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Scientific Article

Clinical Outcomes of Proton Beam Therapy for Unresectable Locally Advanced Pancreatic Cancer: A Single-Center Retrospective Study

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Purpose: We retrospectively researched the treatment outcome of proton beam therapy (PBT) and assessed its efficacy for inoperable locally advanced pancreatic cancer (LAPC) at our institution.

Methods and Materials: Fifty-four patients (28 men and 26 women, median age 67 years ranging from 40-88 years) were diagnosed with unresectable stage III LAPC and administered PBT from April 2009 to March 2020. Patients who could not complete PBT, had new distant metastases during the treatment, or did not have enough follow-up time were excluded from this study. All patients were clinically staged based on the International Union of Cancer TNM staging system (eighth edition) using computed tomography, magnetic resonance imaging, and positron emission tomography and were diagnosed as stage III (histologic type: 18 patients with adenocarcinoma and 36 clinically diagnosed patients). PBT was performed using the passive method, with a median total dose of 67.5 GyE (range, 50-77 GyE/25-35 fractions).

Chemotherapy was used in combination during PBT in 46 patients (85.2%). Overall survival (OS), local progression-free survival (LPFS), progression-free survival, and median OS time were analyzed by Kaplan-Meier and log-rank tests. Univariate and multivariate analyses were performed for the following factors: maximum standardized uptake value (SUVmax), Eastern Cooperative Group performance status (PS), tumor site, total irradiation dose, concurrent chemotherapy, and primary tumor site. Cutoff values for SUVmax and tumor diameter were estimated using receiver operating characteristic curves and the area under the curve based on OS. Multivariate analysis was evaluated using the Cox proportional hazards models. Adverse events were evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Results: The median observation period was 17.4 months, ranging from 4.0 to 89.7 months. The median tumor diameter was 36.5 mm, ranging from 15 to 90 mm, the median SUVmax was 5.85 (range, 2.1-27.6), and their cutoff values were estimated to be 37 mm and

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4.8 mm, respectively. The 1- and 2-year OS was 77.8% and 35.2%, respectively, with a median OS time of 18.2 months, and only one patient survived >5 years. Twelve patients (22.2%) developed local recurrence, and 1- and 2-year LPFS rates were 89.7% and 74.5%, respectively; progression-free survival at 1 year was 58.8%. The PS score, tumor site, and irradiation dose were the prognostic factors related to OS that showed a significant difference. On the other hand, there was a significant difference in factors involved in LPFS, at 96.7%/77.9% in the first year and 86.6%/54.4% in the second year in the groups with tumor dose ≥67.5 GyE and <67.5 GyE, respectively (P = .015). Treatment-related acute toxicities were neutropenia (grade 1/2/3 at 3.7%/11.1%/31.5%, respectively), leukopenia (grade 1/2/3 at 1.8%/7.4%/20.4%, respectively), and thrombocytopenia (grade 1/2 at 1.8%/7.4%, respectively), whereas the late effects including peptic ulcer were captured only grade 2+. The late adverse events of grade 3 or higher were not observed.

Conclusions: PBT achieving 67.5 Gy combined with standard chemotherapy showed excellent local control for unresectable LAPC. Total irradiation dose, tumor site, and PS score at an initial diagnosis could be important prognostic factors. In this study, the dose-effect relationship was found, so an increase in dose should be considered to improve prognosis.

Introduction

It is well known that the prognosis of pancreatic cancer is extremely poor, with an overall 5-year survival rate of only 1% to 5%,[1-3] and pancreatic cancer is one of the most severe refractory malignant tumors, which is the fourth leading cause of cancer deaths in Japan.[4] Complete surgical resection has traditionally been only considered as the curative strategy. However, only 10% to 20% of all patients with pancreatic cancer are indicated for surgical resection, whereas the other 30% to 40% of patients with pancreatic cancer are categorized as unresectable locally advanced pancreatic cancer (LAPC) because of local invasion and the other 50% to 60% patients show already distant metastasis when they are diagnosed.[5] The prognosis of pancreatic cancer with a 5-year survival rate is estimated at only 10% to 20%, even in the resectable patient group.[6]

Because the pancreas is located near the radiosensitive gastrointestinal tract, it is difficult to deliver a sufficient dose to the target site while minimizing the dose to the organs surrounding the pancreas. Therefore, in many clinical reports using conventional radiation therapy, a dosage of about 50 Gy is selected. In contrast to conventional radiation therapy, proton beam therapy (PBT) takes advantage of Bragg peak properties and can deliver a high radiation dose to the tumor while largely sparing normal tissues. Based on these facts, PBT could be expected to make local control more safe than conventional radiation therapy.

In Japan, the Japanese Society for Radiation Oncology (JASTRO) established a unified protocol that led to a proton treatment policy for LAPC in 2016, and it has been covered by insurance since 2022. In recent years, advanced photon-based technologies such as ablative stereotactic magnetic resonance image-guided adaptive radiation therapy (A-SMART) therapy have also received attention for minimizing both acute and late toxicity while increasing doses.

On the other hand, chemotherapy has made progress in recent years.

An Eastern Cooperative Group (ECOG) compared chemoradiation therapy (CRT) and chemotherapy alone with gemcitabine (GEM) for LAPC. They reported that the median overall survival (OS) time in the CRT group was better than that of the chemotherapy-alone group[7] (11.1 months vs 9.2 months; P = .017), and CRT was recommended as one of the primary standard treatments for LAPC. However, it is not enough to dramatically improve treatment outcomes. After GEM was introduced as a key drug, the prognosis for patients with pancreatic cancer improved slightly.[8,9] Since then, various systemic chemotherapy agents have been investigated solely and in combination for the treatment of advanced pancreatic cancer.[10]

The purpose of this study was to retrospectively evaluate clinical outcomes of concurrent CRTs using a proton beam for LAPC in our proton center.

Methods and Materials

Patients

Among patients with pancreatic cancer who underwent PBT at our center between April 2009 and March 2020, 54 sequential patients with LAPC were selected. They were defined as unresectable cancer without distant metastasis, with an ECOG performance status (PS) score of 0 to 2 and adequate physical condition to tolerate chemotherapy. There were no patients who underwent dose escalation via photons for the sake of comparison with protons.

The definition of "unresectable" in this study was based on the general rules of the Japanese Pancreatic Association Guidelines, seventh edition,[11] and the National Comprehensive Cancer Network Guidelines, 2024, version 2.0,[12] as follows: tumors invading >180° into the celiac artery, the common hepatic artery, or the superior mesenteric artery on computed tomography (CT) imaging, or arterial deformation or stenosis because of tumor abutment. Inclusion criteria were as follows: (1) localized pancreatic cancer with no distant metastases

extending beyond the pancreatic surface and invading surrounding blood vessels; (2) patients who completed planned PBT and were followed after treatment; (3) patients without distant metastases at diagnosis or during PBT; and (4) patients with or without pre-PBT chemotherapy. Patients who underwent surgical pancreatectomy after PBT or who had multiple cancers were excluded.

All patients were evaluated, and CT and positron emission tomography (PET)-CT were used to determine the clinical tumor stage of pancreatic cancer based on the International Union of Cancer-Tumor, Node, Metastasis Classification of Malignancies, eighth edition. All primary pancreatic cancers were also evaluated by maximum standard uptake value (SUVmax) on PET-CT.

PBT

A custom-made indexed vacuum lock bag was used for immobilizing patients, and the Xio-MN (Hitachi) treatment planning system was used to calculate the dose distribution of PBT. A respiratory gating system (Anzai Medical) was used during PBT planning and treatment. Anteroposterior and lateral radiographs were taken for positioning every day. Irradiation was usually performed 5 days a week. Proton energy levels were 150 MeV and 210 MeV at 2 to 3 portals, and the Bragg peak spread was adjusted as much as possible until planned target volumes (PTV) was irradiated at 90% isodose of the prescribed dose. Irradiation protocols varied widely, as shown in Table 1. In Japan, dose fractionation by JASTRO has been regulated since 2016, but before that time, various irradiation doses were selected, such as 77.7 GyE/35 fractions (Table 1).

The representative 67.5 GyE/25 fractions protocol was irradiated in field-in-field methods, and the others were treated with conventional fractionated irradiation. The gross target volume was defined as the area containing the pancreatic tumor and metastatic lymph nodes based on the information from dynamic contrast-enhanced CT, magnetic resonance imaging (MRI), and PET. The clinical target volume (CTV)1 was defined as the gross target volume plus a 5 mm margin, but in the case of lesions invading blood vessels, CTV1 included the area near the root of the celiac and superior mesenteric arteries.

CTV2 was a combination of CTV1 added with a prophylactic area containing regional lymph nodes. The 5 to 7 mm margins were provided for CTV1 and CTV2 to create the PTV1 and PTV2. Irradiation ranged from 1.8 to 2.0 GyE/fraction for PTV1 and 0.7 to 0.9 GyE/fraction for PTV2. For simple fractionation, the prescribed dose was administered to PTV1.

The protocol was determined by the dose of irradiation sustained in the gastrointestinal tract, primarily derived from the tumor site. Maximum doses were not to exceed 50 GyE in the stomach, duodenum, and small intestine, 55 GyE in the colon, and 48 GyE in the spinal cord. Dose constraints were $D_{mean} < 30$ Gy for the liver and V18 < 30% for the kidneys. The biologically effective dose (BED; α/β ratio of 10) and 2 Gy fractional equivalent dose were calculated for each dose group.

Concurrent and adjuvant therapy

A total of 26 patients had already received chemotherapy at their initial hospitals before they came to our center. Prechemotherapy was done at the previous physician's discretion, and tegafur gimeracil oteracil potassium (TS-1; 1 case), GEM (7 cases), TS-1 + GEM (7 cases), GEM + nab-paclitaxel (9 cases), and FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin; 2 cases) were administered.

A total of 46 patients had received concurrent chemotherapy with PBT, including GEM, TS-1, nab-paclitaxel, and their combination at the physician's discretion in our hospital. Concomitant chemotherapy was not selected for the remaining 8 patients because of the patient's age, renal dysfunction, history of allergy, and myelosuppression. The conditions for concurrent chemotherapy and pretreatment chemotherapy are shown in Table 1.

Clinical evaluation and follow-up

All patients were followed up every 3 months at our proton center and evaluated based on the results of physical and imaging examinations. When patients were unable to come to the hospital because of poor physical conditions, we contacted them and confirmed their health conditions. Acute adverse events were defined as those that occurred during or within 90 days after completion of PBT. Late adverse events were defined >90 days after completion of PBT. They were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events. Imaging modality was done by CT, MRI, or 18F-fluorodeoxyglucose (FDG)-PET/CT. The response criteria in CT and MRI have used the new Response Evaluation Criteria in Solid Tumors version 1.1.

Statistical analysis

All statistical evaluations were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (the R Foundation for Statistical Computing). More precisely, a modified version of R commander designed to add statistical functions frequently used in biostatistics[13] was used. The Kaplan-Meier method and log-rank test were applied to estimate survival probabilities and compare the survival rates, respectively. Univariate and multivariate analyses with Cox proportional hazards models were performed to determine

Table 1 Patients' characteristics

			Total irradiation dose			
Patients' characteristics.		***Median (range)**		**BED (Gy)***	**EQD2 (Gy)***	**No. of patients**
Age (y)		67* (40-88)				
Sex (male/female))		29/25	77 GyE/35 fr	93.9	78.3	19
ECOG-PS score (0/1/2)		27/17 /10	70.4 GyE/32 fr	85.9	71.6	1
T (3/4)		54	67.5 GyE/25 fr	85.7	71.4	15
N (0/1/2)		37/15/2	66 GyE/30 fr	80.5	67.1	5
Follow-up period (mo)		17.4* (4-89.7)	61.6 GyE/28 fr	75.2	62.6	2
Primary tumor sites (head/body)		28/26	60 GyE/30 fr	72	60	2
Tumor diameter (mm)		36.5* (15-90)	59.4 GyE/27 fr	72.5	60.4	3
CA19-9		185.5* (6-24,245)	56 GyE/28 fr	67.2	56	2
SUVmax of FDG-PET		5.85* (2.1-27.6)	55 GyE/25 fr	67.1	55.9	2
		No. of patients	54 GyE/27 fr	64.8	54	2
	>67.5 GyE	20	50 GyE/25 fr	60	50	1
	(78.3 Gy: 71.6-78.3 Gy)		Median	72.5	61.5	54
Total irradiation dose	60-67.5 GyE	24	* BED and EQD2 are calculated as α/β=10			
(EQD2 median:range)	(71.4 Gy: 60-71.4 Gy)					
	<60 GyE	10				
	(56.0 Gy: 50-60.4 Gy)					
Pre-RT chemotherapy†	With/without	26/28				
TS-1		1				
GEM		7				
TS-1 + GEM		7				
GEM + nab-PTX		9				
FOLFIRINOX		2				
Concurrent chemotherapy	with/without	46/8				

Abbreviations: BED = biologically effective dose; CA19-9 = carbohydrate antigen 19-9; ECOG-PS = Eastern Cooperative Oncology Group performance status; EQD2 = 2 Gy fractional equivalent dose; FDG = 18F-fluorodeoxyglucose; FOLFIRINOX = fluorouracil, leucovorin, irinotecan, and oxaliplatin; fr, fraction; GEM = gemcitabine; nab-PTX = nab-paclitaxel; PET = positron emission tomography; RT = radiation therapy; TS-1 = tegafur gimeracil oteracil; SUVmax = maximum standardized uptake value.
*BED and EQD2 are calculated as α/β = 10.
TS-1, GEM, nab-PTX, FOLFIRINOX.

the factors associated with OS and local progression-free survival (LPFS). All *P* values were 2-sided; variables with a *P* value <.1 in univariate analysis were included in the multivariate analysis, and those with *P* values were considered statistically significant. The cutoff values for SUVmax and tumor diameters were estimated at 4.8 and 37 mm, respectively, using the receiver operating characteristic curve and area under the curve (AUC) based on median survival time (MST). The cutoff values for SUVmax and tumor diameters were used as reference values, and each group was divided into 2 groups for univariate analysis. The effect of multiple factors on survival, the hazard ratio, and its 95% CI were evaluated using the Cox proportional hazards models.

OS and progression-free survival (PFS) were defined as the interval between the start of PBT and the date of the last follow-up examination and death, and the date of locoregional progression, respectively. Local progression was defined as tumor progression inside the PTV and diagnoses comprehensively based on the following findings: enlarged tumor size and increased FDG accumulation. LPFS was defined as the time interval between the initiation of PBT and the detection of local progression or death (all causes), whichever occurred first.

Ethics statement

All treatments were discussed at the hospital cancer conference, and written informed consent was obtained from all patients and investigators who followed the recommendations of the Helsinki Declaration. The Ethics committee of our institution approved treatment methods and procedures.

Results

Patients' characteristics

Patients' characteristics are summarized in Table 1. The median age of patients was 67 years (range, 44-88 years). PS scores (0/1/2 for 27/17/10 patients, respectively) for all patients were evaluated on their first visit to our center. All patients had T4 lesions. Seventeen patients (31.5%) had lymph node metastases. Primary tumor sites were equally distributed in the head (51.9%), body (48.1%), and the pancreas. The median size of the tumor was 36.5 mm (range, 15-90 mm), and the median SUVmax of PET-CT was 5.85 (range, 2.1-27.6). Receiver operating characteristic analysis showed that the cutoff value for SUVmax was 4.8 (sensitivity, 0.786; specificity, 0.577; AUC, 0.6595; 95% CI, 0.5-0.8), and the tumor diameter was 37 mm (sensitivity, 0.643; specificity, 0.654; AUC, 0.5501; 95% CI, 0.39-0.71).

OS, LPFS, distant metastasis control, and PFS

The median follow-up time was 17.4 months (range, 4-89.7 months). All patients died of pancreatic cancer (all died of the original disease). Thirty-four patients (63%) had recurrence after the treatment (local recurrence: 12 patients; distant metastasis: 27 patients; both: 5 patients). No patient was accepted for surgical resection after PBT in this study.

The OS rate at 1 and 2 years was 77.8% and 35.2%, respectively, with an MST of 18.2 months. The 1- and 2-year LPFS rate was 89.7% and 74.5%, respectively, and PFS at 1-year was 58.8% (95% CI, 44.4%-70.6%) (Fig. 1). Of the twelve local recurrence patients, 9 (16.6%) had local recurrence within 1 year. On the other hand, 40 patients had no local recurrence during the follow-up period until death.

Distant metastasis after the treatment occurred in 27 patients (50%), in which 5 patients (9.3%) had both local recurrence and distant metastasis. The liver was the most common site of distant metastasis (12 cases), peritoneum (6 cases), lung (6 cases), and bone (6 cases).

Total irradiation dose

Twenty patients (37%) were treated with >67.5 GyE, 24 patients (44%) with 60 to 67.5 GyE, the majority (15/24 cases) with 67.5 GyE, and 10 patients with <60 GyE as conventional fractionation. The median total dose was 67.5 GyE (range, 50-77 GyE/25-35 fractions), BED10 of 72.5 Gy (range, 60-93.9 Gy), and 2 Gy fractional equivalent dose of 61.5 Gy (range, 50-78.3 Gy).

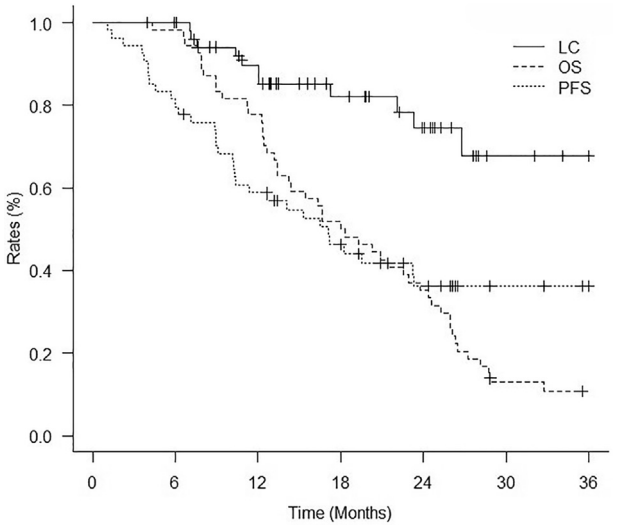

Figure 1 Overall survival (OS), local progression-free survival (LPFS), and progression-free survival (PFS) for all patients. The OS rate at 1 and 2 years was 77.8% and 35.2%, respectively, with an MST of 18.2 months. The LPFS rate at 1 and 2 years was 89.7% and 74.5%, respectively. The PFS rate at 1 year was 58.8% (95% CI, 44.4%-70.6%).

Patients were divided into 2 groups according to total dose (≥67.5 GyE and <67.5 GyE) and analyzed for OS and LPFS. The median OS for the ≥67.5 GyE and <67.5 GyE groups were ≥19.3 months and 13.2 months, respectively, and no significant difference was observed (P = .413). LPFS for the ≥67.5 GyE and <67.5 GyE groups were 96.7% and 77.9%, respectively, in the first year and 86.6% and 54.4%, respectively, in the second year, with a significant difference (P = .015). There was a dose-effect relationship for LPFS but not for OS. Based on the above, the dose-effect relationship is shown for LPFS (Fig. 2).

Prognostic factors

As prognostic factors, patient age, gender, SUVmax, PS score, tumor site, tumor size, pretreatment chemotherapy, hyperthermia, and irradiation dose were analyzed in this study. The results for each prognostic factor are shown in Table 2. Favorable OS results were obtained only for the tumor site (P = .014), total dose, and PS score (P = .001), showing significant differences. Favorable OS results for local control (LC) were obtained for total irradiation dose (P = .009) and PS score (P = .001, Table 3). Other factors did not show any significant differences in univariate analysis (Fig. 3).

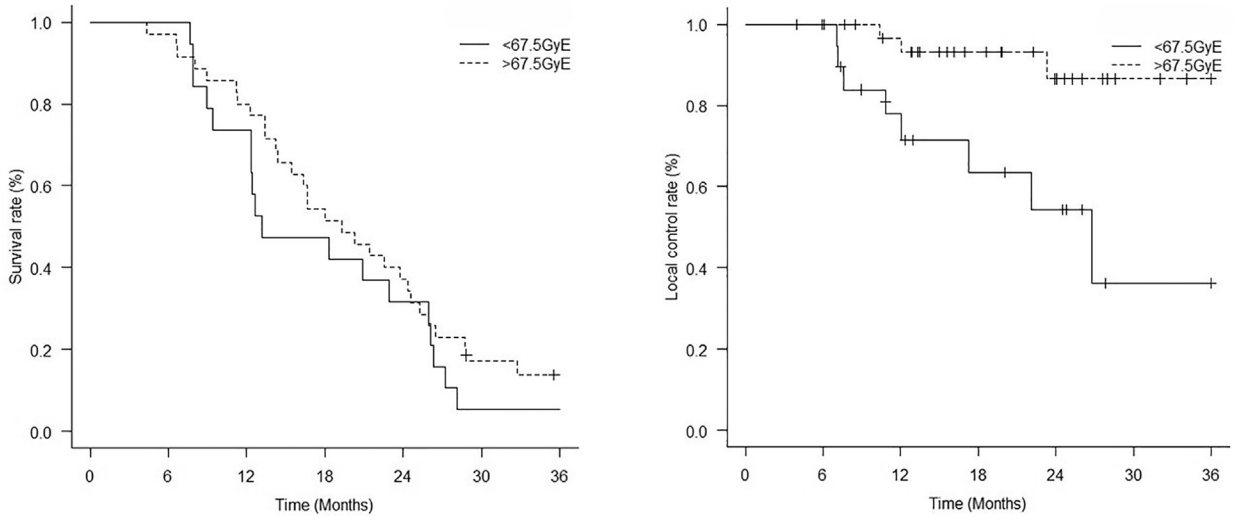

Figure 2 Overall survival rate and local progression-free survival (LPFS) rate for irradiation dose groups. MST at 1 and 2 years was 19.3 and 13.2 months, respectively (P = .413). LPFS for the ≥67.5 GyE group at 1 and 2 years were 96.7% and 86.6%, respectively. LPFS for the <67.5 GyE group at 1 and 2 years were 77.9% and 54.4%, respectively (P = .015). Abbreviation: MST = median survival time.

Treatment-related adverse events

Treatment-related adverse events were evaluated by the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0, and acute adverse events were leukopenia (grade 1/2/3 at 1.8%/7.4%/20.4%, respectively), neutropenia (grade 1/2/3 at 3.7%/11.1%/31.5%, respectively), and thrombocytopenia (grade 1/2 at 1.8%/7.4%, respectively). Late adverse events were gastrointestinal ulcers (grade 1/2 for 2/2 patients, respectively), and no grade 3 or higher late adverse events were observed. Details of the acute and late adverse events are shown in Table 4. Twenty-two patients (40.7%) had grade 1 nonhematologic acute toxicities (nausea 12 and anorexia 10) but no grade 2+. Five patients (9.3%) had grade 1 to 2 gastrointestinal late toxicities (gastric ulcer).

Discussion

Particle beam therapy is more dose-concentrating than x-rays, and the heavier the particle mass, the less it scatters in the body and the sharper the dose distribution. For areas where the dose required for tumor control is higher than

Table 2 Analysis of prognostic factors for local progression-free survival

	Patients (%)	Univariate HR (95% CI)	*P* value	Multivariate HR (95% CI)	*P* value
Age (≥67 y)	27 (50)	0.80 (0.16-4.10)	.789		
Gender (male)	29 (54)	1.51 (0.30-7.65)	.619		
PS score (ECOG-PS)	27 (50)	10.4 (1.2-92.2)	**.001***	8.44 (0.88-80.6)	**.001***
SUVmax (≥4.8)	33 (61)	0.39 (0.05-3.28)	.389		
Tumor site (head)	28 (52)	1.13 (0.18-7.06)	.892		
Tumor diameter (≥37 mm)	27 (50)	0.75 (0.14-4.00)	.739		
Irradiation dose (≥67.5 GyE)	35 (65)	0.14 (0.33-0.63)	**.009***	0.091 (0.01-0.66)	**.017***
Concurrent chemotherapy	46 (85)	0.49 (0.05-4.63)	.892		
Pre-RT chemotherapy (without neoadjuvant)	28 (52)	2.85 (0.63-12.8)	.173	3.221 (0.66-15.7)	.148
Hyperthermia (without hyperthermia)	41 (76)	0.64 (0.10-3.96)	.627		

Abbreviations: ECOG-PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; RT = radiation therapy; SUVmax = maximum standardized uptake value.
*Significant *P* values (<.05)

Table 3 Analysis of prognostic factors for overall survival

			Univariate		Multivariate	
	Patients (%)	MST (mo)	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (≥67 y)	27 (50)	18.3/16.7	1.19 (0.60-2.36)	.409		
Gender (male)	29 (54)	16.7/18.3	1.25 (0.58-2.67)	.702		
PS score (ECOG-PS)	27 (50)	26.1/13.4/7.9	11.2 (4.0-31.0)	**.001***	15.2 (5.04-15.9)	**.001***
SUVmax (≥4.8)	33 (61)	23.7/14.2	1.23 (0.58-2.62)	.351		
Tumor site (head)	28 (52)	13.3/25.0	2.36 (1.16-4.80)	**.014***	2.822 (1.31-6.10)	**.001***
Tumor diameter (≥37 mm)	27 (50)	22.6/13.4	1.53 (0.80-2.91)	.113		
Irradiation dose (≥67.5 GyE)	35 (65)	13.2/19.3	0.51 (0.26-1.02)	.058	0.420 (0.19-0.93)	**.032***
Concurrent chemotherapy	46 (85)	19.3/16.7	2.14 (0.75-6.10)	.154		
Pre-RT chemotherapy (without neoadjuvant)	28 (52)	18.8/15.9	1.03 (0.49-2.10)	.808		
Hyperthermia (without hyperthermia)	41 (76)	22.9/16.7	1.03 (0.48-2.20)	.757		

Abbreviations: ECOG-PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; MST = median survival time; RT = radiation therapy; SUVmax = maximum standardized uptake value.
*Significant *P* values (<.05).

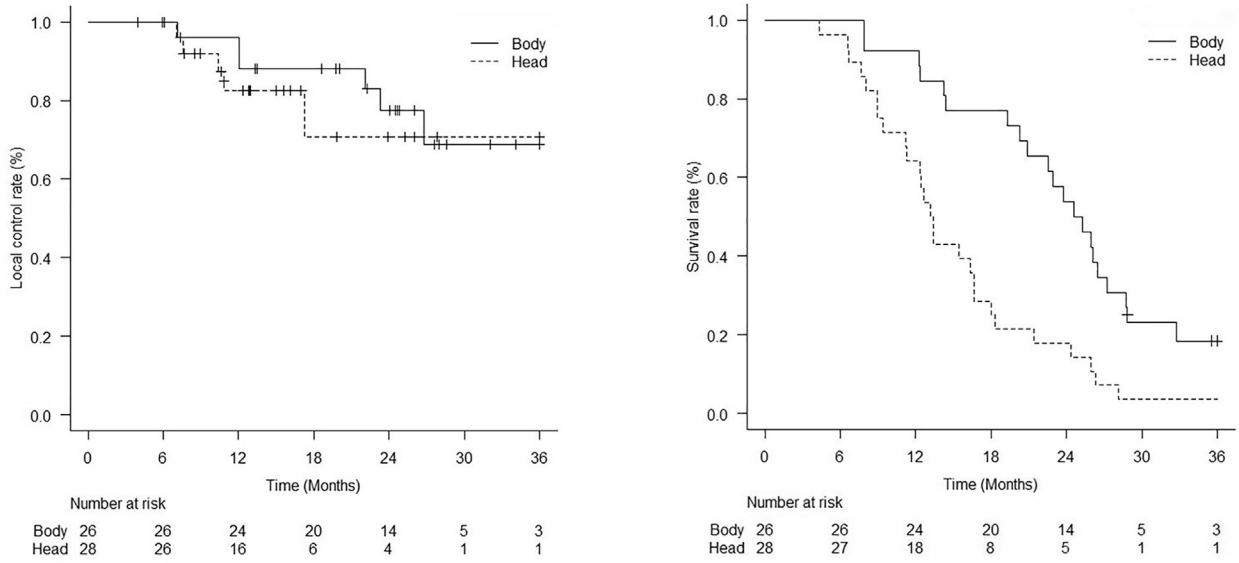

Figure 3 Tumor sites with local progression-free survival (LPFS) rate (a) and overall survival (OS) rate (b). The LPFS rate of the pancreatic head group at 1 and 2 years was 82.5% and 70.8%, respectively. The LPFS rate of the pancreatic body group at 1 and 2 years was 96.2% and 77.4%, respectively. The OS rate of the pancreatic head group at 1 and 2 years was 64.3% and 17.9%, respectively, with an MST of 13.3 months. The OS rate of the pancreatic body group at 1 and 2 years was 92.3% and 53.9%, respectively, with an MST of 25.0 months ($P = .014$).

the tolerable dose of the surrounding normal tissue, even a slightly more dose-intensive quality of radiation is advantageous. If the tumor is in contact with an adjacent critical organ, such as the gastrointestinal tract, the expected therapeutic effect will not be achieved if the dose of the tumor is reduced because of safety considerations.

The significance of particle beam therapy lies in providing an uncompromised treatment by combining safety and efficacy in severe conditions with adjacent critical organs.

Several previous studies of CRT for LAPC reported satisfactory results that the MST for radiation therapy, including 3-dimensional CRT, Stereotactic Body Radio Therapy, and intensity modulated radiation therapy, was 12 to 19 months,[14-17] while the MST for PBT was 18.7 to 25.6 months.[18-24] In addition, grade 3 or higher nonhematologic adverse events occurred in 0% to 47% of patients treated with conventional radiation therapy compared with 0% to 10% of those treated with particle therapy. From these

Table 4 Adverse events

CTCAE (v.5.0)		Acute					Late				
Grade		1	2	3	4	5	1	2	3	4	5
Hematologic	Leukopenia	1	4	11	0	0	0	0	0	0	0
	Neutropenia	2	6	17	0	0	0	0	0	0	0
	Thrombocytopenia	1	4	0	0	0	0	0	0	0	0
Gastrointestinal*	Nausea	12	0	0	0	0	0	0	0	0	0
	Anorexia	10	0	0	0	0	1	1	0	0	0
	Gastric ulcer	0	0	0	0	0	3	2	0	0	0

Abbreviations: CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
*Twenty-two patients (40.7%) had grade 1 acute toxicities but no grade 2+.
Five patients (9.3%) had grade 1 to 2 late toxicities.

studies, particle beam therapy for LAPC is expected to have better local control and fewer adverse events than conventional radiation therapy[18-24] (Table E1).

This study demonstrates that the combination of PBT achieving a dose of 67.5 Gy and standard concurrent chemotherapy provides excellent local control for unresectable LAPC. In general, CRT for LAPC is performed at a dose of around 50 Gy. According to Crane et al,[25] local control was good in the first year, but after 15 months, the rate of local recurrence increased and eventually recurred in most cases. This result showed that pancreatic cancer might not be sufficiently controlled with 50 Gy.

On the other hand, photon beam therapy has made remarkable progress in recent years, and Koay et al[26] pointed out the possibility of dose escalation for LAPC using Stereotactic Body Radio Therapy. Parikh et al[27] used ablative radiation therapy for resectable, borderline pancreatic cancer, and Reyngold et al[28] used ablative radiation therapy for unresectable pancreatic cancer, both reporting good outcomes and few adverse events. Bryant et al[29] performed the first MRI-guided A-SMART for unresectable pancreatic cancer in 5 fractions (hypofractionation) and reported good long-term local control and few adverse events. Their results showed good local control and few adverse events in the long term. Both are photon-based therapies and are expected to evolve from conventional radiation therapy to ablative radiation therapy for pancreatic cancer.

Terashima et al[18] classified 50 cases of LAPC of 50 GyE/25 fractions, 70.2 GyE/26 fractions, and 67.5 GyE/25 fractions according to the proximity of the lesion to the gastrointestinal tract and reported the results combined with chemotherapy with GEM. Among them, the 67.5 GyE/25 fractions protocol used a technique called the "concomitant boost method," in which a dose-escalated volume is superimposed in the area where the dose can be safely increased within the irradiation field. This method reduces the dose in the gastrointestinal tract and maximizes the dose inside the tumor. Based on this technique, in PBT for LAPC, the standard fractionation method (50-56 GyE/25-28 fractions) and simultaneous boost irradiation method (60-67.5 GyE/20-25 fractions) were unified protocols in JASTRO in April 2016. PBT, with the simultaneous boost irradiation method, often combines 1 to 2 subfields with 2 to 4 main fields.

In our center, 44 out of 54 patients (81.5%) were irradiated with this method with a dose of ≥60 GyE. In particular, before the JASTRO unified the protocols in 2016, 77 GyE/25 fractions were selected for 19 of 54 patients (35%) to increase chances for local control. Although there was no significant difference, local control rates were better with the higher doses group. The OS rate was the highest for ≥67.5 GyE but the lowest for the 60 to 67.5 GyE unified protocol (>67.5 GyE/60-67.5 GyE/<60 GyE: 23.1/17.6/14.8 months, respectively). Thus, there is a dose-effect relationship in the local control rate. An increase in dose should be considered to improve prognosis. The survival rate by treatment site in this study was significantly worse for pancreatic head tumors than for pancreatic body tail tumors. The results reported for heavy ion therapy were much better than those of our study. However, the case selection may have affected the outcome (MST 18.2 months vs 21.5-25.2 months) because pancreatic body and tail tumors accounted for a large proportion of the treated cases.

Hiroshima et al[24] reported excellent results of PBT combined with chemotherapy (GEM or TS-1) for LAPC (54.0-67.5 GyE/25-33 fractions). The reported OS at 1 and 2 years were 77.8% and 50.8%, respectively, with an MST of 25.6 months. LPFS at 1 and 2 years were 83.3% and 78.9%, respectively. Compared with their study, our study included slightly more patients without chemotherapy. Although the MST at our center was inferior at 18.2 months, the OS and LC results were similar. Ogura et al[19] treated 123 patients with LAPC with PBT (67.5 GyE/25 fractions) and chemotherapy (GEM) in combination with GEM, showing comparable results for MST (18.7 months), OS, and LC.

Several studies reported the superiority of chemotherapy alone versus CRT for LAPC. Chauffert et al[17]

reported a randomized controlled study between the 5-Fluorouracil/Cisplatin combined radiation therapy group and the chemotherapy-alone group for 119 patients with LAPC. In the report, the chemotherapy-alone group was significantly better than the GEM/CDDP combined radiation therapy group[17] (median OS, 13.0 months vs 8.6 months). In contrast, an ECOG trial reported that GEM combined radiation therapy (MST 11.1 months) had a significantly better outcome compared with GEM monotherapy[7] (MST 9.2 months). Wilson et al[14] analyzed a multicenter randomized controlled trial and showed no significant difference between the 2 treatments. Based on these results, at present, it is not possible to conclude the superiority of either chemotherapy alone or CRT.

The purpose of neoadjuvant therapy is not simply to improve outcomes but also to select outpatients with poor biology and early metastases that will not benefit from focal therapies. Some studies have reported relatively good outcomes with neoadjuvant chemotherapy followed by CRT, but superiority has not yet been achieved.[30-32] The Japan Clinical Oncology Group trial 1106 completed a randomized phase 2 study of CRT with or without induction chemotherapy for LAPC.[33] This study suggested that the CRT using S-1 alone had more promising efficacy with longer survival, compared with GEM induction followed by CRT for LAPC. However, the superiority of neoadjuvant chemotherapy has not been proven in this randomized controlled trial, and it is still in the research stage. In our study, the neoadjuvant chemotherapy group extended the MST by about 3 months compared with the nontreatment group (with vs without: 18.8 vs 15.9 months), but this was not statistically significant.

There are several reports on prognostic factors for pancreatic cancer that the PS score[34-36] and SUVmax[37-39] affect survival. Sperti et al[40] analyzed the SUV of invasive pancreatic ductal carcinoma and reported that a median value of ≥4.0 was significantly associated with poor prognosis.

In our study, only the tumor site and PS score were significantly correlated with survival, and the SUVmax did not show a significant difference. Although much has been reported in the past about SUVmax as a prognostic factor, this unit is not standardized and may be a controversial biomarker because it depends on the PET protocol and scanner. Tumor size at the first visit resulted favorably by MST, but there was also no significant difference. No reports on the relationship between tumor size and its survival prognosis with Concurrent Chemoradiotherapy were found, even after searching previous reports.

The effectiveness of hyperthermia has been covered by insurance in Japan since 1990, based on reports that radiation therapy and chemotherapy can be sensitized if the tumor is heated to 42.5°C or higher. Although there are various reports on hyperthermia therapy for pancreatic cancer, we believe that the effectiveness of hyperthermia therapy is limited because of the risk of increased adverse events because of heating to gastric and duodenal temperatures using the radiofrequency heating method with 2 pairs of electrodes placed front and back, and the lack of proof that the tumor is evenly heated to 42.5°C or higher so that the therapeutic effect of hyperthermia is limited.[41]

A systematic review summarizing the adverse events of PBT for pancreatic cancer has been reported, pointing out that survival outcomes are comparable with those of conventional radiation therapy but that nonhematologic adverse events of grade 3 or higher are very low.[42]

In our study, no acute gastrointestinal adverse events occurred. Although mild gastric ulcers (grade 1: 3; grade 2: 2) were observed as late gastrointestinal adverse events, they did not affect the survival time. CT scans were taken every week during PBT to ensure the correct position of irradiation. This insurance may be one of the reasons why few radiation adverse events occurred in this study. In addition, our center had cases in which esophagogastroduodenoscopy was not performed regularly during the treatment period, and the possibility of asymptomatic gastrointestinal adverse events cannot be ruled out. What should be emphasized more is that our outcomes can be achieved with little to no acute or late toxicities, even in comparison with the most advanced photon-based technology, A-SMART. In recent years, there have been reports that recurrence from gastrointestinal area does not necessarily increase, even if it is an involved field.[43-45] When concurrent CRT is scheduled, irradiation focused on the lesion has become mainstream in consideration of reducing the risk of adverse events in the gastrointestinal tract. In our study, because the prophylactic region was included in CTV, it could be possible to reduce gastrointestinal adverse events further with more localized irradiation.

In abdominal solid tumors, the tolerable dose of the adjacent gastrointestinal tract is low, limiting the dose and range of irradiation. For such cases, positive results have been reported using a 2-stage treatment in which a spacer is surgically implanted in advance to ensure a safety margin of ≥1 cm between the tumor and the intestinal tract, followed by irradiation with a radical dose of particle beams.[46,47]

This strategy can be safely implemented in pancreatic cancer as well, and Matsumoto et al[48] reported a 100% local control rate with a radical dose (64-80 GyE/8-26 fractions) of PBT after spacer implantation. Although this treatment is not indicated for pancreatic head cancer close to the duodenum, it is the most indication for pancreatic cancer confined to the pancreatic body tail without invasion into the colon, stomach, or duodenum and marked retroperitoneal invasion, including the celiac artery and root of the superior mesenteric artery. If pancreatic body and tail cancers can be safely irradiated with high doses after spacer implantation, further improvement in prognosis can be expected.

Furthermore, remarkable advances in chemotherapy have improved the outcome of pancreatic cancer. There are unresectable cases that respond well to chemotherapy,

and long-term survival cases have also been reported.[49,50] The new scanning techniques, such as spot-scanning,[51] can irradiate more concisely. The scanned beam allows the manipulation of beams from various angles and with the required energies. In combination with advanced computer science technology, intensity modulated proton therapy can be achieved, and these strategies are expected to spread to many facilities. Future chemotherapy could control small distant metastases, thereby increasing the importance of local control and further emphasizing the role of radiation therapy. Thus, the combination of new systemic chemotherapy, new radiation techniques, and high-dose irradiation with preirradiation spacer implantation may lead to better outcomes and fewer adverse events.

Conclusions

We reported an excellent local control in 54 patients with LAPC treated with PBT, achieving 67.5 Gy and chemotherapy. Total irradiation dose, tumor site, and PS score at initial diagnosis could be important prognostic factors. In this study, a dose-effect relationship was observed, especially in LPFS, suggesting the need for dose escalation to improve prognosis.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistic. *CA Cancer J Clin*. 2012;2015:87-108.
2. Carpelan-Holmström M, Nordling S, Pukkala E, et al. Does anyone survive pancreatic ductal adenocarcinoma? A nationwide study re-evaluating the data of the Finnish Cancer Registry. *Gut*. 2005;54:385-387.
3. Egawa S, Toma H, Ohigashi H, et al. Japan pancreatic cancer registry; 30th year anniversary: Japan Pancreas Society. *Pancreas*. 2012;41:985-992.
4. Matsuda T, Marugame T, Kamo K, et al. Cancer incidence and incidence rates in Japan in 2005: Based on data from 12 population−based center registries in the Monitoring of Cancer incidence in Japan (MCIJ) project. *Jpn J Clin Oncol*. 2011;41:139-147.
5. Gillen S, Schuster T, Meyer Zum Büschenfelde C, 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.
6. Geer RJ, Brennan MF. Prognostic indicators for survival after resection of pancreatic adenocarcinoma. *Am J Surg*. 1993;165:68-72. discussion 72-73.
7. Loehrer Sr PJ, Feng Y, Cardenes H, et al. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: An Eastern Cooperative Oncology Group trial. *J Clin Oncol*. 2011;29:4105-4112.
8. Burris 3rd HA, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer. A randomized trial. *J Clin Oncol*. 1997;15:2403-2413.
9. Ishii H, Furuse J, Boku N, et al. Phase II study of gemcitabine chemotherapy alone for locally advanced pancreatic carcinoma: JCOG506. *Jpn J Clin Oncol*. 2010;40:573-579.
10. Park HS, Lee HS, Park JS, et al. Prognostic Scoring Index for patients with metastatic pancreatic adenocarcinoma. *Cancer Res Treat*. 2016;48:1253-1263.
11. Japan Pancreas Society. *General Rules for the Study of Classification of Pancreatic Cancer*. 8th Edition 2023.
12. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Pancreatic Adenocarcinoma, ver 2*. 2024.
13. Kanda Y. Investigation of the freely available easy-to-use software "EZR" for medical statistics. *Bone Marrow Transplant*. 2013;48:452-458.
14. Wilson JM, Fokas E, Dutton SJ, et al. ARCII A phase II trial of the HIV protease inhibitor Nelfinavir in combination with chemoradiation for locally advanced inoperable pancreatic cancer. *Radiother Oncol*. 2016;119:306-311.
15. Sudo K, Yamaguchi T, Ishihara T, et al. Phase II study of oral S-1 and concurrent radiotherapy in patients with unresectable locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys*. 2011;80:119-125.
16. Zhong J, Switchenko J, Behera M, et al. Chemotherapy with or without definitive radiation therapy in inoperable pancreatic cancer. *Ann Surg Oncol*. 2018;25:1026-1033.
17. Chauffert B, Mornex F, Bonnetain F, et al. Phase III trial comparing induction chemotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000-01 FFCD/SFRO study. *Ann Oncol*. 2008;19:1592-1599.
18. Terashima K, Demizu Y, Hashimoto N, et al. A phase I/II study of gemcitabine-concurrent proton radiotherapy for locally advanced pancreatic cancer without distant metastasis. *Radiother Oncol*. 2012;103:25-31.
19. Ogura Y, Terashima K, Nanno Y, et al. Factors associated with long-term survival in gemcitabine-concurrent proton radiotherapy for non-metastatic locally advanced pancreatic cancer: A single-center retrospective study. *Radiat Oncol*. 2022;17:32.

20. Shinoto M, Yamada S, Terashima K, et al. Carbon ion radiation therapy with concurrent gemcitabine for patients with locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys*. 2016;95:498-504.
21. Maemura K, Mataki Y, Kurahara H, et al. Comparison of proton beam radiotherapy and hyper-fractionated accelerated chemoradiotherapy for locally advanced pancreatic cancer. *Pancreatology*. 2017;17:833-838.
22. Kawashiro S, Mori S, Yamada S, et al. Dose escalation study with respiratory-gated carbon-ion scanning radiotherapy using a simultaneous integrated boost for pancreatic cancer: Simulation with four-dimensional computed tomography. *Br J Radiol*. 2017;90: 20160790.
23. Shinoto M, Terashima K, Suefuji H, et al. A single institutional experience of combined carbon-ion radiotherapy and chemotherapy for unresectable locally advanced pancreatic cancer. *Radiother Oncol*. 2018;129:333-339.
24. Hiroshima Y, Fukumitsu N, Saito T, et al. Concurrent chemoradiotherapy using proton beams for unresectable locally advanced pancreatic cancer. *Radiother Oncol*. 2019;136:37-43.
25. Crane CH, Varadhachary GR, Yordy JS, et al. Phase II trial of cetuximab, gemcitabine, and oxaliplatin followed by chemoradiation with cetuximab for locally advanced (T4) pancreatic adenocarcinoma: Correlation of Smad4(Dpc4) immunostaining with pattern of disease progression. *J Clin Oncol*. 2011;29:3037-3043.
26. Koay EJ, Hanania AN, Hall WA, et al. Dose-escalated radiation therapy for pancreatic cancer: A simultaneous integrated boost approach. *Pract Radiat Oncol*. 2020;10:e495-e507.
27. Parikh PJ, Lee P, Low DA, et al. A multi-institutional phase 2 trial of ablative 5-fraction stereotactic magnetic resonance-guided on-table adaptive radiation therapy for borderline resectable and locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys*. 2023;117: 799-808.
28. Reyngold M, O'Reilly EM, Varghese AM, et al. Association of ablative radiation therapy with survival among patients with inoperable pancreatic cancer. *JAMA Oncol*. 2021;7:735-738.
29. Bryant JM, Palm RF, Herrera R, et al. Multi-institutional outcomes of patients aged 75 years and older with pancreatic ductal adenocarcinoma treated with 5-fraction ablative stereotactic magnetic resonance image-guided adaptive radiation therapy (A-SMART). *Cancer Control*. 2023;30: 10732748221150228.
30. Kurt E, Kurt M, Kanat O, et al. Phase II study of induction chemotherapy with gemcitabine plus 5-fluorouracil followed by gemcitabine-based concurrent chemoradiotherapy for unresectable locally advanced pancreatic cancer. *Tumori*. 2006;92:481-486.
31. Brade A, Brierley J, Oza A, et al. Concurrent gemcitabine and radiotherapy with and without neoadjuvant gemcitabine for locally advanced unresectable or resected pancreatic cancer: A phase I-II study. *Int J Radiat Oncol Biol Phys*. 2007;67:1027-1036.
32. Huguet F, André T, Hammel P, et al. Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. *J Clin Oncol*. 2007;25:326-331.
33. Ioka T, Fukutomi A, Mizusawa J, et al. Randomized phase II study of S-1 and concurrent radiotherapy with versus without induction chemotherapy of gemcitabine for locally advanced pancreatic cancer (LAPC): Final analysis of JCOG1106. *Ann Oncol*. 2016;27(suppl 6):621 PD.
34. Tabernero J, Chiorean EG, Infante JR, et al. Prognostic factors of survival in a randomized phase III trial (MPACT) of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone in patients with metastatic pancreatic cancer. *Oncologist*. 2015;20:143-150.
35. Erdogan B, Turkmen E, Uzunoglu S, Tanriverdi O, Cicin I. Performance status is an important prognostic factor in second line treatment of pancreaticobiliary adenocarcinoma. *Hepato Gastroenterology*. 2013;60:1479-1483.
36. Tas F, Sen F, Odabas H, Kılıc L, Keskın S, Yıldız I. Performance status of patients is the major prognostic factor at all stages of pancreatic cancer. *Int J Clin Oncol*. 2013;18:839-846.
37. Nakata B, Nishimura S, Ishikawa T, et al. Prognostic predictive value of 18F-fluorodeoxygucose positron emission tomography for patients with pancreatic cancer. *Int J Oncol*. 2001;19:53-58.
38. Maemura K, Takao S, Shinchi H, et al. Role of positron emission tomography in decisions on treatment strategies for pancreatic cancer. *J Hepato-Bil Pancreat Surg*. 2006;13:435-441.
39. Bang S, Chung HW, Park SW, et al. The clinical usefulness of 18-fluorodeoxyglucose positron emission tomography in the differential diagnosis, staging, and response evaluation after concurrent chemoradiotherapy for pancreatic cancer. *J Clin Gastroenterol*. 2006;40:923-929.
40. Sperti C, Pasquali C, Chierichetti F, Ferronato A, Decet G, Pedrazzoli S. 18-Fluorodeoxyglucose positron emission tomography in predicting survival of patients with pancreatic carcinoma. *J Gastrointest Surg*. 2003;7:953-960.
41. Shimomura O, Endo M, Makishima H, et al. Triple modal treatment comprising with proton beam radiation, hyperthermia, and gemcitabine/nab-paclitaxel for locally advanced pancreatic cancer: A phase I/II study protocol (TT-LAP trial). *BMC Cancer*. 2023;23:624.
42. Verma V, Lin SH, Simone 2nd CB, Mehta MP. Clinical outcomes and toxicities of proton radiotherapy for gastrointestinal neoplasms: A systematic review. *J Gastrointest Oncol*. 2016;7:644-664.
43. Murphy JD, Adusumilli S, Griffith KA, et al. Full-dose gemcitabine and concurrent radiotherapy for unresectable pancreatic cancer. *Int J Radiat Oncol Biol Phys*. 2007;68:801-808.
44. Kawakami H, Uno T, Isobe K, et al. Toxicities and effects of involved-field irradiation with concurrent cisplatin for unresectable carcinoma of the pancreas. *Int J Radiat Oncol Biol Phys*. 2005;62: 1357-1362.
45. Yamazaki H, Nishiyama K, Koizumi M, et al. Concurrent chemoradiotherapy for advanced pancreatic cancer: 1000 mg/m^2 gemcitabine can be administered using limited field radiotherapy. *Strahlenther Onkol*. 2007;183:301-306.
46. Fukumoto T, Komatsu S, Hori Y, Murakami M, Hishikawa Y, Ku Y. Particle beam radiotherapy with a surgical spacer placement for advanced abdominal leiomyosarcoma results in a significant clinical benefit. *J Surg Oncol*. 2010;101:97-99.
47. Komatsu S, Hori Y, Fukumoto T, Murakami M, Hishikawa Y, Ku Y. Surgical spacer placement and proton radiotherapy for unresectable hepatocellular carcinoma. *World J Gastroenterol*. 2010;16:1800-1803.
48. Matsumoto I. Novel therapeutic strategy with particle radiotherapy for pancreatic cancer. *J Biliary Tract Pancreas*. 2011;32:869-874. [in Japanese].
49. Asano T, Hirano S, Nakamura T, et al. Survival benefit of conversion surgery for patients with initially unresectable pancreatic cancer who responded favorably to nonsurgical treatment. *J Hepatobilliary Pancreat Sci*. 2018;25:342-350.
50. Furuse J, Shibahara J, Sugiyama M. Development of chemotherapy and significance of conversion surgery after chemotherapy in unresectable pancreatic cancer. *J Hepatobiliary Pancreat Sci*. 2018;25: 261-268.
51. Smith A, Gillin M, Bues M, et al. The M. D. Anderson proton therapy system. *Med Phys*. 2009;36:4068-4083.