



A Phase I/II Study of Gemcitabine-Concurrent Proton Radiotherapy for Locally Advanced Pancreatic Cancer without Distant Metastasis

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A Phase I/II Study of Gemcitabine-Concurrent Proton Radiotherapy for Locally Advanced Pancreatic Cancer without Distant Metastasis

遠隔転移を伴わない局所進行膵癌に対する Gemcitabine 同時併用陽子線治療の
第 I/II 相試験

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Keywords: proton radiotherapy, gemcitabine, pancreatic cancer, locally advanced,
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A Phase I/II Study of Gemcitabine-Concurrent Proton Radiotherapy for Locally Advanced Pancreatic Cancer without Distant Metastasis.

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This study has not been presented previously.

Conflicts of interest: none

ABSTRACT

Purpose: We conducted the study to assess the feasibility and efficacy of gemcitabine-concurrent proton radiotherapy (GPT) for locally advanced pancreatic cancer (LAPC).

Materials and Methods: Of all 50 patients who participated in the study, 5 patients with gastrointestinal (GI)-adjacent LAPC were enrolled in P-1 (50 Gy equivalent [GyE] in 25 fractions) and 5 patients with non-GI-adjacent LAPC in P-2 (70.2 GyE in 26 fractions), and 40 patients with LAPC regardless of GI-adjacency in P-3 (67.5 GyE in 25 fractions using the field-within-a-field technique). In every protocol, gemcitabine (800 mg/m²/week for 3 weeks) was administered concurrently. Every patient received adjuvant chemotherapy including gemcitabine after GPT within the tolerable limit.

Results: The median follow-up period was 12.5 months. The scheduled GPT was feasible for all except 6 patients (12%) due to acute hematologic or GI toxicities. Grade 3 or greater late gastric ulcer and hemorrhage were seen in 5 patients (10%) in P-2 and P-3. The one-year freedom from local-progression, progression-free, and overall survival rates were 81.7%, 64.3%, and 76.8%, respectively.

Conclusion: GPT was feasible and showed high efficacy. Although the number of patients and the follow-up periods are insufficient, the clinical results seem very encouraging.

Keywords: proton radiotherapy, gemcitabine, pancreatic cancer, locally advanced, chemoradiotherapy

INTRODUCTION

The prognosis of pancreatic cancer is poor, with a 5-year survival rate of about 5% in total [2]. Only radical surgical resection has been shown to cure the condition, although the 5-year survival rate remains low at about 10-20%. And only 15-20% of all patients with pancreatic cancer can be treated by resection, while the other patients cannot undergo resection because of local invasion or distant metastasis at diagnosis [4,9].

For the treatment of non-resectable pancreatic cancers, chemoradiotherapy (CRT) with concurrent 5-fluorouracil (5-FU) is historically considered the standard therapy for locally advanced pancreatic cancer (LAPC) [6,18,26]. Recently, based on a background of favorable results of gemcitabine-based chemotherapy [1,9], and the fact that gemcitabine is a potent radio-sensitizer [16], many studies on gemcitabine-concurrent CRT have been performed for LAPC [7,17,20,24], and indicate the possibility of an improvement in survival. These studies have shown that reduction of the irradiation doses and target fields was necessary when gemcitabine was administered at or near the full dose (1000 mg/m²). In contrast, a reduction of the gemcitabine dose was needed when irradiation was administered at doses over 50 Gy, which is necessary for the local control of malignant tumors. The reason for these restrictions of the chemoradiotherapy was speculation that the region of gastrointestinal (GI) tract located near the pancreas was irradiated beyond tolerable doses. Consequently, we thought that proton beam radiotherapy could deliver higher dose above 50Gy concurrently with a higher dose of gemcitabine to a larger field containing the draining and paraaortic lymph nodes and peripheral regions surrounding the celiac artery and superior mesenteric artery.

Radiotherapy using protons or carbon-ions is currently attracting worldwide interest because of its physical properties including superior dose distribution to a target, which allows selective irradiation to the tumor, while minimizing irradiation of the surrounding normal tissues [10,15,25]. In our pilot study, proton beam radiotherapy alone was performed at doses of 40 and 50 GyE for patients with LAPC between November 2004 and October 2006 [12]. Although local control and survival did not reach significance in comparison with other treatments, such as chemotherapy alone or CRT, we confirmed the feasibility and safety of proton radiotherapy. Based on this pilot study, we started gemcitabine-concurrent proton radiotherapy (GPT) for LAPC to assess the feasibility and efficacy of this regimen. To our knowledge, this is the first report on the clinical use of concurrent gemcitabine and proton radiotherapy for the

treatment of pancreatic cancer.

PATIENTS AND METHODS

Patient Eligibility

Patients with LAPC which was defined as borderline resectable cancer and unresectable cancer without distant metastases [29], that was cytologically or histologically confirmed to be adenocarcinoma, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, and were in adequate physical condition to tolerate chemotherapy were eligible for this study. Patients with a history of abdominal radiotherapy or previous treatment of the pancreatic tumor were excluded.

All patients provided written informed consent prior to enrollment. The study was approved by the institutional review board and registered on the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR, <http://www.umin.ac.jp/ctr>, UMIN ID: UMIN000002173).

Pretreatment Workup

At baseline, all patients underwent an abdominal contrast-enhanced computed tomography (CT) scan, chest CT scan, positron emission tomography with ^{18}F -fluorodeoxy glucose (FDG-PET), and gastrointestinal fiberoscopy (GIF) and were assessed for tumor markers (CA19-9, CEA, DUPAN-2 and SPAN-1). The disease was staged according to the International Union Against Cancer (UICC) TNM staging system, 6th edition.

Treatment Regimen

Concurrent and Adjuvant Chemotherapy

In all protocols, all patients were scheduled to receive intra-venous infusion of gemcitabine (800 mg/m^2) for 30 minutes for the initial 3 weeks (days 1, 8, and 15) during 5 weeks of proton radiotherapy. We determined the dose of gemcitabine according to the studies by Casper et al. [3] and Burris et al. [1], and the schedule according to the study by Murphy et al [20]. Gemcitabine was administered if the absolute granulocyte count was $>2000/\text{mm}^3$ and the platelet count was $>70000/\text{m}^3$ on the scheduled day.

Following GPT, all patients received systemic gemcitabine-based chemotherapy for as long as possible.

Proton radiotherapy

Hyogo Ion Beam Medical Center (HIBMC) treats patients with both proton and carbon-ion beams. We decided to use proton therapy for this study, because proton beams can be delivered to the target from any direction by using a rotating gantry so that irradiation of the GI tract is minimized. However, a rotating gantry is not available for carbon ion therapy. Furthermore, we anticipated that the administration of gemcitabine would have a sensitizing effect on proton therapy, as previously shown in human pancreatic cancer cells [5].

The patients were treated with 150-210MeV proton beams. A respiratory gating system was used for all patients to irradiate the beam during the exhalation phase. Patient set-up was performed daily by subtraction of the 2 sets of orthogonal digital radiographs before irradiation. The translation and rotation of the patient detected by the positioning system were compensated for by adjustment of the treatment couch. The setup was continued until the bony landmarks on the digitally reconstructed radiographs agreed within 1 mm. The biologic effects of proton therapy at our institution were evaluated in vitro and in vivo. The relative biologic effectiveness (RBE) values were determined to be 1.1 by biologic experiments [11]. Because all tissues are assumed to have almost the same RBE, doses expressed in GyE are directly comparable to photon doses.

Treatment Planning

Proton beam treatment plans were developed using a CT-based 3-dimensional treatment planning system. The gross tumor volume (GTV) was defined as the primary tumor plus the apparent lymph nodes as determined by a fusion contrast-enhanced CT subsidiary using FDG-PET. The clinical target volume (CTV) comprised the addition of a 5-mm margin to the GTV and prophylactic irradiation regions containing the draining lymph nodes and paraaortic lymph nodes as well as peripheral regions surrounding the celiac artery and superior mesenteric artery. We defined the CTV to contain the prophylactic region because metastases to regional lymph nodes have been recognized as prognostic factors in some studies of CRT [8] and resection [23,28] for LAPC. The planning target volume (PTV) was defined as the CTV plus a setup margin (5 mm) and a respiratory gating margin (1-5 mm), which was measured on CT images between inspiratory and expiratory phases. In general, the stomach, small bowel including the duodenum, kidneys, and spinal cord were defined as organs-at-risk (OAR). The dose restrictions for stomach, duodenum, and spinal cord were approximately 50 GyE, 50 GyE, and 45 GyE, respectively [13-14]. Additionally, we planned the

irradiated volumes of the stomach, duodenum, and kidneys to be as small as possible.

Dose-Fractionation

A total of 3 protocols were used in this study. In the early phase of the study, 2 protocols were used contemporaneously; protocol P-1 (50 GyE in 25 fractions) was used for patients with GI-adjacent LAPC, and P-2 (70.2 GyE in 26 fractions) was used for those with non-GI-adjacent LAPC. The non-GI-adjacent LAPC were defined as tumors that could be treated with irradiation plans that covered the GTV: over 95% of the prescribed dose in P-2 (70.2 GyE), which kept the dose administered to the GI-tract under 50 GyE. The others were defined as GI-adjacent LAPC who were treated with P-1. After the early phase, all patients were treated with protocol P-3 (67.5 GyE in 25 fractions) using the field-within-a-field technique.

In P-1, a total dose of 50 GyE was delivered in 25 fractions over 5 weeks to the PTV, based on our pilot study [12] and the report of 5-FU-concurrent CRT [19], in which irradiation doses of 39.6-50.4 Gy did not result in any late GI toxicity. In P-2, 70.2 GyE in 26 fractions over 6 weeks was delivered to the PTV. This approach was designed based on our experiences in treating head and neck cancers and lung cancer as well as other tumors, in which 70.2 GyE in 26 fractions was employed after dose escalation from 65 GyE in 26 fractions [21].

In P-3, 67.5 GyE in 25 fractions over 5 weeks was delivered using the field-within-a-field technique. With this technique, we used 3 types of split doses: 2 + 0.7 GyE, 1.8 + 0.9 GyE, and 1.6 + 1.1 GyE. For example, we delivered 1.8 GyE to the whole PTV (Fig. 1a) and 0.9 GyE to the PTV excluding the GI tract including stomach, small bowel, and large bowel, in one fraction (Fig. 1b). Consequently, a maximum dose of 2.7 GyE was administered as a single fraction (total 67.5 GyE) to the majority of the PTV (Fig. 1c), in parallel with limiting the dose to the GI tract to approximately 1.8 GyE (total 45 GyE). With this technique, it became possible to treat all patients with the P-3 protocol alone, independent of GI-adjacency.

Follow-Up

All patients received abdominal contrast-enhanced CT every 3 months and tumor marker monitoring every month after GPT. GIF was performed at the end of the GPT and every 3 months thereafter to evaluate GI toxicity. Toxicity was assessed using the Common Terminology Criteria for Adverse Events (CTCAE)

Comparison of the Protocols

To clarify the characteristics and effectiveness of the field-within-a-field technique, we analyzed the treatment plans for proton therapy using a dose-volume histogram (DVH) and compared P-3 with P-1 and P-2 in terms of $D_{80\%}$, $D_{50\%}$, and $D_{20\%}$ ($D_{x\%}$ indicates the dose delivered to $x\%$ of the target volume) of the GTV, CTV, and PTV, as well as D_{\max} (a maximum dose to the target) of the stomach and duodenum.

Evaluation of Local Control

As the radiographic changes caused by the GPT were not significant, local control was judged comprehensively by changes in the maximum tumor diameter, the inner density on contrast-enhanced CT, the levels of tumor markers including CA19-9 and CEA, which are particularly useful for pancreatic cancer [30], and the accumulation on FDG-PET. We conclusively defined local progression as radiographic enlargement of the primary tumor or locoregional recurrence or tend to increase in tumor markers for at least three months without any distant metastases.

End Points and Statistical Analysis

The primary end points were feasibility and toxicity, and the secondary end points were freedom from local progression (FFLP), progression-free survival (PFS), and overall survival (OS). These were estimated from the date of the GPT initiation to the date of the event or the last follow-up.

The FFLP, PFS, and OS rates were calculated using the Kaplan-Meier method. Unpaired Student's t-test was used to compare parameters of dose-volume histograms between the protocols. Statistical analyses were carried out with SPSS Version 17.0 software (SPSS, Chicago, Illinois, USA).

Role of Funding Source

The sponsors of the study did not play any role in the study design, data collection, data analysis, data interpretation, or writing of the report.

RESULTS

Patient and Tumor Characteristics

A total of 50 eligible patients with LAPC were enrolled in this study between

February 2009 and August 2010. Five patients were enrolled in P-1, 5 in P-2, and 40 in P-3. The patient characteristics are summarized in Table 1.

The analyses of proton therapy performed using the dose-volume histogram (DVH) are shown in Table 2. When compared between P-1 (for non-GI-adjacent LAPC) and P-3 using Student's t-test, all of the parameters, except $D_{80\%}$ of the PTV, were significantly higher in P-3 than in P-1, even though P-3 included many patients with GI-adjacent LAPC. The comparison between P-2 and P-3 did not detect any significant difference. We could not find a significant difference for D_{\max} of the stomach among P-1, P-2, and P-3. While there was a possibility that bias of tumor location (all 5 patients in P-2 had tumors in the body/tail of the pancreas) and tumor size (apparently smaller in P-2 than P-3) affected to the statistical result, the mean dose of D_{\max} to the duodenum in P-3 was significantly lower than in P-2. These findings support the superiority of the field-within-a-field technique.

Adjuvant Chemotherapy

Among 50 patients, 45 patients (90%) were able to continue adjuvant systemic gemcitabine-based chemotherapy after GPT. Five patients (10%) failed because of unacceptable toxicity of the adjuvant chemotherapy or rapid disease progression.

Feasibility and Toxicity

P-1 and P-2 protocols

All 5 patients completed the scheduled GPT in P-1. Four patients completed treatment in P-2; one patient (20%) could not complete proton therapy at 62.1 GyE in 23 fractions due to gastric bleeding caused by acute radiation mucositis and was cured by medication only. There was no late toxicity in that case. In P-1 and P-2, hematologic toxicities were tolerable. The acute and late toxicities in all protocols are summarized in Table 3.

P-3 protocol

Of the 40 patients in P-3, 5 patients (13%) could not receive the third gemcitabine administration because of acute hematologic and GI toxicities. The most common toxicities were neutropenia, anorexia, and weight loss (Table 3).

The major late toxicities were gastric hemorrhage and ulcer. Late gastric ulcer with hemorrhage of grade 3 or greater was observed in 4 (10%) of 40 patients. All of them had pancreatic cancer arising in the body/tail of pancreatic region. Among these 4 patients, 3 patients (8%) were cured with medication (grade 3), but 1

patient (3%) died of gastric hemorrhage 6 months after GPT (grade 5). This death might have been related to the GPT because gastric ulcer and erosion were confirmed by GIF on the posterior wall of the lower gastric body 2 weeks prior to death. This patient had received the maximum dose of 52 GyE to the stomach.

Local Control, Distant Metastases and Survival

The 1-year FFLP, PFS, and OS rates for all patients were 81.7% (95% CI: 65-99%), 64.3% (95% CI: 48-81%), and 76.8% (95% CI: 64-89%), respectively (Fig. 2 and 3), and 79.9% (95% CI: 58-100%), 60.8% (95% CI: 41-80%), and 78.8% (95% CI: 65-93%), respectively for patients treated with P-3. Of all 50 patients, local progression developed in only 4 patients (8%), while distant metastasis developed in 15 patients (30%), within one year. Frequent sites of distant metastasis were the liver in 9 patients (18%), lung in 1 patient (2%), and the peritoneum in 3 patients (6%). Five patients (10%) were already diagnosed with liver metastases at the end of GPT. None of the patients died of local progression. One patient (2%) who developed both locoregional and distant metastases died of gastric hemorrhage (grade 5). Twelve patients (24%) have survived over 12 months to date without any signs of local or distant tumor progression.

DISCUSSION

Our study indicated the high feasibility and tolerability of proton radiotherapy concurrently with high dose gemcitabine at 800mg/m² on days 1, 8, and 15 during proton beam radiotherapy. The low frequency of grade 3 or greater acute GI toxicities, even at doses as high as 70.2 GyE (P-2) or 67.5 GyE (P-3), suggests superior dose localization of the proton beams to the target. However, late GI toxicities in P-3 (gastric ulcer and hemorrhage of grade 5) cannot be disregarded. We recognized that gastric peristalsis might bring unexpected high dose to the stomach, leading to severe complications in those patients, but it is a limitation of the current treatment planning technique. To prevent these major late toxicities, we have restricted irradiation doses to the GI tract by regulating the target fields and gantry angles and selecting an optimal split dose for the field-within-a-field technique. In contrast to the gastric toxicities, we did not encounter critical ulcer or hemorrhage in the duodenum, although it was irradiated at a dose similar to that of the stomach. The reason that no serious GI toxicity occurred in patients with pancreatic body/tail cancer seems to stem from the tolerability of the duodenum. As this lower frequency of duodenal toxicity is very interesting, we continued

careful observation of the duodenum by duodenal fiberoscopy.

From our clinical experience, it appears that the field-within-a-field technique that we used at P-3 enabled us to reduce the irradiation of OAR while maintaining the necessary doses to the PTV. Our analyses of the DVH indicate that using the field-within-a-field technique can increase the dose to the PTV of patients with GI-adjacent LAPC. Despite an increase in the dose to the PTV, the maximum dose to the stomach and duodenum was not increased. In addition, the optimal split dose of the field-within-a-field technique can be selected according to the tumor adjacency to the GI tract, so that the OAR are irradiated within a tolerable limit. Accordingly, GPT performed using the field-within-a-field technique contributed to solving of the mentioned three problems: reduction of irradiation dose, gemcitabine dose, and irradiation field.

Murphy et al. demonstrated that FFLP was a significant factor of OS on multivariate analysis [20]. To improve FFLP, our GPT was designed to deliver proton beams at a higher dose to a large CTV with concurrent administration of gemcitabine. As a result, the 1-year FFLP and OS rates in our study were greater than expected, with high rates of 81.7% and 76.8%, respectively. This high FFLP rate is considered to be due to a large CTV, which was locally irradiated by proton beams at a high dose; thus, the good OS rate was achieved with low toxicities. However the 1-year PFS rate was 64.3% which is low compared with the high FFLP and OS rates, this PFS rate is apparently better than that of other treatment modalities for patients with LAPC. Namely, the reported PFS rates are approximately 10-20% for CRT [7,17,22] and 10-15% for gemcitabine-based chemotherapy alone [1,9]. It is likely that the substantial local control of the primary tumor exerted by GPT decreased distant metastases and that the use of concurrent and adjuvant gemcitabine has contributed to the prolongation of life of patients with LAPC.

The one-year OS rate obtained in our study is apparently better than that obtained for patients treated with chemo-photon therapy [7,17,20]. Therefore, we consider that proton therapy using the field-within-a-field technique combined with concurrent gemcitabine or another promising chemotherapy has the potential to improve survival, including radical cure, for patients with LAPC.

CONCLUSIONS

GPT for LAPC was feasible and tolerable, and GPT using the field-within-a-field technique resulted in high FFLP and OS rates in our study. Although the number of patients enrolled in this study is too small and the

follow-up periods are too short to draw any definitive conclusions, the clinical results obtained to date seem very encouraging.

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Table 1. Patient Characteristics

	Protocol P-1 (n = 5)	Protocol P-2 (n = 5)	Protocol P-3 (n = 40)
Characteristic			
Follow-up time, months			
Median (Range)	12.3 (8.2-18.6)	19.6 (17.7-21.5)	12.1 (3.2-22.3)
Age, years			
Median (Range)	57 (55-75)	56 (45-72)	64 (49-83)
Gender			
Male	3	2	18
Female	2	3	22
ECOG-PS			
0	2	3	27
1	3	2	10
2	0	0	3
UICC-TNM			
T3N1M0	0	1	4
T4N0M0	1	2	6
T4N1M0	4	2	30
Tumor location			
Head	1	0	18
Body/tail	4	5	22
Tumor size, cm			
Median (Range)	4.6 (3.1-5.6)	3.2 (4.5-7.2)	3.7 (2.5-7)
CEA, ng/mL			
Median (Range)	3.8 (1-12)	1.6 (1-6)	3 (0.9-16.4)
CA19-9, U/mL			
Median (Range)	999 (0-6010)	73.2 (15-731)	185 (0-27600)

Abbreviations: ECOG indicates Eastern Cooperative Oncology Group; PS, performance status; UICC-TNM, the International Union Against Cancer (UICC) TNM staging system.

Table 2. Summary of proton therapy

	P-1	P-2	P-3	t-test	t-test
	50 GyE/25 fr	70.2 GyE/26 fr	67.5 GyE/25 fr	(P-1, P-3)	(P-2, P-3)
	Median (range), GyE	Median (range), GyE	Median (range), GyE	<i>P</i> -value	<i>P</i> -value
GTV D _{80%}	49.9 (49.6-50)	58.2 (43.6-68.1)	53.4 (43.1-66.4)	<0.01	0.12
GTV D _{50%}	50.2 (50-50.4)	64.4 (49.2-70.1)	61.1 (50.2-67.6)	<0.01	0.22
GTV D _{20%}	50.6 (50.4-50.8)	66.6 (52.3-70.4)	66 (57.1-68.1)	<0.01	0.88
CTV D _{80%}	49.9 (49.4-50.4)	56.1 (41.9-65.6)	52.5 (41.7-60)	<0.01	0.19
CTV D _{50%}	50.3 (50-50.5)	64.4 (48.9-69.1)	62.6 (53.2-67.1)	<0.01	0.68
CTV D _{20%}	50.7 (50.5-51)	66.6 (51.6-70.8)	67.4 (65.4-68.2)	<0.01	0.85
PTV D _{80%}	49.7 (49.4-50.1)	51.6 (36.6-60.7)	49.4 (40.8-61)	0.72	0.42
PTV D _{50%}	50.3 (50-50.5)	61.4 (46.2-67.6)	59.5 (46.3-66.5)	<0.01	0.50
PTV D _{20%}	50.8 (50.6-51.2)	66.3 (50.8-70.4)	66.9 (63.1-68)	<0.01	0.89
Stomach					
D _{max}	51 (4-52)	46 (39-56)	48 (38-52)	0.52	0.54
Duodenum					
D _{max}	41 (40-46)	51 (51-52)	48.5 (42-52)	<0.01	<0.01

Abbreviations: GyE indicates gray equivalents; fr, fractions; GTV, gross tumor volume; CTV, clinical target volume; PTV, planning target volume; D_{x%}, dose delivered to x% of the target volume; D_{max}, maximum dose.

Table 3. Acute and late adverse events of grade 3 or greater

Toxicity	P-1 (n = 5)		P-2 (n = 5)				P-3 (n = 40)							
	Acute		Acute		Late		Acute				Late			
	Grade 3		Grade 3		Grade3		Grade 3		Grade 4		Grade 3		Grade 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	N	(%)
Hematologic														
Leukopenia	1	(20)	3	(60)			15	(38)	1					
Neutropenia	1	(20)	2	(40)			9	(23)	2					
Anemia			1	(20)										
Thrombocytopenia			1	(20)			2	(5)						
Gastrointestinal														
Nausea							2	(5)						
Vomiting							1	(3)						
Anorexia	1	(20)	1	(20)			3	(8)			1	(3)		
Epigastralgia	1	(20)					2	(5)						
Gastric ulcer					1	(20)					3	(8)	1	(3)
Miscellaneous														
Weight loss							3	(5)						
Fatigue	1	(20)					1	(3)			1	(3)		

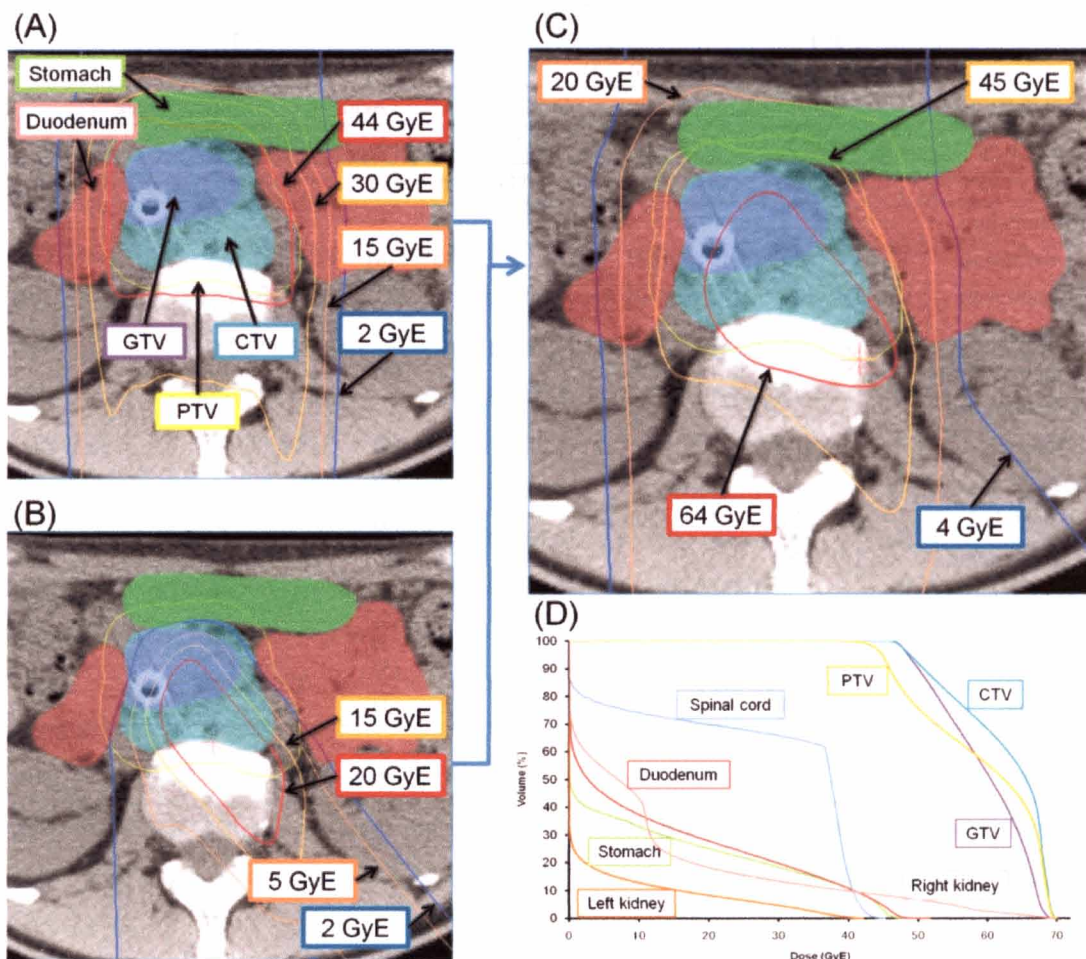


Fig. 1. A representative patient with locally advanced pancreatic cancer that was adjacent to the GI tract, treated with the gemcitabine-concurrent proton therapy (GPT) under protocol-3 (using the field-within a-field technique).

(a) Dose distribution of the proton beam only at 1.8 GyE per fraction. A total dose of 45 GyE, which was the minimal dose administered to the PTV, was administered to the entire PTV.

(b) Dose distribution at 0.9 GyE per fraction. A total dose of 22.5 GyE was irradiated to the PTV except for the GI tract (stomach and duodenum).

(c) Summation of 1.8 GyE and 0.9 GyE in daily fractions. A total dose of 67.5 GyE was administered as the maximum dose, while the stomach and duodenum were only irradiated with approximately 45 GyE.

(d) The dose-volume histogram of this plan for gross tumor volume (GTV), clinical target volume (CTV), planning target volume (PTV), and the organs-at-risk (stomach, duodenum, bilateral kidneys, and spinal cord).

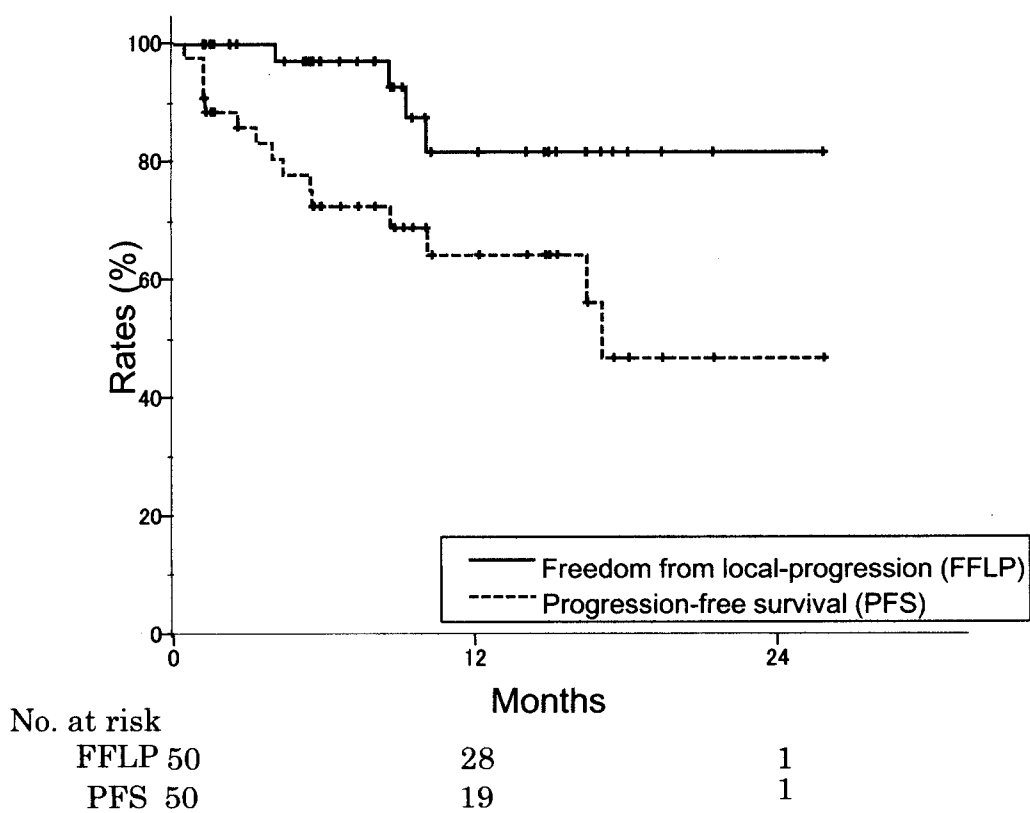


Fig. 2. The freedom from local-progression (solid line) and progression-free (dashed line) survival rates for all patients.

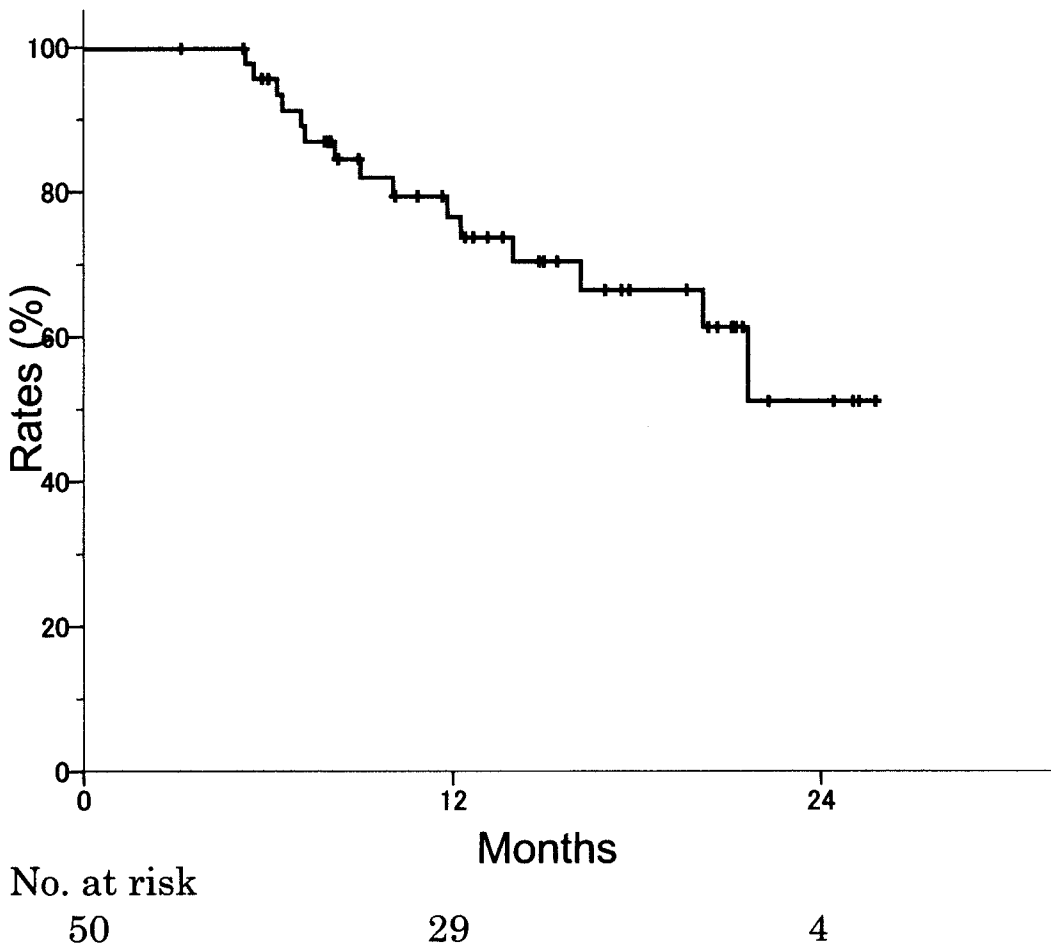


Fig. 3. The overall survival rate for all patients.