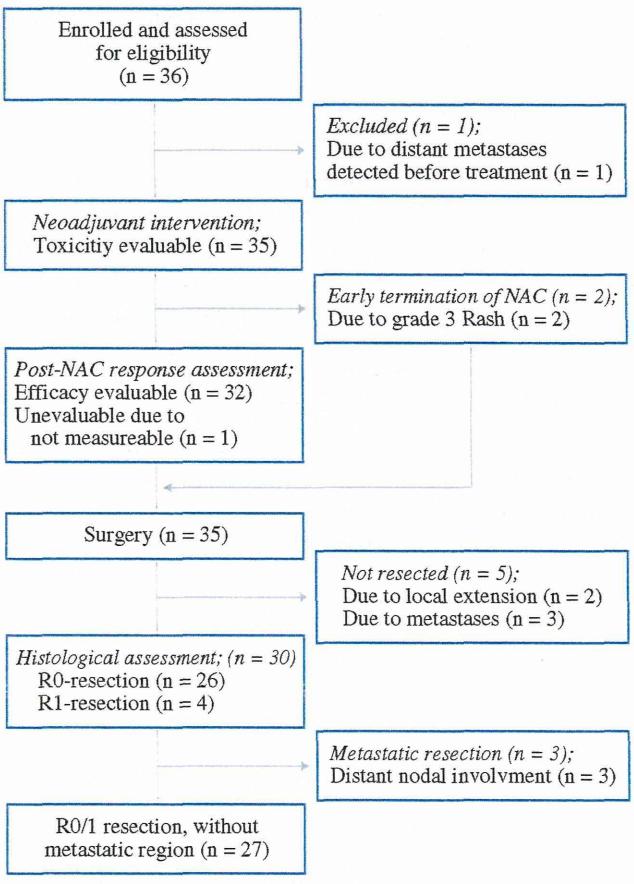

FIG. 1 Flow chart showing the number of patients proceeding through each stage of the study with reasons for exclusion

TABLE 1 Patient demographics

Characteristic	Value
Total cohort eligible	35
Gender (Male:Female)	20;15
Age (years), median (range)	65, 47–77
Location	
Head	25
Body–tail	9
Whole	1
Tumor size (cm), median (range)	2.5, 1.2–7.0
Pretreatment resectability	
Resectable	19
Borderline	16
Pretreatment CA19-9 value (U/ml), median (range)	157.5, <2.0–5,000

nonhematological toxicities were elevations in aminotransferases. In terms of hematological toxicity, neutropenia (63 %) and leukopenia (49 %) were commonly noted. Three patients who experienced grade 4 neutropenia required dose reduction of gemcitabine. One patient developed grade 3 thrombocytopenia. All patients recovered, and there was no treatment-related death in the preoperative period.

Radiologic Tumor Response

Of the 35 patients, 33 had data pairs for baseline and post-NAC follow-up MD-CT available for centralized review. In one patient, tumor size was not measureable as a result of an inability to radiologically identify the border of the tumor. Of the remaining 32 patients with evaluable CT, the estimated median pretreatment size of the tumor was 25 mm, ranging from 12 to 70 mm. Partial response was documented in six patients (19 %) as determined by RECIST of the pre- and post-NAC. The other 26 patients had stable disease. There was no progressive disease documented radiologically. A waterfall plot of the response to characterize antitumor activity demonstrated that 22 patients (69 %) had some degree of tumor shrinkage (Fig. 2a).

Tumor Marker Response

Of 35 patients, 33 had data pairs for baseline and post-NAC serum tumor marker levels. Of 33 patients, 27 patients had levels of CA19-9 above the cutoff (37 U/ml). The median value of CA19-9 for the 27 assessable patients decreased from 274.9 U/ml at baseline to 83 U/ml after NAC ($P < 0.0001$ by Wilcoxon t test). A waterfall plot of the response demonstrated that 24 of 27 patients (89 %) had some degree of CA19-9 decrease and that 15 (56 %) of 27 patients had a more than 50 % decrease in the CA19-9 value (Fig. 2b).

TABLE 2 Treatment-related adverse events ($n = 35$)

Adverse event	Grade[a] 1	2	3	4	1–4, n (%)	3/4, n (%)
Hematological						
Anemia	7	1	0	0	8 (23)	0
Leukopenia	3	10	4	0	17 (49)	4 (11)
Neutropenia	2	8	9	3	22 (63)	12 (34)
Thrombocytopenia	7	1	1	0	9 (26)	1 (2.9)
Nonhematological						
Fatigue	4	0	0	0	4 (11)	0
Diarrhea	2	0	0	0	2 (5.7)	0
AST elevated	6	4	0	0	10 (29)	0
ALT elevate	5	3	0	0	8 (23)	0
Anorexia	3	0	0	0	3 (8.6)	0
Nausea	3	0	0	0	3 (8.6)	0
Vomiting	1	0	0	0	1 (2.9)	0
Mucositis	4	1	0	0	5 (14)	0
Hyperpigmentation	4	0	0	0	4 (11)	0
Constipation	4	2	0	0	6 (17)	0
Dermatitis	0	1	0	0	1 (2.9)	0
Cholangitis	0	1	2	0	3 (8.6)	2 (5.7)
Rash	3	0	4	0	7 (20)	4 (11)
Gastritis	0	0	2	0	2 (5.7)	2 (5.7)

AST aspartate aminotransferase, *ALT* alanine aminotransferase

[a] Worst grade reported during the preoperative period

Resectability and Surgical Outcomes

According to operative findings, five patients were judged to have unresectable disease due to distant metastases and aggressive local extension (Fig. 1). Thirty (86 %) patients underwent resection with curative intent. Of the operative procedures performed for resection, 19 SSPPD, seven DP, and four SSPTP were performed. Half of operations were standard pancreatectomies with combined resection of adjacent major vessels. Overall perioperative morbidity was 40 % for patients who underwent pancreatectomy. The details of the postoperative complications are listed in Table 3. There was one postoperative death. In this case, there were no abdominal complications, but the patient experienced sudden death from suspected arrhythmia at 2 weeks after surgery. Postoperative gemcitabine was administered in 24 cases (80 %).

Pathological Findings, Including Grade, Stage, and Response to Neoadjuvant Treatment

Histological assessment of resected specimens in 30 cases treated with NAC-GS is summarized in Table 4.

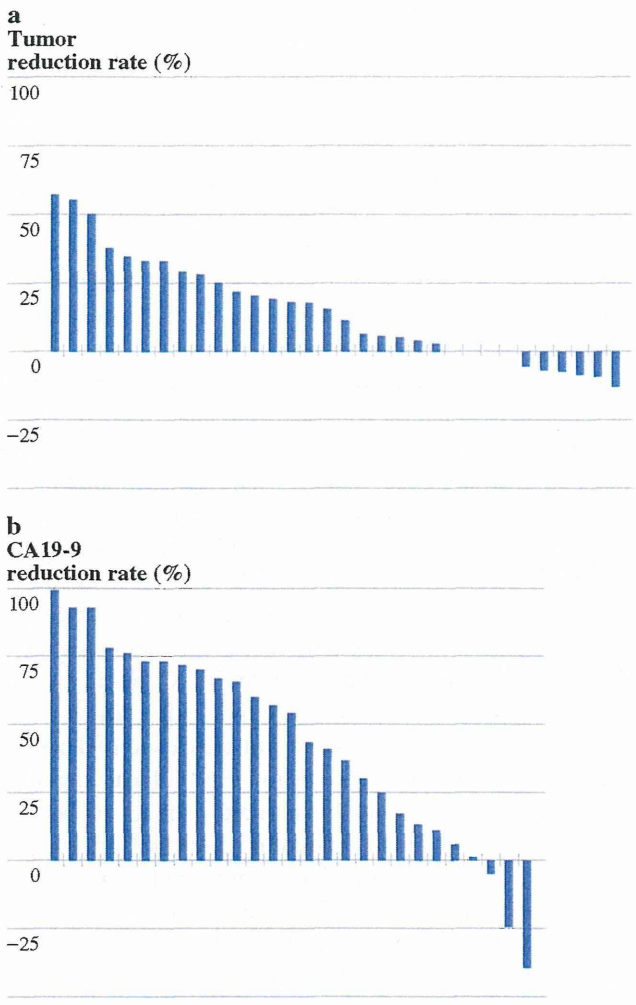

FIG. 2 Waterfall plot of reduction rate for radiological tumor size and serum CA19-9. **a** Radiological tumor reduction rate ($n = 33$). The data represent the rate of tumor size reduction, calculated as [(baseline − posttreatment)/baseline]. There were 5 cases with 0 % reduction. **b** Serum CA19-9 reduction rate ($n = 32$). The data represent the rate of CA19-9 reduction, calculated as [(baseline − posttreatment)/baseline]

The majority of the patients had neoplasm with T3. Nodal involvement was observed in 15 cases (50 %). Three patients had M1 stage IV disease due to the nodal metastases within resected para-aortic lesions. There was no case of macroscopic residual tumor (R2) in resected cases. R0 resection was performed in 26 cases (87 % in resected cases). Histological response evaluation according to Evans' classification revealed six cases that were grade IIB. More than half of the cases were documented as grade IIA.

Survival and Recurrence

The median follow-up time was 19.7 months (95 % confidence interval 17.2–24.6) for all cohorts. The median overall survival was 19.7 months (95 % confidence interval 13.7 to not reached) based on an intent-to-treat analysis. Actuarial 2-year survival rate was 45.7 % (Fig. 3a). Patients who underwent resection without distant metastases ($n = 27$) after NAC-GS had an increased median overall survival (34.7 months) compared with 10.0 months for those without resection or resection with distant metastases ($n = 8$, Fig. 3b). The actuarial 2-year survival rate of the patients with resection was 55.6 %, which was significantly better that the value (12.5 %) in those without resection or with resection including metastases. Median recurrence-free survival for resection without metastases was 20 months. The survival probability at 2-year for initially resectable tumor ($n = 19$) was 57.9 %, which was marginally higher than that for borderline tumors ($n = 16$, 31.5 %) ($P = 0.071$, Fig. 3c).

TABLE 3 Postoperative complications in 30 resections

Complication	Grading by Clavien–Dindo classification[a]	
	Any grade (%)	Grade 3b or more (%)
Pancreatic fistula[b]	3 (10)	0 (0)
Delayed gastric emptying[b]	1 (3.3)	0 (0)
Bile leak	0 (0)	0 (0)
Surgical site infection	2 (6.7)	1 (3.3)
Catheter-related infection	1 (3.3)	0 (0)
Lymph leak	2 (6.7)	0 (0)
Antibiotic-related enterocolitis	1 (3.3)	0 (0)
Cardiovascular complications	1 (3.3)	1 (3.3)
Pulmonary complications	0 (0)	0 (0)
Urinary complications	0 (0)	0 (0)
Total	12 (40)	2 (6.7)

[a] Postoperative complications were listed by grading according to the classification reported by Dindo et al.[37]

[b] Pancreatic fistula and delayed gastric emptying were defined according to the international definition reported by Bassi et al. and Wente et al.[38,39]

DISCUSSION

This study investigated outcomes after NAC-GS for resectable and borderline PDAC. The adverse effects of NAC-GS were similar to those of the same regimen when used for unresectable disease.[30] These adverse effects were manageable, and loss of operative chance due to toxicity was not noted, although there were three cases of early termination of NAC. Compared with other gemcitabine-based regimens, NAC-GS was acceptably safe.[14–16]

One of the potential advantages of NAC is to deliver high dose intensity without the potential delays caused by surgical complications and delayed recovery. The relative

TABLE 4 Pathological findings in 30 resected tumors

Factor	Category	*n* (%)
T	T1	1 (3)
	T2	1 (3)
	T3	28 (93)
N	N0	15 (50)
	N1	15 (50)
M	M0	27 (90)
	M1	3 (10)
Stage	IA	1 (3)
	IB	0 (0)
	IIA	13 (43)
	IIB	13(43)
	III	0 (0)
	IV	3 (10)
Residual tumor	R0	26 (87)
	R1	4 (13)
Treatment effect[a]	I	7 (23)
	IIA	17 (57)
	IIB	6 (20)
	III–IV	0 (0)

[a] Pathological response by the chemotherapy was evaluated by central review according to the classification reported by Evans et al.[28]

dose intensity of NAC-GS was >90 % for both agents. Two-thirds of the patients had documented radiological tumor shrinkage, and most experienced a reduction in tumor markers during NAC. These results indicated that NAC-GS had a modest effect in most patients. A potential drawback of NAC is that delaying surgery may allow disease in some patients to progress to an unresectable stage. In this series, ~10 % of the cases had radiological tumor progression, although none of the progressive changes reached the progressive disease criteria defined by RECIST. All patients, including the patients in whom the tumor progressed but remained resectable or borderline at the time of surgery, had a favorably high resection rate (86 %) and R0 resection rate (74 %, intent to treat based) compared with previous series.[31–33]

The survival impact of neoadjuvant therapy is difficult to estimate or compare with that from other reports. This is primarily the result of the heterogeneity of the patient population in previous studies.[34] The optimal strategy for resectable and borderline PDAC remains controversial. Surgery followed by postresectional systemic chemotherapy with gemcitabine provided a 2-year survival rate of 45–50 %, which was significantly better than that provided by surgery alone.[8–10] Although adjuvant chemotherapy is the optimal therapy for patients with PDAC that is resected without macroscopic residual tumor, all patients who underwent planned resection did not gain a survival benefit. This is because metastatic and/or severe local extension was found after laparotomy in some patients or because these patients experienced delayed recovery from surgical morbidity.[35] Taking these factors into consideration, the 2-year survival obtained with surgery and adjuvant chemotherapy for eligible patients in this study would be estimated as ~30–40 % based on an estimated

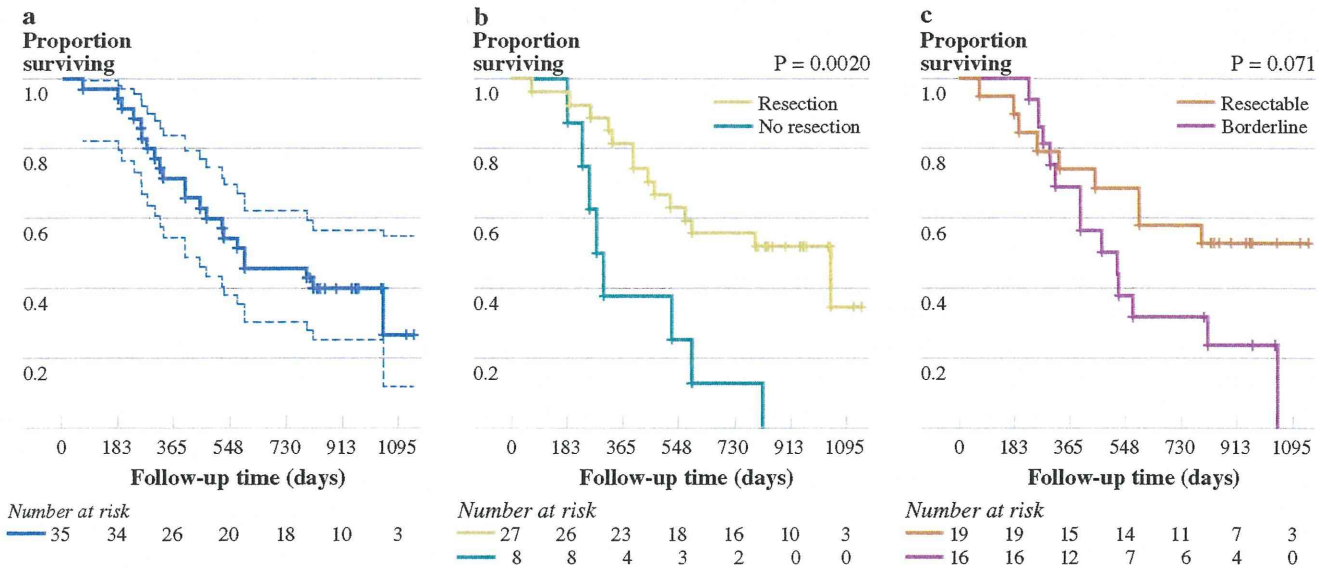

FIG. 3 Kaplan–Meier plots of survival. **a** Overall survival for the entire cohort ($n = 35$). **b** Survival comparison between with and without resection. *Yellow line* indicates resection without distant metastases ($n = 27$). *Green line* indicates patients without resection or resection with distant metastases ($n = 8$). **c** Survival comparison between initially resectable and borderline tumors. *Red line* indicates the initially resectable tumors ($n = 19$). *Purple line* indicates the initially borderline tumors ($n = 16$)

resectability of 70–80 % (compared with 45.7 % of all cohorts in this study). Because no controlled randomized trials have ever compared adjuvant to neoadjuvant therapy, comparison between subgroups could only be performed in a descriptive manner.

A phase 3 study was recently initiated to determine the efficacy of neoadjuvant gemcitabine and platinum for patients with resectable PDAC.[36] GS may also be a good candidate for control studies comparing adjuvant and neoadjuvant therapy. In conclusion, NAC-GS was well tolerated and safe when used in a multi-institutional setting. The R0 resection rate and 2-year survival rate are encouraging for patients with resectable and borderline PDAC.

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膵癌術前化学療法としての Gemcitabine+S-1 療法（GS 療法）の 第Ⅱ/Ⅲ相臨床試験（Prep-02/JSAP-05）

試験実施計画書

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0. 概要

0.1. 臨床試験課題名

膵癌術前化学療法としての Gemcitabine+S-1 療法（GS 療法）の第Ⅱ/Ⅲ相臨床試験（Prep-02/JSAP-05）

0.2. 目的

＜第Ⅱ相＞

肉眼的癌遺残のない(R0, 1）切除が可能な膵癌を対象とし、術前化学療法としての GS（Gemcitabine+S-1 ）療法の安全性と切除率の担保を確認する。

Primary endpoint（主要評価項目）　：切除率

Secondary endpoint（副次評価項目）：有害事象

＜第Ⅲ相＞

肉眼的癌遺残のない(R0, 1)切除が可能な膵癌を対象とし、術前化学療法としての GS（Gemcitabine+S-1）療法の有用性を、標準療法である手術先行治療を対照として、ランダム化比較試験で検証する。

Primary endpoint（主要評価項目）　：全生存期間

Secondary endpoints（副次評価項目）：有害事象、切除率、癌遺残度、リンパ節転移率、
組織学的効果、無再発生存期間、
腫瘍マーカー、治療薬用量強度、再発形式、腫瘍縮小率

0.3. 対象症例

適格基準（4.1）を全て満たし、除外基準（4.2）のいずれにも該当しない患者を本試験の対象とする。

1） 画像および病理所見にて通常型膵癌（浸潤性膵管癌）と診断される

2） 遠隔転移を有しない

3） 肉眼的癌遺残のない（R0, 1）切除が可能と判断される

4） 病巣摘除に必要な根治手術（膵頭切除、尾側膵切除、膵全摘）に耐術可能

5） 初回治療例

6） PS(ECOG 分類)が 0～1 の患者

7） 主要臓器（骨髄・肝・腎・肺等）の機能が保持されている患者

① 白血球数：3,500/mm^3 以上、12,000/mm^3 未満

② 好中球数：2,000/mm^3 以上

③ ヘモグロビン量：9.0g/dL 以上

④ 血小板数：100,000/mm^3 以上

⑤ 総ビリルビン：2.0 mg/dL 以下※

※閉塞性黄疸に対する減黄術を受けている患者は3.0 mg/dL 以下とする。

⑥ AST：150 U/L 以下

⑦ ALT：150 U/L 以下

⑧ クレアチニン：1.2mg/dL 以下

⑨ クレアチニンクリアランス：50mL/min 以上

(Cockcroft-Gault 式*による推定も可とするが、実測値がある場合は実測値を適格基準として用いる)

*: 男性 Ccr = 体重×(140-年齢)/(72×クレアチニン)

女性 Ccr = 体重×(140-年齢)/(72×クレアチニン)×0.85

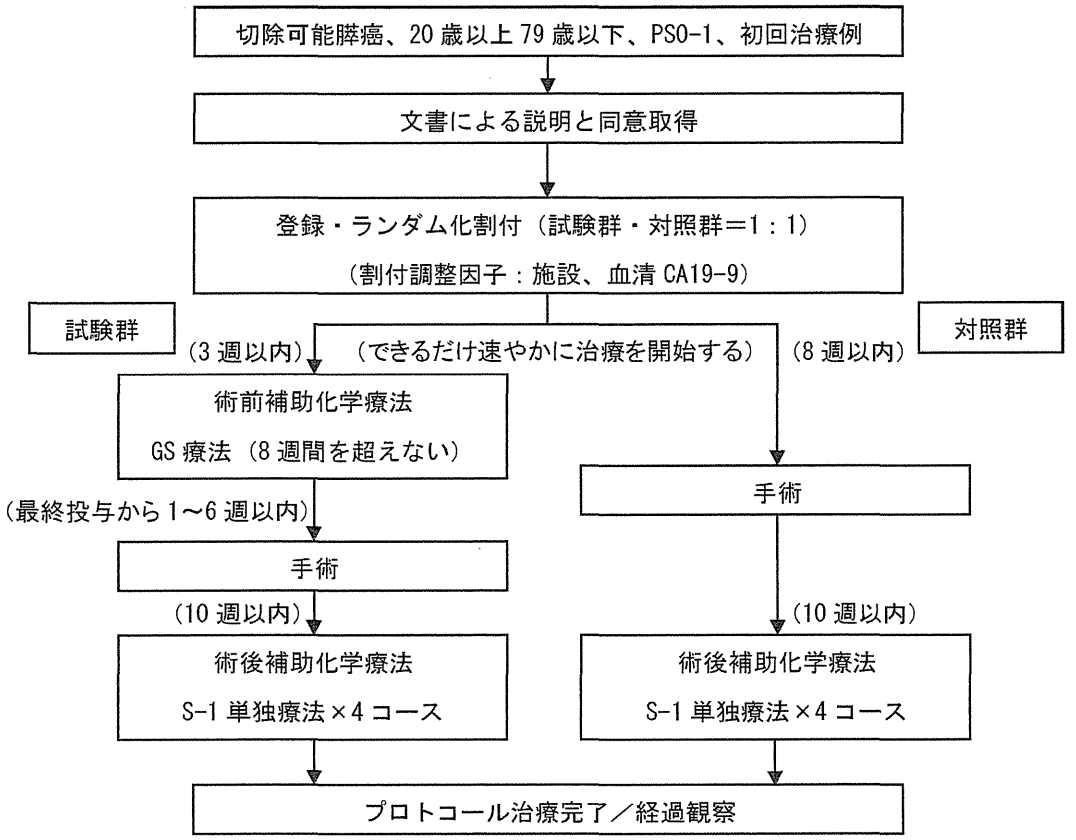
8） 経口摂取が可能な患者

9）患者本人より文書にて同意が得られている

10）登録時の年齢が 20 歳以上 79 歳以下で本試験の同意を得るのに十分な判断力がある

0.4. 試験のデザイン

オープンラベルによる多施設共同第Ⅱ/Ⅲ相ランダム化比較臨床試験



0.5. 治療方法

試験群：術前化学療法を行い、手術（外科的切除）を行った後、術後補助化学療法を行う。
対照群：手術（外科的切除）を行った後、術後補助化学療法を行う。

【 術前化学療法 】

GEM は 2 週投与 1 週休薬、S-1 は GEM 投与日から 1 週間、朝夕食後の 1 日 2 回経口投与することを標準とする。8 週間以内に合計 GEM 4 回投与、S-1 4 週間内服を目標とするが、8 週間以内に投与回数が目標に達しない場合でもプロトコール治療中止とはせずに手術を行う。

S-1 は GEM 投与当日の夕食後から内服し、各 GEM 投与から 8 日目の朝食後まで内服を行う。

【 術後補助化学療法 】

S-1 による術後補助化学療法を行う。S-1 80 mg/m^2 で 4 週間投薬 2 週間休薬のスケジュールで、計 4 コース投薬を行う。S-1 単独療法は 4 コースにて完了とする。

0.6. 予定症例数と試験期間

目標症例数　：360 例（II 相部分 80 例、III 相部分 280 例）
試験期間　　：5 年（2013 年 1 月～2017 年 12 月）
登録期間　　：3 年（2013 年 1 月～2015 年 12 月）
追跡期間　　：登録終了後 2 年

目　次

本試験で用いる基準・定義

①病理学的事項

本試験における膵癌の組織型分類は膵癌取扱い規約第 6 版に従う。

アンダーラインで示す分類を本試験の対象とする。

(1) 上皮性腫瘍

A. 外分泌腫瘍

1. 漿液性嚢胞腫瘍
   - a) 漿液性嚢胞腺腫
   - b) 漿液性嚢胞腺癌
2. 粘液性嚢胞腫瘍
   - a) 粘液性嚢胞腺腫
   - b) 粘液性嚢胞腺癌
     - i) 非浸潤
     - ii) 微小浸潤
     - iii) 浸潤
3. 膵管内乳頭粘液性腫瘍
   - a) 膵管内乳頭粘液性腺腫
   - b) 膵管内乳頭粘液性腺癌
     - i) 非浸潤
     - ii) 微小浸潤
     - iii) 浸潤
   - c) その他
     膵管内管状腫瘍等
4. 異型上皮および上皮内癌
5. <u>浸潤性膵管癌</u>
   - a) <u>乳頭腺癌</u>
   - b) <u>管状腺癌</u>
     - i) <u>高分化型</u>
     - ii) <u>中分化型</u>
   - c) <u>低分化腺癌</u>
   - d) <u>腺扁平上皮癌</u>
   - e) <u>粘液癌</u>
   - f) <u>退形成癌</u>
     - i) <u>巨細胞型</u>
     - ii) <u>破骨細胞様巨細胞型</u>
     - iii) <u>多形細胞型</u>
     - iv) <u>紡錘細胞型</u>
   - g) <u>その他</u>
6. 腺房細胞腫瘍
   - a) 腺房細胞腺腫
   - b) 腺房細胞癌

B. 内分泌腫瘍

1. 高分化内分泌腫瘍
2. 高分化内分泌癌
3. 低分化内分泌癌

C. 併存腫瘍

D. 分化方向の不明な上皮性腫瘍

1. Solid-pseudopapillary tumor
2. 膵芽腫
3. 未分化癌