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Original Article

Concurrent chemoradiotherapy using proton beams for unresectable locally advanced pancreatic cancer

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ABSTRACT

Background and purpose: We investigated clinical outcomes of proton beam concurrent chemoradiotherapy (CCRT) for unresectable, locally advanced pancreatic cancer (LAPC) patients.

Materials and methods: Records from 42 unresectable LAPC patients (21 male and 21 female, 39–83 years old) with IIB/III clinical staging of 1/41 treated by proton beam CCRT were retrospectively reviewed. Twelve patients received a conventional 50 Gray equivalents (GyE) in 25 fractions protocol and 30 others received a higher dose protocol of 54.0–67.5 GyE in 25–33 fractions. Gemcitabine or S-1 (Tegafur, Gimeracil and Oteracil) was used concurrently. Toxicity, overall survival (OS) and local control (LC) were examined.

Results: Acute adverse events of grades 1, 2, 3 and 4 were found in 4, 15, 17 and 2 patients, respectively. All grade 3 and 4 events were hematologic. Late adverse events of grades 1 and 2 were found in 3 and 2 patients, respectively. No late adverse effects of grade 3 or higher were observed. The 1-year/2-year OS rates from the start of CCRT were 77.8/50.8% with median survival time (MST) of 25.6 months. The 1-year/2-year LC rate from CCRT start was 83.3/78.9% with a median time to local recurrence of more than 36 months. Total irradiation dose was the only significant factor in univariate analyses of OS and LC ($p = 0.015$ and 0.023, respectively).

Conclusion: Proton beam CCRT lengthened survival periods compared to previous photon CCRT data and higher dose irradiation prolonged LC and OS for unresectable LAPC patients. Proton beam therapy is therefore safe and effective in these cases.

Pancreatic cancer carries a very poor prognosis and the number of deaths per year it causes has steadily risen to approximately 35,000 in 2013, making it the fourth leading cause of cancer deaths in Japan [1]. Surgical resection is currently the only curative treatment but less than 20% of cases are resectable at presentation and up to 25–30% of newly diagnosed patients with non-distant metastatic lesions are divided into borderline resectable and unresectable locally advanced pancreatic cancer (LAPC) patients based upon the extent of vascular involvement [2].

In recent years, intensive chemotherapies such as FOLFIRINOX and a combination of gemcitabine (Gem) and nab-Paclitaxel have improved clinical outcomes of unresectable LAPC patients [3,4]; however, many patients have difficulty in continuous treatment due to serious incidences of adverse events [5,6]. Concurrent chemoradiotherapy (CCRT) is another treatment option for unresectable LAPC patients. In the CCRT of unresectable LAPC, Gem is one of the most often used and recommended anticancer drugs in Japan [7]. With a broad spectrum of antitumor activity against a variety of solid tumors, it also acts as a potent radio-sensitizer in pancreatic cancers [8]. Clinical trials of concurrent Gem and radiotherapy have shown a greater effect than 5-fluorouracil (5-FU) CCRT for LAPC patients [9–11]. Outside of Gem, the combination of Tegafur/Gimeracil/Oteracil (S-1) has been proven comparable to Gem in the CCRT of LAPC patients [12,13].

The ultimate goal of radiotherapy within the context of CCRT for the unresectable LAPC patients is local control of the tumor and conventional photon RT delivered from 3 or 4 directions is most often chosen for this purpose. Pancreatic tumors are difficult to approach due to their close proximity to the gastrointestinal tract (GI tract), whose radiation sensitivity precludes sufficient delivery of on-target energy [14]. Therefore, a total irradiation dose of 50 gray (Gy) (daily 1.8–2 Gy) is recommended for the treatment of LAPC patients in Japan. Unfortunately, the 50 Gy dose of radiotherapy is only palliative against aggressive pancreatic cancers. Proton beams, on the other hand, can provide less penetration, prevent

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errant energy delivery to non-tumor targets, and deliver higher doses to the tumor than photon RT.

The purpose of this study is to therefore investigate the clinical outcomes of CCRT using proton beams for unresectable LAPC patients.

Methods and materials

Patients

A total of 42 unresectable LAPC patients treated with CCRT using proton beams at our institute between July 2009 and March 2016 were retrospectively reviewed. This study included 21 men and 21 women, whose age ranged from 39 to 83 (median: 66) years. Computed tomography (CT) or magnetic resonance imaging (MRI) with contrast agents was performed for staging prior to PBT in all patients. Re-evaluation in our institute was performed for 32 patients who had already received chemotherapy at their initial hospital. Clinical staging of IIB/III was 1/41 according to the Union for International Cancer Control (UICC) TNM staging system (7th edition). Regional lymph nodes were defined in accordance with the UICC system as superior and inferior to the head and body of the pancreas, anterior pancreaticoduodenal, posterior pancreaticoduodenal, common bile duct, and proximal mesenteric lymph nodes. Pyloric and celiac lymph nodes were included for head of pancreatic tumors, and the hilum of the spleen and the tail of the pancreatic lymph nodes were included for body and tail of it. "Unresectable" was defined as tumors involving more than 180 degree of celiac artery (CA) or superior mesenteric artery (SMA) on CT scan. A total of 32 patients had already received chemotherapy at their initial hospital before they came to our institute (Table 1). Pre-treatment chemotherapy outside of our center in 32 patients was done at their previous physician's discretion and included GEM, S-1, FOLFOX, nab-PTX and combinations.

All procedures involving human participants, including case reviews of treatments, were conducted in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments (or comparable ethical standards) and approved by the University of Tsukuba Institutional Research Committee (Approval # H29-080). All treatments were discussed at an in-hospital conference and informed consent was obtained from all participants included in the study. We got informed consent from either living patients or the legally designated next-of-kin for those who died, as appropriate.

Proton beam therapy

Before making a treatment plan, CT images without intravenous contrast agent were taken at 2.5 mm intervals during the expiratory phase under a respiratory gating system [15]. We defined the gross tumor volume as primary tumor and metastatic regional lymph nodes. The clinical target volume (CTV) was judged to be an approximately 5 mm margin around the gross tumor volume and the roots of celiac or superior mesenteric arteries (CA, SMA) were involved in cases of lesions which had invaded around the vessels. Regional but non-metastatic regional lymph nodes were not included in the CTV. The stomach, duodenum and intestine were counted as GI tract for our purposes. Beam-dependent margins were directly added to the CTV, such as a 1 cm margin around the CTV, and a 5-mm margin was added to the caudal direction to compensate for unexpected respiration-induced movements. Total irradiation doses were 50 Gray equivalents (GyE) with 25 fractions in 12 cases, 54 GyE in 27 fractions in 2 cases, 56 GyE in 28 fractions in 4 cases, 59.4 GyE in 33 fractions in 1 case, 60 GyE in 30 fractions in 6 cases, and 67.5 GyE in 25 fractions (concomitant boost technique) in 17 cases. The protocol was decided by irradiation dosage sustained by the GI tract, which is mainly derived from tumor location. In the concomitant boost technique, 50 GyE was delivered to cover the entire CTV by anterior and posterior beams and another posterior beam of 17.5 GyE was added as in Terashima's method [16] (Supplementary Fig. 1). The essence of this method is that the boost beam be processed so as not to reach the GI tract. This method was slightly modified so that the irradiation dose of the GI tract in the boost beam was less than 10% of the isocenter dose. We set the dose constraints for the GI tract at 50 GyE and in only 1 patient was the duodenal dose beyond 50 GyE due to the tumor's location. However, we accepted this plan since the volume and dose was small ($D_{0.1cc}$: 51.8 GyE). The relative biological effectiveness value was determined to be 1.1 [17]. During treatment, all patients were treated with 155–230 MeV proton beams, using a passive spreading method, and beams were delivered at the expiratory phase for a maximum of 0.3 seconds under free-breathing conditions [18]. Spinal bones and 2 sets of orthogonal digital radiographs were used for daily confirmation of the position. We routinely use proton-pump inhibitors to preserve the GI tract during the treatment course and treatment was performed after at least 3 hours of fasting (6 hours if the pancreas was especially close to the GI tract).

Table 1
Patients' characteristics.

Number of patients		42
Age		39–83 (66)
Sex (M/F)		21/21
T (3/4)		1/41
N (0/1)		27/15
Stage (IIB/III)		1/41
Total irradiation dose (50 GyE/>50 GyE)		12/30
Pre-treatment (chemotherapy)		32
Concurrent	Chemotherapy (GEM/S-1)	38/4
	Chemotherapy + hyperthermia	23
Post treatment (chemotherapy/surgery)		34/2

The number inside the brackets means median value.
Abbreviations: GEM: Gemcitabine, S-1: Tegafur/Gimeracil/Oteracil, GyE: gray equivalent.

Concurrent and adjuvant therapy

All patients received concurrent chemotherapy (Gem: 38, S-1: 4). Briefly, Gem dosage was 250 mg/m^2 (maximum 6 times) for outpatients and 800 mg/m^2 (maximum 3 times) for inpatients until 2013 after which it was prescribed under a unified 800 mg/m^2 protocol for all patients. In this study, 15 patients were treated with 250 mg/m^2 and 23 with 800 mg/m^2 protocols. Gem was administered during the treatment course and was skipped when the absolute granulocyte count was less than 2000/mm^3, the platelet count was less than 70000/mm^3 on a scheduled dosage day, or if any condition diagnosed by physicians contraindicated administration. The oral dosage of S-1 was prescribed twice daily, 5 times a week according to body-surface area (<1.25 m^2, 80 mg/day; >1.25 to <1.5 m^2, 100 mg/day; >1.5 m^2, 120 mg/day) and was also skipped whenever contraindicated by performance status, blood and/or biochemical data.

A total of 23 patients received hyperthermia during the treatment course depending on machine availability. Hyperthermia was administered at 60 min/session once a week immediately after proton beam therapy (PBT), 5 to 6 times in total, employing an 8-MHz RF-capacitive heating device (Thermotron-RF8; Yamamoto Vinita Co., Ltd., Osaka, Japan).

A total of 36 patients received adjuvant therapy after PBT (chemotherapy 34, surgery 2). Adjuvant therapy was contraindicated in the remaining 6 patients due to their physical condition.

Evaluation and statistical analysis

All patients were scheduled to come to our institute every 3 months and imaging examinations were conducted prior to their visit if their physical condition was well. Acute and late toxicities were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 4.0) [19]. Relapse was evaluated according to the Response Evaluation Criteria in Solid Tumors (version 1.1) [20]. Univariate analyses for prognoses were examined using Cox's regression. For the analysis of characteristics such as age, tumor diameters and CA19-9, we made two well-balanced groups from patients. In the analysis of total irradiation doses, they were classified into conventional (50 GyE) and higher (>50 GyE) groups because a well-balanced and delimited value was not found. We examined overall survival (OS) and local control (LC) rates using the Kaplan–Meier method and comparisons were done by log rank test. Correlation between LC and OS were examined using Pearson's correlation coefficient. All analyses were performed using SPSS version 24.0 (IBM Inc. Armonk, NY, USA). A p value <0.05 was defined as significant.

Results

As of July 2018, a total of 21 patients were alive, and 21 remaining patients had died of pancreatic cancer. The follow-up period range was 2.4–47.6 (median: 14.0) months in all patients and 3.4–47.6 (median: 14) months in the living patients. A total of 25 patients showed recurrence after treatment (local recurrence: 6, distant metastases: 17, and both: 2).

Acute adverse events of grades 1, 2, 3 and 4 were found in 4, 15, 17 and 2 patients, respectively. All grade 3 and 4 events were hematologic. Late adverse events of grades 1 and 2 were found in 3 and 2 patients, respectively (gastric ulcer at 5.3 months and anorexia in at 12.5 months after PBT). Acute adverse events more than grade 5 and late adverse events more than grade 3 were not observed. Details of the acute and late toxicities are shown in Table 2.

The OS rate at 1-year/2-year from the start of CCRT was 77.8/50.8% with median survival time (MST) of 25.6 months and OS from the initial treatment was 84.5/58.7% with an MST of 27.5 months. The 1-year/2-year LC rate from the start of CCRT was 83.3/78.9% with a median time to local recurrence of more than 36 months and LC from the initial treatment was 90.1/76.7% with a median time to local recurrence of more than 36 months (Table 2, Fig. 1). Local recurrence was observed in 8 patients, with six suffering from local recurrence within 1 year and 5 dying within 18 months. On the other hand, 22 out of 24 patients who did not have local recurrence within 1 year did not suffer from local recurrence until death or final follow-up (Supplementary Fig. 2). The MST of the patients without local recurrence was 25.6 months, much longer than that of those with local recurrence (13.1 months).

With regard to prognostic factors, only the total irradiation dose was significant in OS and LC in univariate analyses and patients receiving higher doses showed longer OS and LC (p = 0.015 and 0.023, respectively), (Table 3, Fig. 2-(a, b)). A more detailed analysis of classifying patients into three groups by the irradiation dosage is shown in Fig. 2-(c, d). The median OS was 13.1, 28.4, and 42.5 months for 50, 54–60, and 67.5 GyE protocols, respectively, and median time to local recurrence was 10.9 months in 50 GyE and more than 36 months in the 54–60 and 67.5 GyE protocols, respectively. Higher doses caused a superior trend in OS and LC.

Fig. 3 depicts a representative case of a 71-year old man with unresectable LAPC. The primary tumor was located in the pancreatic body and clinical staging was T4N0M0. He received proton beam therapy to a total dose of 67.5 GyE in 25 fractions (using the concomitant boost technique) concurrently with chemotherapy (Gem: 800 mg/m^2; 3 times) and hyperthermia (6 times) during the treatment course. Reduced tumor volume was observed 25 months later. This patient is still alive without local recurrence or distant metastases 37 months after CCRT using proton beams.

Discussion

Clinical studies of CCRT reported in LAPC patients are summarized in Supplementary Table 1. For 3-dimensional conformal radiotherapy (3DCRT), the OS ranges from 2.8 to 13% at 2 years and the MST ranges from 10.3 to 15.8 months [21–25]. As for intensity modulated radiotherapy (IMRT), the OS range is 22–32.9% at 2 years and MST ranges from 15.3 to 22.6 months with two recently published reports of IMRT indicating MSTs of over 20 months [25–28]. In an IMRT study that delivered a 60–66 Gy dose to a macroscopic tumor using a simultaneous and integrated boost technique, the MST was 19 months and the median time to local recurrence was 13 months [29]. Stereotactic body radiotherapy succeeded in shortening the treatment period and the MST ranged from 10.6 to 15 months [30–32]. A large cohort study with

Table 2
Outcome of the patients and adverse events.

Number of patients	OS from CCRT 1 Y/2 Y (median)	OS from initial Tx 1 Y/2 Y (median)	LC from CCRT 1 Y/2 Y (median)	LC from initial Tx 1 Y/2 Y (median)	Site of recurrence local/distant/both	Death of disease	Adverse events (grade 1/2/3/4/5)	
							Acute	Late
42	77.8/50.8% (25.6 M)	84.5/58.7% (27.5 M)	83.3/78.9% (>36 M)	90.1/76.7% (>36 M)	7/17/2 (16.7/40.5/4.8%)	21 (50%)	4/15/17/2/0	3/2/0/0/0

Adverse events		Acute					Late				
CTCAE ver 4.0 Grade		1	2	3	4	5	1	2	3	4	5
Hematologic	Leukopenia	5	15	17							
	Neutropenia	7	14	13	2						
	Anemia	26	8	2							
	Thrombocytopenia	24	6	2							
Gastrointestinal	Nausea	2					1				
	Vomiting										
	Anorexia	2					1	1			
	Gastric ulcer						3	1			

Abbreviations: OS: overall survival, LC: local control, Tx: treatment, Y: years, M: months.
Grade of upper table shows the maximum grade of each patient.
Grade of lower table shows every events.

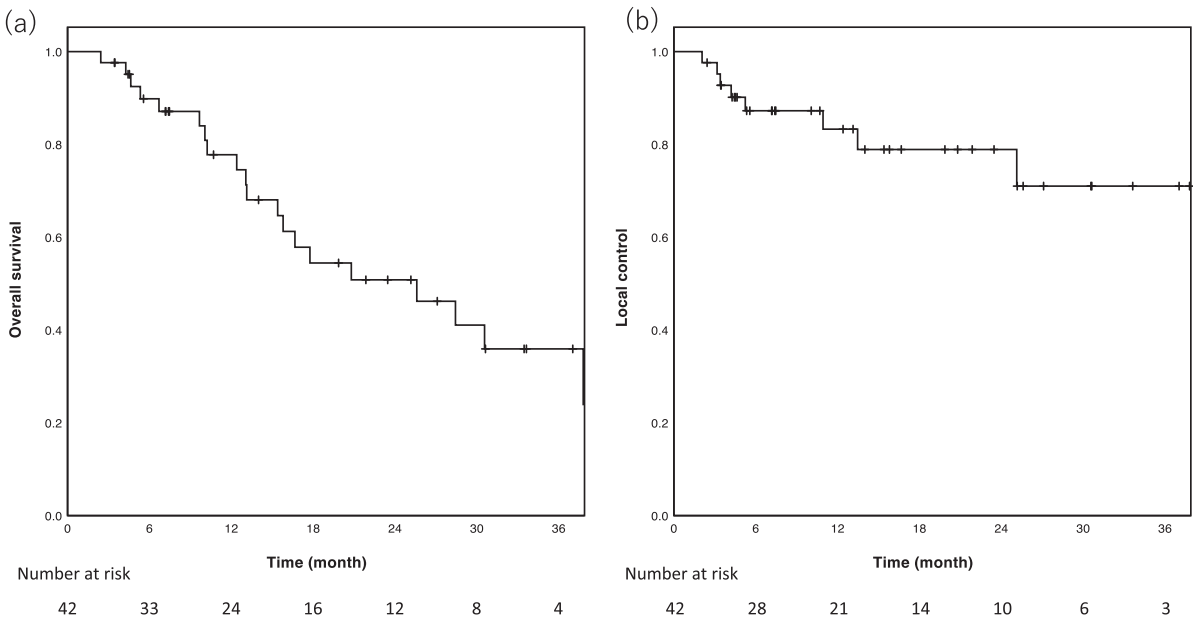

Fig. 1. Survival curves. (a) Overall survival rate. (b) Local control rate.

Table 3
Analysis of prognostic factors.

	OS Univariate analysis	LC Univariate analysis
Age (≦65 vs > 65)	0.144	0.516
Sex	0.792	0.802
N (0 vs 1)	0.397	0.742
Tumor diameter (≦30 mm vs > 30 mm)	0.195	0.805
CA19-9 (≦200 U/mL vs > 200 U/mL)	0.203	0.509
Pre-treatment (with vs without)	0.357	0.281
Total irradiation dose (50 GyE vs > 50 GyE)	0.015*	0.023*
Hyperthermia (presence vs absence)	0.355	0.252

* Significant.

propensity matching reported that the outcome of SBRT was not inferior to IMRT and was at least improved over conventional radiation techniques [33]. As for proton beam therapy (PBT), some dosimetry studies have confirmed a physical advantage of proton beams over photon beams, namely a tissue-sparing benefit, leading to the idea that outcomes may be improved by safely increasing proton beam doses [34,35]. In the clinical PBT studies, the OS ranges from 31 to 45% at 2 years with an MST between 18.4 and 22.3 months although the reports are very few and the patient cohort was smaller than in photon beam studies [16,36,37]. Our data, in which the 2-year OS is 50.8% with MST of 25.6 months, is numerically superior to photon RT and equivalent or superior to PBT even when borderline resectable patients are omitted and only unresectable LAPC patients are analyzed. Moreover, the 1-year/2-year OS and LC were 67.1%/11% and 49.2%/0%, respectively, while MST and median time to local recurrence were 15.7 and 10.6 months, respectively, for 25 patients who received conventional photon chemoradiotherapy (50–50.4 Gy) at our institute at the same time as this study. These data suggest that PBT has a potential of superior anti-tumor effect over existing RT for the treatment of unresectable LAPC patients [21–33].

Reasoning for the superiority of PBT is based on higher dose delivery, as patients with higher doses had a significantly longer OS compared to conventional dosing. However, it is premature to state that higher doses universally lead to better outcomes as the challenging 67.5 GyE protocol still risks high dose exposure to the GI tract. Therefore, although the classification numbers may shrink, there needs to be a more detailed examination of the relationship between irradiation dose and outcome. To this end, our study used 50 GyE, 54 to 60 GyE and 67.5GyE classifications and, as a result, we found that higher doses did trend toward longer LC and OS.

During the study period, a total of 19 patients experienced Grade 3 or 4 acute adverse events. However, these events were hematologic and can be explained by chemotherapy. As for gastrointestinal events, no patient suffered from more than a grade 2 event, lending credence the lower acute toxicity of PBT. Furthermore, no patient manifested a late GI-related adverse event of more than Grade 3, reinforcing the idea of CCRT using proton beams as a relatively less adverse modality compared to more aggressive therapies. In the previous study of Nichols et al. [38], it was verified that PBT in the range of 50.4–59.4 GyE was safely performed without any grade 3 GI toxicity. However, with regard to the 67.5 GyE in 25 fractions protocol, Takatori, et al. [39] reported PBT-induced ulcers in 45/91 patients from the same institute as the Terashima, et al. study [16]. Although we cannot directly compare treatment planning and methods in detail, the main difference between the Terashima, et al. study and ours is in the definition of the CTV. They included the primary tumor plus metastatic regional lymph nodes with prophylactic regions containing the drainage lymph nodes and paraaortic lymph nodes. Their CTV also involved peripheral regions surrounding the CA and SMA. Our CTV, on the other hand, contained the primary tumor plus only metastatic regional lymph nodes and peripheral regions surrounding the CA or SMA in cases of lesions which had invaded around the vessels. Non-metastatic regional lymph nodes for prophylactic irradiation were not included in our CTV. It may be possible that differences in the irradiation field caused less severe adverse events in our study. In parts other than treatment planning, routine use of proton-pump inhibitors and fasting before treatment might help to alleviate severe adverse events.

Unresectable LAPC is well-known to undergo distant metastases and the role of radiotherapy as local therapy within the con-

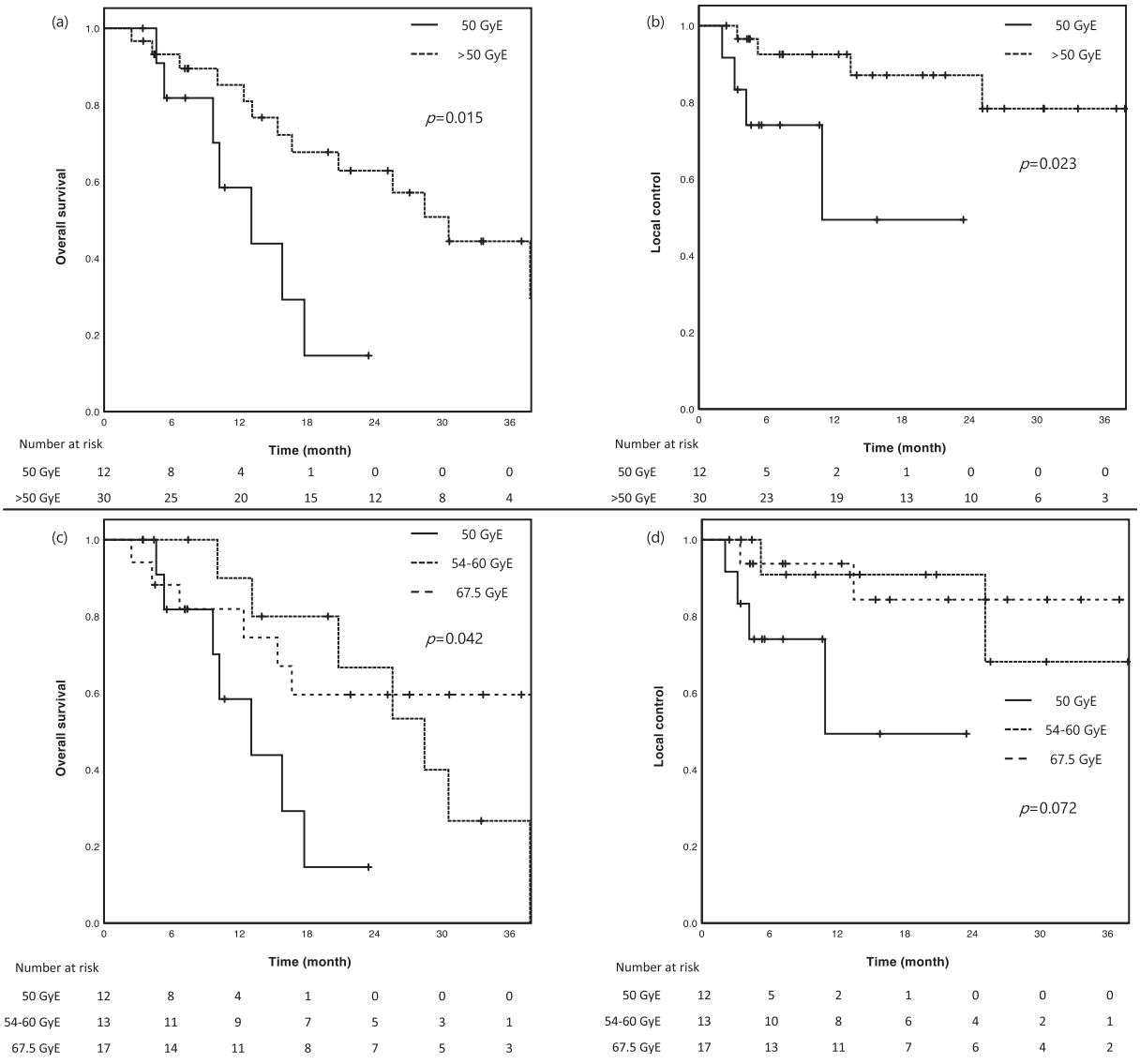

Fig. 2. Survival curves classified to irradiation dose. (a, c) Overall survival rate. (b, d) Local control rate. (a, b): Straight line: 50 GyE. Dotted line: > 50 GyE. (c, d): Straight line: 50 GyE. Dotted line: 54–60 GyE. Broken line: 67.5 GyE (concomitant boost).

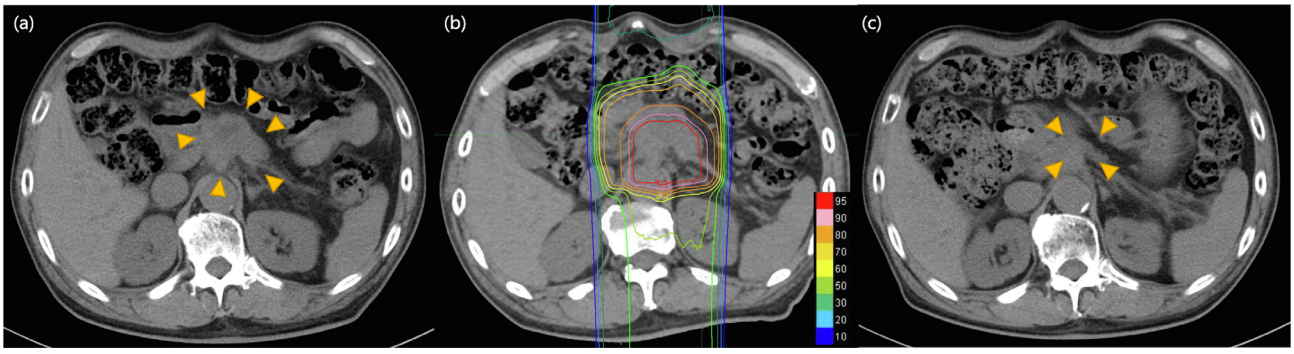

Fig. 3. Case presentation. 71-year old man with pancreatic cancer. (a) CT before treatment. Arrows indicate gross tumor volume. (b) Dose distribution image. Total irradiation dose is 67.5 GyE and isodose lines represent 95–10% of the isocenter dose from inside to outside. (c) CT 25 months after CCRT using proton beams. Arrows indicate a reduced tumor.

text of CCRT is not well established [40]. Historically, irradiation field size has been reduced according to chemotherapeutic intensity but controversy remains as to how much local lesion control could affect outcome of those LAPC patients in which distant metastases are frequent and lethal [10,41]. However, OS was closely related with LC in our study and those patients without local

recurrence trended toward longer survival than patients with local recurrences as shown in Supplementary Fig. 2. Moreover, several studies dealing with unresectable LAPC patients report that high dose irradiation improves LC and OS [25,27,31,32]. Taken together, we can therefore consider that excellent control of the primary lesions due to high irradiation dose delivery can control primary tumor activity and prolong survival of unresectable LAPC patients.

In our previous simulation study, the mean primary tumor dose from our 67.5 GyE in 25 fractions protocol (using concomitant boost technique) was 66.2 GyE in GI tract-separated tumors, 62.1 GyE in tumors adjacent to the GI tract, and 64.1GyE as a whole [42]. As shown in the detailed dose classification analysis in Fig. 2, the OS and LC of patients treated with a 67.5 GyE protocol were much higher than the conventional 50 GyE protocol and equivalent or higher than with 54–60 GyE, making it a reasonable and convincing result. Furthermore, dose escalation using concomitant boost technique can improve treatment effectiveness. Considering that no patient suffered from severe GI tract toxicity, higher dose delivery using the concomitant boost technique coupled with the physical characteristics of proton beams has the potential to safely and effectively replace the conventional protocol. Further studies into this could clarify the clinical significance of dose escalation using the concomitant boost technique.

In our study, a total of 23 patients were concurrently treated by hyperthermia as machine time allowed. Hyperthermia is known to increase the blood supply to tumors and improve delivery of large doses of cytotoxic oxygen and drugs [43]. It also acts as a radiation- and chemo-sensitizer while inhibiting transcription factors like NF-kB that play a crucial role in pancreatic carcinoma development and progression [43–45]. As pancreatic cancer features chemo-radio resistance and hypoxia, these patients are presumably good candidates for hyperthermic therapy. Although Maebayashi et al. [46] previously reported that CCRT combined with hyperthermia prolonged OS, hyperthermia did not function as a significant prognostic factor for OS and LC in our study. Future optimization studies are necessary to prove the efficacy of hyperthermic therapy in proton beam CCRT.

There are several limitations of this study. First, because this is a retrospective study, our patient population might have been biased toward favoring the effectiveness of PBT for survival or improvement of quality of life. However, the selection of PBT or photon therapy was arbitrarily done by the patients or referring physicians without prompting on our part. Additionally, to further reduce any bias, we performed univariate analyses using several factors. Second, variations of chemotherapy regimens, use of hyperthermia and our irradiation dose protocol might have introduced bias as an especially wide variety of pre-treatment chemotherapy regimens complicated determination of relevance to outcome. Even if we had no say in the pre-treatment chemotherapy and did not base our protocols on patient performance or clinical staging, some bias inevitably remained. Finally, because of the potentially rapid progression of disease, some patients could not be regularly examined at our institute. We made every effort to get as much data as possible through mail to these patients and physicians but patients who were shifted to palliative care or died soon after treatment would complicate any data gathering with regard to exact local treatment effect.

Clinical reports of PBT for unresectable LAPC patients are extremely scarce but clinical outcomes are satisfactory among CCRT reports to this point. To the best of our knowledge, this is the first study to prove the effectiveness of CCRT using proton beams by clarifying that high dose administration to tumors leads to improved prognosis for unresectable LAPC patients. We therefore consider that the physical advantages of proton beams can increase the value of radiotherapy in local CCRT treatment strategies for these patients.

In conclusion, CCRT using proton beams resulted in longer survival than previously reported CCRT data using photon RT, and high dose irradiation to the primary tumor prolonged LC and OS for unresectable LAPC patients without any severe GI toxicity. PBT is therefore a safe and effective treatment method for these patients.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.03.012.

References

[1] Hori M, Matsuda T, Shibata A, Katanoda K, Sobue T, Nishimoto H, et al. Cancer incidence and incidence rates in Japan in 2009: a study of 32 population-based cancer registries for the Monitoring of Cancer Incidence in Japan (MCIJ) project. Jpn J Clin Oncol 2015;45:884–91.
[2] Stathis A, Moore MJ. Advanced pancreatic carcinoma: current treatment and future challenges. Nat Rev Clin Oncol 2010;7:163–72.
[3] Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369:1691–703.
[4] Ghorani E, Wong HH, Hewitt C, Calder J, Corrie P, Basu B. Safety and efficacy of modified FOLFIRINOX for advanced pancreatic adenocarcinoma: a UK single-centre experience. Oncology 2015;89:281–7.
[5] Takeda Y, Katsura Y, Ohmura Y, Morimoto Y, Ishida T, Motoyama Y, et al. Combination chemotherapy in patients with metastatic or recurrent pancreatic cancer–a single institution experience. Gan to kagaku ryoho Cancer Chemother 2015;42:2360–3.
[6] Ueno H, Ikeda M, Ueno M, Mizuno N, Ioka T, Omuro Y, et al. Phase I/II study of nab-paclitaxel plus gemcitabine for chemotherapy-naive Japanese patients with metastatic pancreatic cancer. Cancer Chemother Pharmacol 2016;77:595–603.
[7] Clinical Guideline for Pancreatic Cancer Revision Comittee. Clinical guideline for pancreatic cancer 2016. J Gastroenterol 2017;114:627–36.
[8] Lawrence TS, Chang EY, Hahn TM, Hertel LW, Shewach DS. Radiosensitization of pancreatic cancer cells by 2',2'-difluoro-2'-deoxycytidine. Int J Radiat Oncol Biol Phys 1996;34:867–72.
[9] Li C-P, Chao Y, Chi K-H, Chan W-K, Teng H-C, Lee R-C, et al. Concurrent chemoradiotherapy treatment of locally advanced pancreatic cancer: Gemcitabine versus 5-fluorouracil, a randomized controlled study. Int J Radiat Oncol Biol Phys 2003;57:98–104.
[10] Yamazaki H, Nishiyama K, Koizumi M, Tanaka E, Ioka T, Uehara H, et al. Concurrent chemoradiotherapy for advanced pancreatic cancer: 1,000 mg/m2 gemcitabine can be administered using limited-field radiotherapy. Strahlentherapie und Onkologie: Organ der Deutschen Rontgengesellschaft [et al] 2007;183:301–6.
[11] Burris HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Madiano MR, 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;15:2403–13.
[12] Ioka T, Ikeda M, Ohkawa S, Yanagimoto H, Fukutomi A, Sugimori K, et al. Randomized phase III study of gemcitabine plus S-1 (GS) versus S-1 versus gemcitabine (GEM) in unresectable advanced pancreatic cancer (PC) in Japan and Taiwan: GEST study. J Clin Oncol 2011;29:4007-.
[13] Ueno H, Ioka T, Ikeda M, Ohkawa S, Yanagimoto H, Boku N, et al. Randomized phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: GEST study. J Clin Oncol 2013;31:1640–8.

[14] Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constine LS, Eisbruch A, et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys 2010;76:S10–9.
[15] Ohara K, Okumura T, Akisada M, Inada T, Mori T, Yokota H, et al. Irradiation synchronized with respiration gate. Int J Radiat Oncol Biol Phys 1989;17:853–7.
[16] Terashima K, Demizu Y, Hashimoto N, Jin D, Mima M, Fujii O, 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.
[17] Kagawa K, Murakami M, Hishikawa Y, Abe M, Akagi T, Yanou T, et al. Preclinical biological assessment of proton and carbon ion beams at Hyogo Ion Beam Medical Center. Int J Radiat Oncol Biol Phys 2002;54:928–38.
[18] Fukumitsu N, Hashimoto T, Okumura T, Mizumoto M, Tohno E, Fukuda K, et al. Investigation of the geometric accuracy of proton beam irradiation in the liver. Int J Radiat Oncol Biol Phys 2012;82:826–33.
[19] Institute NC. Common terminology criteria for adverse events (CTCAE). US Department of Health and Human Services, National Cancer Institute; 2010.
[20] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.
[21] Murphy JD, Adusumilli S, Griffith KA, Ray ME, Zalupski MM, Lawrence TS, et al. Full-dose gemcitabine and concurrent radiotherapy for unresectable pancreatic cancer. Int J Radiat Oncol Biol Phys 2007;68:801–8.
[22] Loehrer Sr PJ, Feng Y, Cardenes H, Wagner L, Brell JM, Cella D, 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;29:4105–12.
[23] Cardenes HR, Moore AM, Johnson CS, Yu M, Helft P. A phase II study of gemcitabine in combination with radiation therapy in patients with localized, unresectable, pancreatic cancer: a Hoosier Oncology Group study. Am J Clin Oncol 2011;34:460–5.
[24] Mukherjee S, Hurt CN, Bridgewater J, Falk S, Cummins S, Wasan H, et al. Gemcitabine-based or capecitabine-based chemoradiotherapy for locally advanced pancreatic cancer (SCALOP): a multicentre, randomised, phase 2 trial. Lancet Oncol 2013;14:317–26.
[25] Lee KJ, Yoon HI, Chung MJ, Park JY, Bang S, Park SW, et al. A comparison of gastrointestinal toxicities between intensity-modulated radiotherapy and three-dimensional conformal radiotherapy for pancreatic cancer. Gut Liver 2016;10:303–9.
[26] Ben-Josef E, Shields AF, Vaishampayan U, Vaitkevicius V, El-Rayes BF, McDermott P, et al. Intensity-modulated radiotherapy (IMRT) and concurrent capecitabine for pancreatic cancer. Int J Radiat Oncol Biol Phys 2004;59:454–9.
[27] Krishnan S, Chadha AS, Suh Y, Chen HC, Rao A, Das P, et al. Focal radiation therapy dose escalation improves overall survival in locally advanced pancreatic cancer patients receiving induction chemotherapy and consolidative chemoradiation. Int J Radiat Oncol Biol Phys 2016;94:755–65.
[28] Chung SY, Chang JS, Lee BM, Kim KH, Lee KJ, Seong J. Dose escalation in locally advanced pancreatic cancer patients receiving chemoradiotherapy. Radiother Oncol 2017;123:438–45.
[29] Zschaeck S, Blümke B, Wust P, Kaul D, Bahra M, Riess H, et al. Dose-escalated radiotherapy for unresectable or locally recurrent pancreatic cancer: Dose volume analysis, toxicity and outcome of 28 consecutive patients. PLoS One 2017;12:e0186341-e.
[30] Polistina F, Costantin G, Casamassima F, Francescon P, Guglielmi R, Panizzoni G, et al. Unresectable locally advanced pancreatic cancer: a multimodal treatment using neoadjuvant chemoradiotherapy (gemcitabine plus stereotactic radiosurgery) and subsequent surgical exploration. Ann Surg Oncol 2010;17:2092–101.
[31] Chuong MD, Springett GM, Freilich JM, Park CK, Weber JM, Mellon EA, et al. Stereotactic body radiation therapy for locally advanced and borderline resectable pancreatic cancer is effective and well tolerated. Int J Radiat Oncol Biol Phys 2013;86:516–22.
[32] Herman JM, Chang DT, Goodman KA, Dholakia AS, Raman SP, Hacker-Prietz A, et al. Phase 2 multi-institutional trial evaluating gemcitabine and stereotactic body radiotherapy for patients with locally advanced unresectable pancreatic adenocarcinoma. Cancer 2015;121:1128–37.
[33] de Geus SWL, Eskander MF, Kasumova GG, Ng SC, Kent TS, Mancias JD, et al. Stereotactic body radiotherapy for unresected pancreatic cancer: A nationwide review. Cancer 2017;123:4158–67.
[34] Ling TC, Slater JM, Mifflin R, Nookala P, Grove R, Ly AM, et al. Evaluation of normal tissue exposure in patients receiving radiotherapy for pancreatic cancer based on RTOG 0848. J Gastrointest Oncol 2015;6:108–14.
[35] Thompson RF, Mayekar SU, Zhai H, Both S, Apisarnthanarax S, Metz JM, et al. A dosimetric comparison of proton and photon therapy in unresectable cancers of the head of pancreas. Med Phys 2014;41:081711-n/a.
[36] Sachsman S, Nichols RC, Morris CG, Zaiden R, Johnson EA, Awad Z, et al. Proton therapy and concomitant capecitabine for non-metastatic unresectable pancreatic adenocarcinoma. Int J Particle Therapy 2014;1:692–701.
[37] Maemura K, Mataki Y, Kurahara H, Kawasaki Y, Iino S, Sakoda M, et al. Comparison of proton beam radiotherapy and hyper-fractionated accelerated chemoradiotherapy for locally advanced pancreatic cancer. Pancreatology 2017;17:833–8.
[38] Nichols Jr RC, George TJ, Zaiden Jr RA, Awad ZT, Asbun HJ, Huh S, et al. Proton therapy with concomitant capecitabine for pancreatic and ampullary cancers is associated with a low incidence of gastrointestinal toxicity. Acta Oncol 2013;52:498–505.
[39] Takatori K, Terashima K, Yoshida R, Horai A, Satake S, Ose T, et al. Upper gastrointestinal complications associated with gemcitabine-concurrent proton radiotherapy for inoperable pancreatic cancer. J Gastroenterol 2014;49:1074–80.
[40] Muniraj T, Jamidar PA, Aslanian HR. Pancreatic cancer: a comprehensive review and update. Dis Mon 2013;59:368–402.
[41] Kawakami H, Uno T, Isobe K, Ueno N, Aruga T, Sudo 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;62:1357–62.
[42] Fukumitsu N, Okumura T, Hiroshima Y, Ishida T, Numajiri H, Murofushi KN, et al. Simulation study of dosimetric effect in proton beam therapy using concomitant boost technique for unresectable pancreatic cancers. Jpn J Radiol 2018;36:456–61.
[43] Law MP, Ahier RG, Field SB. The effect of prior heat treatment on the thermal enhancement of radiation damage in the mouse ear. Br J Radiol 1979;52:315–21.
[44] Adachi S, Kokura S, Okayama T, Ishikawa T, Takagi T, Handa O, et al. Effect of hyperthermia combined with gemcitabine on apoptotic cell death in cultured human pancreatic cancer cell lines. Int J Hyperthermia 2009;25:210–9.
[45] Prabhu L, Mundade R, Korc M, Loehrer PJ, Lu T. Critical role of NF-κB in pancreatic cancer. Oncotarget 2014;5:10969–75.
[46] Maebayashi T, Ishibashi N, Aizawa T, Sakaguchi M, Sato T, Kawamori J, et al. Treatment outcomes of concurrent hyperthermia and chemoradiotherapy for pancreatic cancer: Insights into the significance of hyperthermia treatment. Oncol Lett 2017;13:4959–64.