Cancer Chemother Pharmacol (2010) 66:527–534
DOI 10.1007/s00280-009-1193-4

ORIGINAL ARTICLE

A phase II study of induction chemotherapy with gemcitabine plus S-1 followed by chemoradiotherapy for locally advanced pancreatic cancer

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Received: 10 August 2009 / Accepted: 19 November 2009 / Published online: 5 December 2009

Abstract
Purpose The aim of this study was to investigate the feasibility and efficacy of induction chemotherapy with gemcitabine and S-1 followed by chemoradiotherapy for locally advanced pancreatic cancer.
Methods Patients with locally advanced unresectable pancreatic cancer received four cycles of induction chemotherapy consisting of 30-min intravenous infusions of gemcitabine 1,000 mg/m^2 on days 1 and 8 and oral S-1 40 mg/m^2 twice daily on days 1–14 of a 21-day cycle. Those without disease progression received chemoradiotherapy of 30 Gy in ten fractions with 250 mg/m^2 of gemcitabine on days 1 and 8.
Results A total of 20 patients were treated. Median follow-up time was 431 days (range 133–1,014 days). Four cycles of induction chemotherapy were completed in 18 patients, and 16 patients received chemoradiotherapy, which was completed without delay in all. Grade 3–4 toxicities associated with induction chemotherapy were neutropenia (50%); anemia (20%); thrombocytopenia (10%); febrile neutropenia (5%); nausea (10%); anorexia (10%); and vomiting, fatigue, dehydration, stomatitis, and rash (5%). Grade 3–4 toxicities among those receiving chemoradiotherapy were neutropenia (13%) and anemia (6%). Median progression-free survival was 8.1 months. Median overall survival was 14.4 months, with a 1-year survival rate of 54.2%.
Conclusions The regimen of induction chemotherapy with gemcitabine and S-1 followed by chemoradiotherapy used in the present study demonstrated promising activity in locally advanced pancreatic cancer. Further consideration of radiation schedule and duration of induction chemotherapy is required to enhance the efficacy of this strategy.

Keywords Chemotherapy · Pancreatic neoplasms · Radiotherapy · Gemcitabine · S-1

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Introduction

Pancreatic cancer is the fifth leading cause of cancer death in Japan and one of the most lethal types of cancer; approximately, 20,000 patients are diagnosed and about the same number of patients die from this disease every year [1]. The majority of patients present with unresectable disease at the time of diagnosis, because of local involvement or metastatic spread. Unresectable pancreatic cancer due to vascular involvement (celiac, hepatic, or supra-mesenteric artery) without radiographically distant metastases is categorized as locally advanced disease.

Traditionally, chemoradiotherapy has been considered as a standard treatment for locally advanced pancreatic cancer, because randomized trials conducted by Moertel et al. [2–4]

and the Gastrointestinal Tumor Study Group (GITSG) demonstrated a survival advantage for chemoradiotherapy compared with chemotherapy or radiotherapy alone. However, a recent French randomized controlled trial reported that chemotherapy with gemcitabine was superior to chemoradiotherapy (median survival 13.0 vs. 8.6 months) [5]. On the other hand, The Eastern Cooperative Oncology Group (ECOG) reported that chemoradiotherapy conferred a survival advantage when compared with gemcitabine chemotherapy (median survival 11.0 vs. 9.2 months) [6]. Thus, the role of chemoradiotherapy is controversial, especially because of the introduction of gemcitabine.

Most patients with locally advanced pancreatic cancer treated with chemoradiotherapy eventually develop metastatic progression. Moreover, minute hepatic or peritoneal metastases are found in one-third of patients with radiographically diagnosed locally advanced pancreatic cancer at staging by laparoscopy or laparotomy [7–9]. Thus, even in locally advanced disease, it is necessary to deliver more effective systemic chemotherapy earlier as well as to give loco-regional treatment to improve the outcome.

Gemcitabine has been widely used as a standard systemic chemotherapeutic agent for advanced pancreatic cancer. Although some combination therapies including gemcitabine have shown survival benefit, these are not considered as standard regimens. S-1 is an oral fluoropyrimidine derivative that combines tegafur (FT) with two modulators; 5-chloro-2, 4-dihydroxypyridine (CDHP) and oteracil potassium (Oxo) in a 1:0.4:1 molar concentration ratio. The efficacy of S-1 has already been shown in a variety of solid tumors, particularly gastric cancer [10, 11]. A phase II trial of S-1 monotherapy for metastatic pancreatic cancer has shown a response rate of 37.5% and median survival of 9.2 months [12]. Moreover, phase II trials of a combination of gemcitabine and S-1 have demonstrated objective response rates of 44–48% and median survival of 10–12 months [13, 14].

In the present study, we conducted the early phase II trial consisting of induction chemotherapy using gemcitabine and S-1 to prevent or evaluate early metastatic progression followed by consolidative chemoradiotherapy for locally advanced pancreatic cancer.

Patients and methods

Patient eligibility

Patients with histologically confirmed locally advanced pancreatic adenocarcinoma were eligible for this study. Inclusion criteria were as follows: diagnosis of unresectable disease due to vascular involvement (i.e., celiac, hepatic, or supra-mesenteric artery) or to occlusion of superior mesenteric or portal vein on contrast-enhanced computed tomography (CT); age of ≥20 years; ECOG performance status of 0 or 1; no prior anticancer treatment; adequate bone marrow function (white blood cell count >4,000 cells/mm^3, absolute neutrophil count >2,000 cells/mm^3, hemoglobin level >9.0 g/dL, platelet count >100,000 cells/mm^3), liver function (serum total bilirubin <2.0 mg/dL, transaminase <150 IU/L), and renal function (serum creatinine <1.2 mg/dL); life expectancy of ≥3 months; and provision of written informed consent. Exclusion criteria were as follows: the presence of pleural effusion or ascites, severe complications, such as heart disease, renal disease, mental disorder, infection, intestinal paresis, uncontrolled diabetes mellitus, drug allergy, and lactation or pregnancy. This study was approved by the institutional review board at the National Cancer Center and conducted in accordance with the Good Clinical Practice guidelines of Japan. This was a single center, open-label phase II trial.

Treatment

Patients received four cycles of induction gemcitabine plus S-1 chemotherapy consisting of gemcitabine 1,000 mg/m^2 (Eli Lilly Japan K.K., Kobe, Japan) via a 30-min intravenous infusion on days 1 and 8 and oral S-1 (Taiho Pharmaceutical Co., Ltd, Tokyo, Japan) 40 mg/m^2 twice daily on days 1–14 every 3 weeks. Three dose levels of S-1 were established according to the body surface area (BSA) as follows: BSA <1.25 m^2, 80 mg/day; BSA 1.25−1.50 m^2, 100 mg/day; and BSA >1.50 m^2, 120 mg/day. These dosing schedules were investigated in a previous phase I study for advanced pancreatic cancer [15]. If patients experienced absolute neutrophil count <1,000 cells/mm^3, platelet count <70,000 cells/mm^3, or unacceptable non-hematological toxicities (≥grade 3), both gemcitabine and S-1 were withheld until recovery. If patients experienced absolute neutrophil count <500 cells/mm^3 or platelet count <25,000 cells/mm^3 or if they could not receive gemcitabine on day 8 or S-1 for more than 7 days because of any toxicities, the dose of gemcitabine was reduced to 800 mg/m^2 and the dose of S-1 was reduced by 20 mg/day in the subsequent cycle.

Subsequently, patients without disease progression received chemoradiotherapy within 2–6 weeks, after the last dose of chemotherapy. A total dose of 30 Gy/10 fractions using once-daily fractionation was delivered with a 10 MV X-ray unit. Treatment planning was performed with a CT-based planning system; the gross tumor volume (GTV) was defined as the primary tumor and metastatic lymphadenopathy as visualized on each CT image with contrast enhancement. The clinical target volume (CTV) was defined as the GTV plus a 1.0-cm margin, to account for subclinical tumor spread. The planning target volume (PTV) was defined as the CTV plus a 1.0- to 2.0-cm margin along the cranio-caudal axis and a 1.0-cm lateral margin,

to account for physiological organ motion and daily set-up error. The prescribed dose was determined at the central part of the PTV. A 4-field technique was used to minimize irradiated volume of the liver and the kidneys. Prophylactic lymph node irradiation was not performed. Gemcitabine at a dose of 250 mg/m^2 was administered intravenously for 30 min before radiotherapy on days 1 and 8.

After chemoradiotherapy was completed, maintenance chemotherapy with gemcitabine was started within 2–4 weeks. Gemcitabine was administered once weekly at a dose of 1,000 mg/m^2 in a 30-min intravenous infusion for three consecutive weeks, followed by a week of rest. Two cycles of gemcitabine were defined as the protocol treatment. Treatments were continued until disease progression, patient refusal, or unacceptable toxicity.

Evaluation

Physical and laboratory examination were performed at least once every week. Contrast-enhanced CT was performed every two cycles of induction chemotherapy, after the completion of chemoradiotherapy, and every two cycles of maintenance gemcitabine chemotherapy. Objective tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST). Progression-free survival (PFS) was calculated from the day of initial therapy until the day of disease progression. Progression was defined as confirmation of progressive disease on the RECIST or deterioration of the patients' general condition. Overall survival (OS) was calculated from the day of initial therapy until the day of death from any cause. Carbohydrate antigen 19-9 (CA19-9) was measured once every month. Toxicities were evaluated according to the National Cancer Institute—Common Toxicity Criteria version 2.0.

Statistical design and analyses

The primary end point was PFS at 6 months. A PFS rate of 50% at 6 months was expected in this trial. The planned sample size was 20 patients. If $\leq$5 of the 20 patients were progression free at 6 months, the treatment would have been assessed as invalid because the upper limit of the 95% confidential interval (CI) was calculated as 49.1%. PFS and OS were analyzed using the Kaplan–Meier methods.

Results

Patient characteristics

A total of 20 patients were enrolled in this study between February 2005 and October 2006. Patient characteristics are shown in Table 1.

Protocol treatments were completed in all 20 patients by April 2007. Data were collected in May 2008. Median follow-up time was 431 days (range 133–1,014 days).

Treatment administration

A schema of the trial is shown in Fig. 1. All 20 patients received at least one cycle of induction chemotherapy; 2 of the 20 patients showed disease progression (general deterioration and progression at the primary site with duodenal obstruction) during the induction chemotherapy. Four cycles of the induction chemotherapy were completed in 18 patients. Two of these 18 patients showed disease progression (peritoneal dissemination and obstructive jaundice) after the completion of the induction chemotherapy. Relative dose intensity for induction gemcitabine and S-1 was 0.92 and 0.89, respectively. Subsequently, 16 patients received chemoradiotherapy, which was completed without delay in all. Of these 16, one developed liver metastasis after the completion of chemoradiotherapy. Therefore, a final total of 15 patients received 2 cycles of maintenance chemotherapy with gemcitabine. Relative dose intensity for maintenance gemcitabine was 0.88.

Laparotomy was performed in six patients after the evaluation of the above-mentioned protocol treatments. Of these, two underwent laparotomy with the intention of intraoperative radiotherapy, and four with the intention of curative resection. None of the six patients had extra-pancreatic disease. Two received intraoperative radiotherapy, three underwent surgical resection with pathological negative margin, and one had exploratory laparotomy alone because of vascular involvement.

Safety

During the induction chemotherapy, toxicities were evaluated in all 20 patients. The data are summarized in Table 2.

Table 1 Patient characteristics (n = 20)

Characteristic	Number
Age, years: median (range)	63.5 (33–75)
Sex: male/female	10/10
Performance status: 0/1	15/5
Primary site: pancreatic head/body	11/9
Tumor size, mm: median (range)	40.5 (13–100)
Stage of tumor	
IIA: T3 N0 M0	3
III: T4 N0 M0	10
III: T4 N1 M0	7
Baseline CA19-9, U/ml: median (range)	444 (0.1–10760)

CA19-9 carbohydrate antigen 19-9

Tumor stage was evaluated according to TNM classification 6th edition

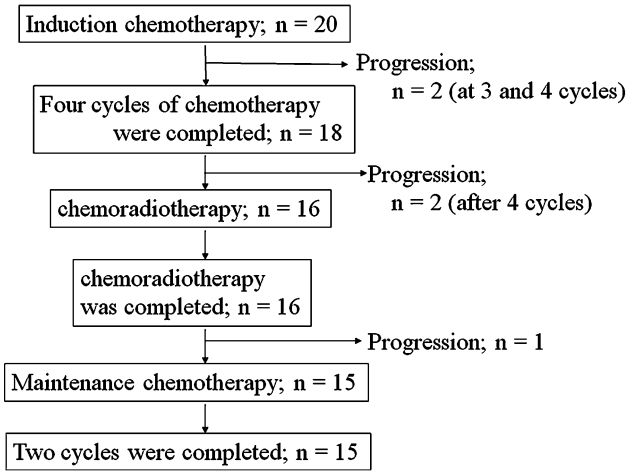

Fig. 1 Outcomes of treatment

Grade 3 or 4 hematological toxicities were observed in 13 (65%) patients. These recovered promptly after the withdrawal of gemcitabine and S-1, and were manageable by dose modification in the next cycle. Febrile neutropenia occurred in one patient, associated with grade 3 infection, stomatitis and anorexia. Nausea, anorexia, rash, and stomatitis were common non-hematological toxicities. Dose reduction in gemcitabine and S-1 was required in six patients.

Chemoradiotherapy was started on schedule up to 4 weeks after finishing chemotherapy. Toxicities for chemoradiotherapy were evaluated in 16 patients (Table 3). Grade 3 hematological toxicities were observed in two (12.5%) patients. No patients developed grade 3 or 4 non-hematological toxicities, and chemoradiotherapy was completed in all patients without delay.

Efficacy

Tumor response and survival data were assessable in all 20 patients (Table 4). Five patients (20%) achieved partial response. The median duration of response was 281 days (range 244–930). At the first evaluation, no patients had progressive disease. In 12 (92.3%) of the 13 patients with pretreatment, serum CA19-9 level of 100 IU/ml or greater, the level was decreased more than 50%.

Median PFS was 8.1 months (95% CI 5.5–10.8 months) (Fig. 2). Proportion of patients with PFS at 6 months was 70.0% (95% CI 45.7–88.1%). Patterns of progression are summarized in Table 5. Disease progression was observed in 17 patients at the time of analysis. One patient died without disease progression because of surgical complications. Fifteen patients died of the disease. Two patients remained alive without progression at the time of analysis. Median overall survival was 14.4 months (95% CI 8.7–20.0 months) and 1-year survival was 54.2% (Fig. 3).

Table 2 Toxicities of induction chemotherapy (n = 20)

	Any grade		Grade 3/4	
	n	%	*n*	%
Hematological				
Neutropenia	14	70	10	50
Anemia	11	55	4	20
Thrombocytopenia	11	55	2	10
Febrile neutropenia	1	5	1	5
Non-hematological				
Nausea	9	45	2	10
Vomiting	7	35	1	5
Anorexia	8	40	2	10
Fatigue	6	30	1	5
Dehydration	1	5	1	5
Stomatitis	5	25	1	5
Rash	7	35	1	5
Diarrhea	3	15	0	0

Toxicities were evaluated according to the National Cancer Institute-Common Toxicity Criteria version 2.0

Table 3 Toxicities of chemoradiotherapy (n = 16)

	Any grade		Grade 3/4	
	n	%	*n*	%
Hematological				
Neutropenia	12	75	2	13
Anemia	4	25	1	6
Thrombocytopenia	2	13	0	0
Febrile neutropenia	0	0	0	0
Non-hematological				
Nausea	6	38	0	0
Vomiting	4	25	0	0
Anorexia	6	38	0	0
Fatigue	6	38	0	0

Toxicities were evaluated according to the National Cancer Institute-Common Toxicity Criteria version 2.0

Table 4 Objective response to treatment (n = 20)

Tumor response	n = 20 (%)
Partial response	5 (25)
Stable disease	15 (75)
Progressive disease	0
Baseline CA19-9	≥100 IU/ml, n = 13 (%)
Response (≥50% decline)	12 (92.3)
Non-response	1 (7.7)

Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumor

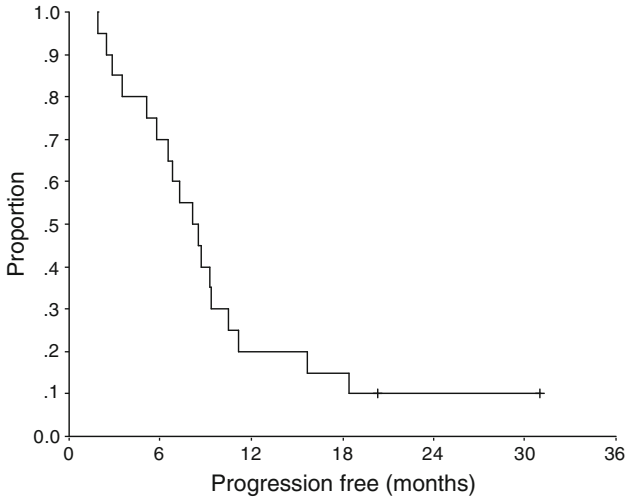

Fig. 2 Kaplan–Meier curve of progression-free survival. Median progression-free survival time was 8.1 months (95% CI 5.5–10.8). Proportion of patients progression free at 6 months was 65%

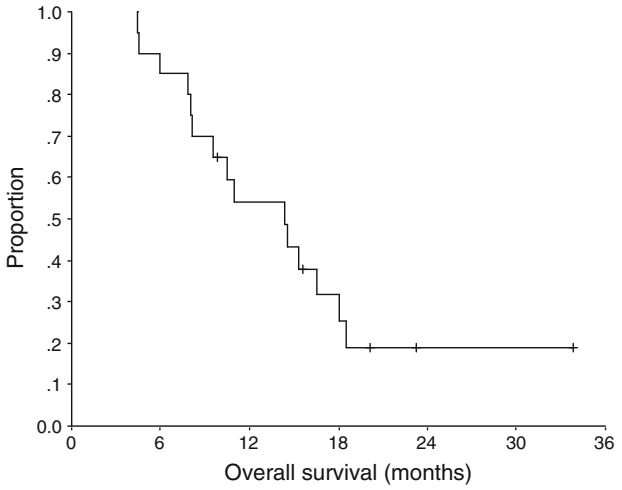

Fig. 3 Kaplan–Meier curve of overall survival. Median survival time was 14.4 months (95% CI 8.7–20.0); 1-year survival rate was 54.2%

Table 5 Patterns of progression

	Oveall $n = 17$	During chemotherapy $n = 4$
Local	3	2
Distant	12	1
Liver	2	0
Peritoneum	5	1
Liver and peritoneum	2	0
Others (lung, distant node)	3	0
General deterioration	2	1

Discussion

Although many clinical trials of chemoradiotherapy have been conducted for locally advanced pancreatic cancer, there has been not much improvement in survival rates for two decades. Median survival is around 10–12 months and accounts of long-term survivors are anecdotal. This indicates the limited efficacy of chemoradiotherapy as a loco-regional therapy. Secondary, latent metastases or early metastatic progressions are commonly observed, and effective systemic chemotherapy is required in this setting. It is difficult to administer sufficient doses of chemotherapeutic agents in maintenance therapy because myelosuppression is usually severe after chemoradiotherapy [5]. Moreover, doses of anticancer agents such as gemcitabine must be limited because of increasing toxicities in conjunction with a definitive dose of radiation [16, 17]. Induction chemotherapy is a reasonable strategy to resolve these problems and to improve treatment outcome. Up-front administration of effective antitumor agents might treat latent metastases and help in selecting appropriate patients for chemoradiotherapy.

The combination of gemcitabine and S-1 was selected as an induction regimen because it has already demonstrated an objective response rate of 44–48% in two phase II trials [13, 14]. A phase III trial to confirm the survival benefit of this regimen is continuing in Japan and Taiwan. Nausea, anorexia, and stomatitis were common non-hematological toxicities, which were manageable by supportive care. Disease progression was observed in four patients (20%) until the end of the chemotherapy. Therefore, these patients were probably not appropriate candidates for chemoradiotherapy at the time of diagnosis. Local progression, heralded by obstructive jaundice and duodenal obstruction, was observed in two of these four patients. It is possible that postponing chemoradiotherapy was a potential risk factor for lack of local control in such patients. Objective response was observed in 25% of all patients. CA19-9 response (a 50% decline in serum levels from a baseline of >100 IU/ml) was observed in 92.3% of patients. Most of the responses were observed during induction chemotherapy.

The concept on which this study was based is short-term radiotherapy. We previously performed a phase I trial of hypofractionated radiotherapy in which 3.0 Gy/day was confirmed to be feasible [18]. The same radiation schedule was investigated in a phase I trial at the MD Anderson Cancer Center. Gemcitabine is a potent radiosensitizer, and the phase I trial reported that a gemcitabine regimen of 350 mg/m^2 weekly had the potential for significant toxicity [19]. Gemcitabine at 250 mg/m^2 weekly was recommended in another phase I trial in which it was administered concomitantly with 50.4 Gy in 28 fractions of 1.8 Gy/day [16]. These trials used large irradiation fields, including prophylactic lymph node irradiation. On the other hand, investigators

at the University of Michigan and their colleagues reported that reduced irradiation fields enabled the concurrent administration of full-dose gemcitabine. They elected to irradiate the primary tumor only without prophylactic lymph node irradiation [29, 30]. Therefore, we performed chemoradiotherapy comprising 30 Gy in ten fractions of 3.0 Gy/day, in a 2-week schedule without prophylactic lymph node irradiation and gemcitabine 250 mg/m^2 weekly. As 30 Gy is a moderate radiotherapy dose, it might not be sufficient to achieve local control. However, lacking confirmatory evidence that high-dose radiotherapy leads to better outcome, this dose was chosen. Moertel et al. reported no statistical difference in survival between high dose (60 Gy) + 5-FU and moderate dose (40 Gy) + 5-FU radiotherapy. Sixteen patients received chemoradiotherapy, and all completed it without delay. No grade 3 or 4 gastrointestinal toxicities developed. The present schedule of chemoradiotherapy was, therefore, demonstrated to be feasible with limited toxicity, although a trial using the same dose and fraction conducted at MD Anderson Cancer Center did not seem to be tolerable. The reduced irradiation volume may make this approach possible. Further investigations of more intensified radiation schedules are warranted to enhance local tumor control.

Following the protocol therapy, laparotomy was performed in six patients. Of these, three underwent surgical resection with a pathologically negative margin. Relief of vascular encasement was observed in these cases. The antitumor activity encourages us to anticipate positive results in the neoadjuvant setting as well as in downstaging for locally unresectable or borderline resectable disease.

The strategy of induction chemotherapy for locally advanced pancreatic cancer has been proposed by several investigators. Prospective and retrospective studies of induction chemotherapy are summarized in Table 6 [20–26]. Huguet et al. [25] retrospectively analyzed 181 patients with locally advanced disease enrolled in the GERCOR prospective study. Of these, 72 received chemoradiotherapy on the basis of no distant metastases after 3 months of chemotherapy. They reported that chemoradiotherapy following chemotherapy improved outcome as compared to chemotherapy alone. Krishnan et al. [26] showed that chemoradiotherapy following chemotherapy improved outcome when compared with initial chemoradiotherapy. Among phase II trials, regimens consisting of gemcitabine plus platinum-based agents (which have shown high-tumor response compared with gemcitabine monotherapy in phase III trials) demonstrated better outcome than others [27, 28]. Hence, such a combination regimen for induction chemotherapy might enhance the results shown by this study. Nonetheless, the present study showed promising results: median survival and 1-year survival rate were 14.4 months and 54.2%, respectively.

In conclusion, our study demonstrated promising antitumor activity of induction chemotherapy with gemcitabine

Table 6 Summary of induction chemotherapy for locally advanced pancreatic cancer

References	*n*	Chemotherapy Chemoradiotherapy	Median OS (months)	1 year (%)
Huguet [25]	56	Gem, GEMOX, FOLFUGEM –	11.7	47.5
	72	Gem, GEMOX, FOLFUGEM 55 Gy/FU	15.0	65.3
Krishnan [26]	274	– 30 or 50.4 Gy/FU, Cape, Gem	8.5	–
	76	Gem/CDDP (2.5mo) 30 or 50.4 Gy/FU, Cape, Gem	11.9	–
Mishra [20]	20	Gem/CPT-11(1.5 months) 50.4 Gy/Gem	8.8	–
Ko [21]	25	Gem/CDDP (6 months) 50.4 Gy/Cape	13.5	62
Moureau-Zabotto [22]	59	GEMOX (2 months) 55 Gy/FU, Oxaliplatin	12.2	52.1
Kurt [23]	24	Gem/FU (2 months) 50.4-54 Gy/Gem	11	–
Goldstein [24]	41	Gem (1 months) 54 Gy/FU	11.7	46.3
Current study	20	Gem/S-1 (3 months) 30 Gy/Gem	14.4	54.2

OS overall survival, *Gem* gemcitabine, *GEMOX* gemcitabine and oxaliplatin, *FOLFUGEM* gemcitabine, leucovorin, and fluorouracil, *Cape* capecitabine, *FU* fluorouracil, *CDDP* cisplatin

plus S-1 followed by chemoradiotherapy in locally advanced pancreatic cancer. Further consideration regarding the radiation schedule and duration of induction chemotherapy is required in this regimen. A prospective randomized trial is needed to resolve whether the strategy of induction chemotherapy followed by chemoradiotherapy can improve survival when compared with initial chemoradiotherapy.

Acknowledgments The authors thank our patients and their families for their participation in this study. We appreciate our secretary, Ms Kayo Takei, for her devotion to the study.

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