18, Heinrich S, Pestalozzi B, Lesurtel M, Berrevoet F, Laurent S, Delpero JR, et al. Adjuvant gemcitabine versus NEOadjuvant gemcitabine/oxaliplatin plus adjuvant gemcitabine in resectable pancreatic cancer: a randomized multicenter phase III study (NEOPAC study). BMC Cancer 2011;11:346.

19. Le Scodan R, Mornex F, Girard N, Mercier C, Valette PJ, Ychou M, et al. Preoperative chemoradiation in potentially resectable pancreatic adenocarcinoma: feasibility, treatment effect evaluation and prognostic factors, analysis of the SFRO-FFCD 9704 trial and literature review. Ann Oncol 2009;20:1387–96.

20. Stessin AM, Meyer JE, Sherr DL. Neoadjuvant radiation is associated with improved survival in patients with resectable pancreatic cancer: an analysis of data from the surveillance, epidemiology, and end results (SEER) registry. Int J Radiat Oncol Biol Phys 2008;72:1128–33.

21. Sata N, Kurashina K, Nagai H, Nagakawa T, Ishikawa O, Ohta T, et al. The effect of adjuvant and neoadjuvant chemo(radio)therapy on survival in 1,679 resected pancreatic carcinoma cases in Japan: report of the national survey in the 34th annual meeting of Japanese Society of Pancreatic Surgery. J Hepatobiliary Pancreat Surg 2009;16:485–92.

22. Artinyan A, Anaya DA, McKenzie S, Ellenhorn JD, Kim J. Neoadjuvant therapy is associated with improved survival in resectable pancreatic adenocarcinoma. Cancer 2011;117:2044–9.

23. Laurence JM, Tran PD, Morarji K, Eslick GD, Lam VW, Sandroussi C. A systematic review and meta-analysis of survival and surgical outcomes following neoadjuvant chemoradiotherapy for pancreatic cancer. J Gastrointest Surg 2011;15:2059–69.

24. Gillen S, Schuster T, Meyer Zum BEslick GD, Lam Friess H, Kleeff J. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. PLoS Med 2010;7:e1000267.

25. Ohigashi H, Ishikawa O, Eguchi H, Takahashi H, Gotoh K, Yamada T, et al. Feasibility and efficacy of combination therapy with preoperative full-dose gemcitabine, concurrent three-dimensional conformal radiation, surgery, and postoperative liver perfusion chemotherapy for T3-pancreatic cancer. Ann Surg 2009;250:88–95.

26. Satoi S, Toyokawa H, Yanagimoto H, Yamamoto T, Kamata M, Ohe C, et al. Neo-adjuvant chemoradiation therapy using S-1 followed by surgical resection in patients with pancreatic cancer. J Gastrointest Surg 2012;16:784–92.

27. Matsuno S, Egawa S, Fukuyama S, Motoi F, Sunamura M, Isaji S, et al. Pancreatic Cancer Registry in Japan: 20 years of experience. Pancreas 2004;28:219–30.

28. Motoi F, Rikiyama T, Katayose Y, Egawa S, Unno M. Retrospective evaluation of the influence of postoperative tumor marker status on survival and patterns of recurrence after surgery for pancreatic cancer based on RECIST guidelines. Ann Surg Oncol 2011;18:371–9.

Table 1. Baseline demographics

	Resectable	Borderline	P-value
Number of patients	582	389	-
Age (y), median (range)	68 (27 - 90)	65 (32 - 87)	<0.001
Sex (male:female)	320 : 262	229 : 160	0.23
Past medical history or Comorbid illness			
Hypertension, n (%)	166 (29)	92 (24)	0.091
Coronary arterial disease, n (%)	66 (11)	36 (11)	0.30
Diabetes mellitus, n (%)	175 (30)	120 (31)	0.80
Other malignancy, n (%)	94 (16)	41 (11)	0.012
Peptic ulcer, n (%)	45 (7.8)	25 (6.4)	0.44
Hepatitis, n (%)	39 (6.7)	20 (5.1)	0.31
Other digestive disease*1, n (%)	98 (17)	49 (13)	0.074
Respiratory disease, n (%)	41 (7.1)	20 (5.1)	0.22
Cerebral Vascular disease, n (%)	25 (4.3)	17 (4.4)	0.96
Jaundice, n (%)	190 (33)	169 (43)	<0.001
Biliary drainage, n (%)	187 (32)	169 (43)	<0.001
Pre-treatment serum tumor marker			
CEA (ng/ml), median (range)	3 (0 - 435)	3.5 (0 - 675)	0.0039
CA19-9 (U/ml), median (range)*2	78 (0 - 47470)	203.75 (0 - 220540)	<0.001

*1: Other digestive disease included appendicitis (n=47), cholecystolithiasis (n=33), colonic polyps (n=16), pancreatitis (n=10), gastritis (n=8), gastric polyps (n=5), intestinal obstruction (n=4), liver cirrhosis (n=3), reflux esophagitis (n=2), fatty liver (n=2), hepatic hemangioma (n=2), pancreatic cyst (n=2), hemorrhoid (n=2), irritable bowel disease, trauma, situs inversus, colonic derticulitis, ulcerative colitis, Peutz-Jeghers syndrome (n=1), unknown (n=5).

*2: The values of CA19-9 were measured after biliary drainage when the patients with jaundice.

Table 2. Types of Neoadjuvant therapy and Agents

	Resectable	Borderline	P-value
Neoadjuvant therapy, n (%)	185 (32)	203 (52)	<0.0001
Types of therapy			
Radiotherapy, n (%)	114 (20)	140 (36)	<0.0001
irradiation (Gy), median (range)	50 (35.2 - 54)	45 (10.8 - 67.5)	<0.0001
Agents provided			
with Gemcitabine	95	90	
with S1	8	28	
with Gemcitabine+S1	5	13	
with Other agents*1	4	7	
radiation alone	4	7	
Duration*2 (days), median (range)	99.5 (56 - 278)	82 (46 - 391)	<0.0001
Chemotherapy, n (%)	65 (11)	50 (13)	0.43
Agents provided			
Gemcitabine	17	22	
S1	5	2	
Gemcitabine+S1	26	24	
Gemcitabine+Other agents*3	17	2	
Duration*2 (days), median (range)	28 (13 - 138)	81.5 (16 - 137)	0.0029
No record	6	13	

*1 Other agents was 5-FU + CDDP + MMC (n=11).

*2 Duration represents the days from the start of neoadjuvant therapy to operation.

*3 Other agents included 5-FU (n=18) and CDDP (n=1).

Table 3. Adverse events during neoadjuvant therapy

	Grade 1-4 (%)			Grade 3-4 (%)		
	chemotherapy	Radiotherapy	P value	chemotherapy	Radiotherapy	P value
Neutrocytopenia	58.8	65.4	0.30	33.8	20.0	0.0164
Leukocytopenia	53.8	75.5	0.0003	16.3	36.7	0.0007
Anemia	28.2	61.5	<0.0001	1.4	3.9	0.45
Thrombocytopenia	26.7	35.7	0.16	4.0	2.8	0.70
Fatigue	20.8	33.2	0.048	0.0	0.0	>0.99
Allergy	13.7	9.7	0.37	0.0	1.1	>0.99
Nausea/Vomiting	9.7	29.6	0.0006	1.4	2.2	>0.99
Liver dysfunction	3.1	0.4	0.055	0.0	0.0	>0.99
Pigmentation	2.3	1.8	0.70	0.0	0.0	>0.99
Anorexia	1.7	8.6	0.010	0.9	2.2	0.67
Cholangitis/Cholecystitis	0.8	2.5	0.43	0.0	2.1	0.17
Pneumonitis	0.0	2.5	0.094	0.0	1.3	0.56
Body weight loss	0.0	2.1	0.17	0.0	0.0	>0.99
Other*	6.1	2.5	0.93	0.0	0.0	>0.99

*Other non-hematological adverse events included thrmbosis, peptic ulcer, oral mucositis, renal dysfunction, constipation.

Table 4. Resection and R0-resection rate

A. Resectable (n=582)

Group	Surgery first	Neoadjuvant	P value
Total cohort, n	397	185	-
Resection, n	375	171	0.34
Resection rate	94.5 %	92.4 %	
R0 resection, n	305	164	
R0 rate by ontreatment analysis*1	81.3 %	95.9 %	<0.0001
R0 rate by intention to treat analysis*2	76.8 %	88.6 %	0.0003

B. Borderline (n=389)

Group	Surgery first	Neoadjuvant	P value
Total cohort	186	203	-
Resection	156	158	
Resection rate	83.9 %	77.8 %	0.16
R0 resection	118	123	
R0 rate by ontreatment analysis*1	75.6 %	77.8 %	0.57
R0 rate by intention to treat analysis*2	63.4 %	60.6 %	0.61

*1 R0 rate by ontreatment analysis was R0 resection per all resected cases with a record of residual tumor assessment.

*2 R0 rate by intention to treat analysis was R0 resection per total cases with a record of residual tumor assessment including non-resected and non-operated cases as R2 resection.

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 - 1021)	0.0001
Blood loss (ml), median (range)	872 (50 - 16422)	1088 (55 - 12925)	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 (gradeB/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*	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

*1 Leakage includes anastomosis insufficiency except for pancreatic fistula.

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 - 1221)	567 (190 - 1160)	0.0005
Blood loss (ml), median (range)	1137 (20 - 16201)	1400 (60 - 8422)	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*	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

Table 7. Peri-operative outcome in resecteable group

A. Resectable

		Surgery first	Neoadjuvant	P value
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

		Surgery first	Neoadjuvant	P value
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)	

Figure1
Click here to download high resolution image

Figure 1. FLOW DIAGRAM

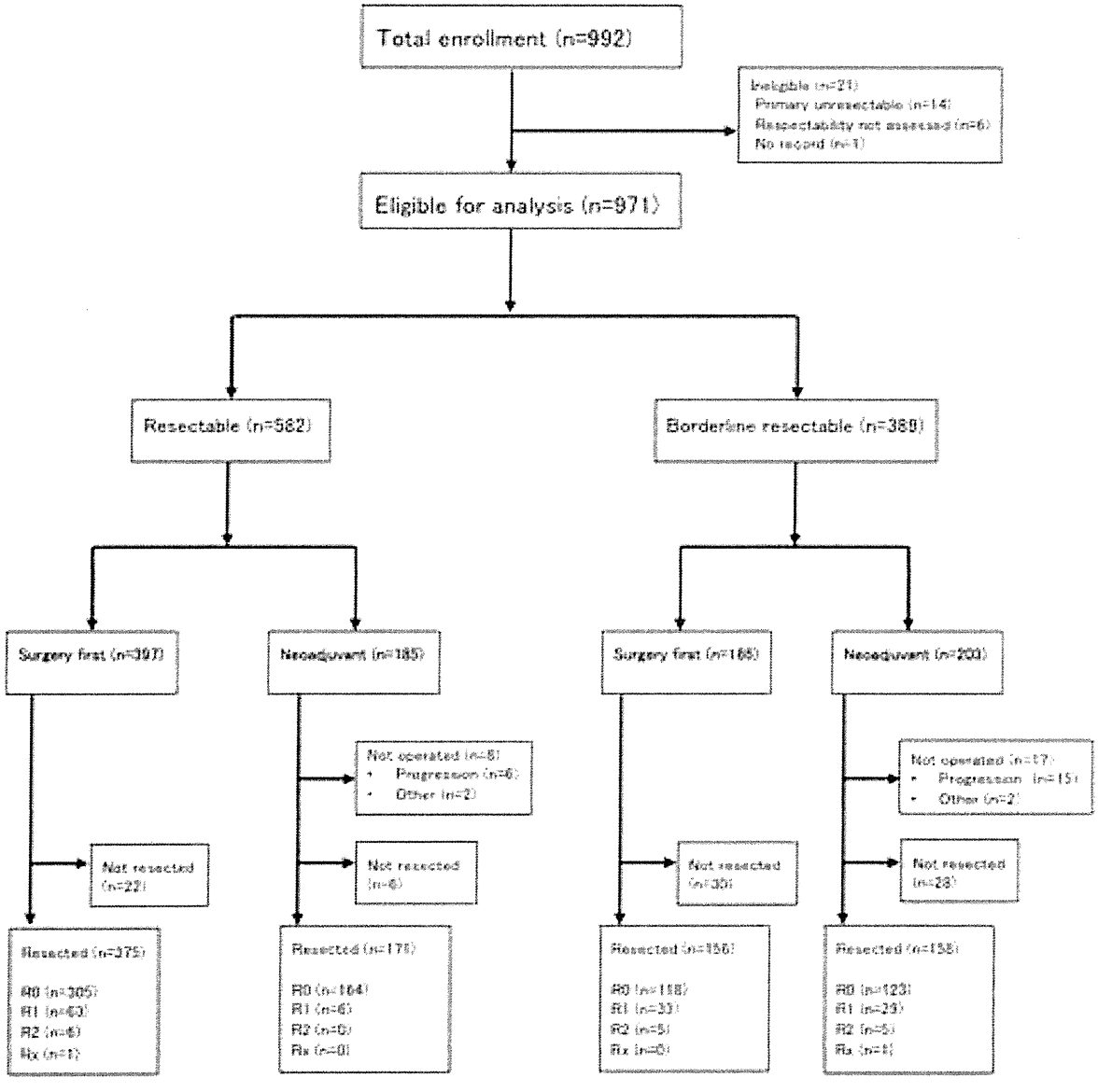
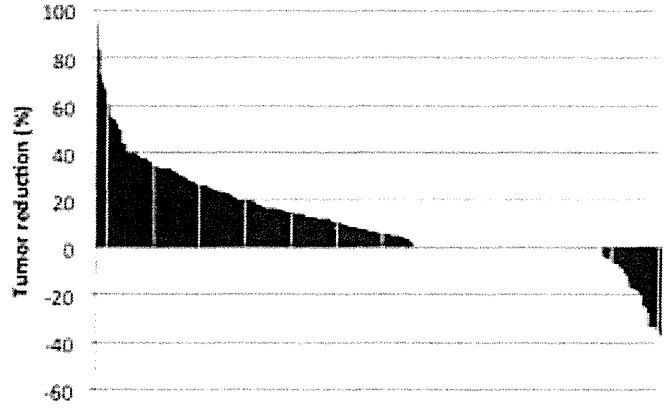


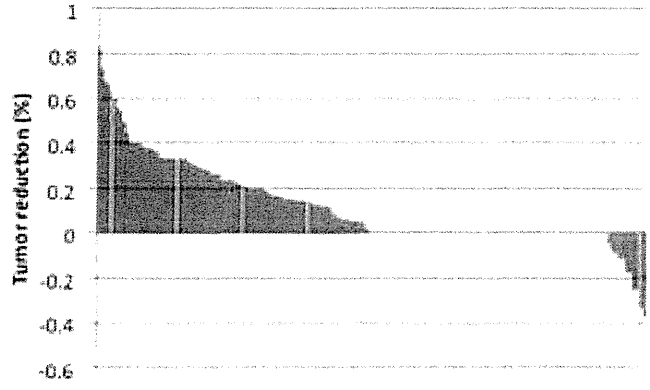
Figure2
Click here to download high resolution image

Figure 2. Radiological tumor response

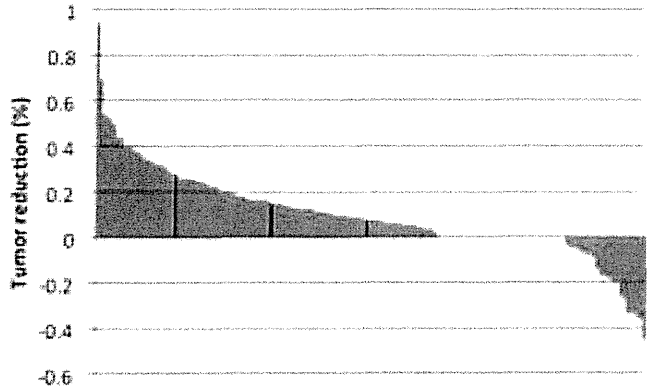
A. All patients receiving preoperative therapy (n=325)



B. Resectable (n=159)



C. Borderline resectable (n=166)



Neoadjuvant chemotherapy with gemcitabine and S-1 for resectable and borderline pancreatic ductal adenocarcinoma: results from a prospective, multi-institutional, phase-II trial

Short title: Neoadjuvant therapy for pancreatic cancer

Fuyuhiko Motoi MD[1),10)], Kazuyuki Ishida MD[2)], Fumiyoshi Fujishima MD[3)], Shigeru Ottomo MD[1)], Masaya Oikawa MD[4),10)], Takaho Okada MD[1)], Hiromune Shimamura MD[5),10)], Shinichi Takemura MD[6),10)], Fuminori Ono MD[7),10)], Masanori Akada MD[8)10)], Kei Nakagawa MD[1)9)], Yu Katayose MD[1),9)10)], Shinichi Egawa MD[1),10)], Michiaki Unno MD[1),9)10)]

[1)]Division of Gastroenterological Surgery, Department of Surgery, Graduate School of Medicine, Tohoku University, Japan

[2)]Department of Diagnostic Pathology, Iwate Medical University, Japan

[3)]Department of Pathology, Tohoku University Hospital, Japan

[4)]Department of Gastroenterological Surgery, Sendai Open Hospital, Japan

[5)]Department of Surgery, National Hospital Organization, Sendai Medical Center, Japan

[6]Department of Surgery, Shirakawa Kosei General Hospital, Japan

[7)]Department of Surgery, Senboku Kumiai General Hospital, Japan

[8)]Department of Surgery, South Miyagi Medical Center, Japan

[9)]Department of Surgery, Division of Surgery and Oncology, Tohoku University, Graduate School of Medicine, Japan

[10)]Miyagi-Hepato-Biliary-Pancreatic Clinical Oncology Group (Miyagi-HBPCOG), Japan

Corresponding author: Fuyuhiko Motoi

Division of Gastroenterological Surgery, Department of Surgery

Graduate School of Medicine, Tohoku University

1-1, Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan

Tel: +81-22-717-7205; Fax: +81-22-717-7209

E-mail: fmotoi@surg1.med.tohoku.ac.jp

No authors have any conflicts of interest.

Sources of support: This work was supported in part by Grants-in-Aid for Scientific Research (C) 21591766 from the Japan Society for the Promotion of Science.

Synopsis

In this phase II study of neoadjuvant chemotherapy with gemcitabine and S-1 for pancreatic cancer, the R0 resection rate and the 2-year survival rate were encouraging for resectable and borderline disease.

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 anti-tumor 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 II 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 endpoint was the 2-year survival rate. Secondary endpoints were feasibility, resection rate, pathological effect, recurrence-free survival and tumor marker status.

Results

Of 36 patients enrolled, 35 were eligible in 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) when 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.

Introduction

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 non-metastatic PDAC, but recurrence rates are high even after R0 resection (5, 6). The ESPAC-1 trial showed a significant survival benefit for adjuvant chemotherapy (7). The CONKO-001 (8) and Japanese trials (9) suggested that adjuvant treatment with gemcitabine offered a good chance for prolonged disease-free survival in patients undergoing curative resection of PDAC.

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 radiation to a vascularized primary tumor, provides early treatment of micro-metastatic 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 when 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 when compared with a similar cohort who underwent surgery-first resection and adjuvant therapy (13). Palmer et al. (14), Heinrich et al. (15), and Sahora et al. (16) reported that NAC with gemcitabine and platinum agents was safe and associated with a high resection rate and an encouraging survival rate. 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 anti-tumor activity in chemo-naïve patients (18) or in patients with gemcitabine-refractory metastatic PDAC (19). The combination of S1 and gemcitabine (GS) for the first-line treatment of unresectable PDAC was associated with promising anti-tumor activity and acceptable toxicity (20)-(23). Based on encouraging results in patients with unresectable PDAC, MiyagiHBPCOG initiated a multi-institutional phase II 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 II, cooperative group study was open to patients with PDAC. Between November 2008 and April 2010, 36 patients from 9 participating institutions from northeastern Japan were enrolled in this trial.

Inclusion criteria were as follows: (*1*) newly diagnosed PDAC; (*2*) age ≥18 years; (*3*) Eastern Cooperative Oncology Group performance status = 0-1; (*4*) complete history and physical examination, and staging evaluation requiring multi-detector-row computed tomography (MD-CT); (*5*) no distant metastases; (*6*) tumor considered as potentially or borderline resectable; (*7*) no previous anti-tumor treatment except for biliary drainage; and (*8*) adequate hematologic, hepatic, renal, and cardiopulmonary functions. Tumor with encasement of the porto-mesenteric vein and/or abutment of major arteries (hepatic or mesenteric artery) within 180 degrees 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 given 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 using the Common Toxicity Criteria (CTCAE ver3.0). After completion of two cycles of GS, surgery was planned to occur at 1 to 6 weeks, and all patients underwent re-staging studies with MD-CT to