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Original Research Article

Efficacy and feasibility of re-irradiation using carbon ions for pancreatic cancer that recurs after carbon-ion radiotherapy

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ABSTRACT

Background and purpose: Patients who receive carbon-ion radiotherapy (C-ion RT) for primary pancreatic cancer may experience locoregional recurrence; however, the treatment options for such patients are limited. We aimed to investigate the feasibility and efficacy of carbon-ion re-irradiation for patients with pancreatic cancer who experienced recurrence after initial C-ion RT.
Materials and methods: Twenty-one patients with recurrent pancreatic cancer who underwent repeat C-ion RT between December 2010 and November 2016 at our institute were retrospectively evaluated. The sites of post-initial C-ion RT failure were in-field central in 16 patients (76.2%) and marginal in 5 (23.8%). The median doses of initial and repeat C-ion RT were both 52.8 Gy (relative biological effectiveness [RBE]). Thirteen patients (61.9%) received concurrent chemotherapy with re-irradiation, while 11 (52.4%) received adjuvant chemotherapy.
Results: The median follow-up period after re-irradiation was 11 months. The 1-year local control, progression-free survival, and overall survival rates were 53.5%, 24.5%, and 48.7%, respectively. Toxicity data was obtained from the patients' charts. Only 1 patient (4.8%) developed grade 3 acute toxicities and none developed grade $\geq$3 late toxicities. Univariate analysis indicated that patients who received adjuvant chemotherapy had significantly improved local control rates compared with those who did not; the 1-year local control rates were 80.0% and 0.0%, respectively (P = 0.0469).
Conclusion: Repeating C-ion RT may be a reasonable option with tolerable toxicity for patients with recurrent pancreatic cancers. Adjuvant chemotherapy appears to improve the local control rate. This is the first study to examine re-irradiation using C-ion for recurrent pancreatic cancer after initial C-ion RT.

1. Introduction

Pancreatic cancer is one of the most lethal cancers worldwide, especially in developed countries [1]. Surgical resection is considered a curative treatment for this disease; however, only 10–20% of patients are diagnosed at operable stages owing to the lack of early symptoms [2]. Furthermore, the optimal management modality for locally advanced pancreatic cancer (LAPC) is controversial as both chemoradiation and chemotherapy alone are widely used to treat it [3–5].

Pancreatic cancers are hypoxic and resistant to low linear energy transfer (LET) radiation [6]. As such, carbon-ion (C-ion) radiotherapy (RT) is a promising treatment for this malignancy given that it delivers high-LET radiation and is toxic to hypoxic cells. Its unique physical characteristics of Bragg's peak, sharp

Abbreviations: 18F-FDG-PET, 18F-fluorodeoxyglucose positron emission tomography; C-ion RT, carbon-ion radiotherapy; CT, computed tomography; CTV, clinical target volume; D2cc, dose covering 2 cc; EBRT, external beam radiation therapy; GS, gemcitabine plus S1; GTV, gross tumour volume; IMRT, intensity-modulated radiotherapy; LAPC, locally advanced pancreatic cancer; LC, local control; LET, linear energy transfer; MRI, magnetic resonance imaging; OS, overall survival; PFS, progression-free survival; PTV, planning target volume; RBE, relative biological effectiveness; S-1, tegafur, gimeracil, and oteracil; SBRT, stereotactic body radiation therapy.

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lateral penumbra, high LET, and increased relative biological effectiveness (RBE) enable the delivery of a more conformal dose distribution with a greater biological effect than photon- or proton-based RT [7].

Promising outcomes have been reported in patients who received C-ion RT for radioresistant inoperable pancreatic cancers [8–10]. Shinoto et al. [10] reported 2-year local control (LC) and overall survival (OS) rates of 82% and 53%, respectively, in 64 patients with LAPC who received C-ion RT. Ben-Josef et al. [11] reported 2-year LC and OS rates of 59% and 30%, respectively, in 50 patients with LAPC who received intensity-modulated radiation (IMRT).

In terms of post-treatment recurrence, surgery is generally the first treatment choice for operable local recurrences [12,13]. While most patients who receive C-ion RT are inoperable owing to their locally advanced status, the efficacy of C-ion RT for postoperative local recurrence of pancreatic cancer has previously been demonstrated [14].

Hayashi et al. [15] evaluated 48 patients with recurrent head and neck malignancies treated with C-ion RT re-irradiation and reported 2-year LC and OS rates of 40.5% and 59.6%, respectively. This provided evidence that re-irradiation using carbon ions is a reasonable treatment with tolerable toxicity for patients with recurrent head and neck malignancies after C-ion RT. We therefore posited that re-irradiation using C-ion RT in locally recurrent pancreatic cancer after C-ion RT would be tolerable.

As no data on re-irradiation using C-ion RT for recurrent pancreatic cancer after initial C-ion RT have been published to date, this study aimed to investigate the feasibility and efficacy of C-ion re-irradiation for patients with pancreatic cancer who experienced recurrence after initial C-ion RT. Towards this goal, we retrospectively analysed the clinical outcomes in patients who underwent this treatment sequence at our institution.

2. Materials and methods

2.1. Study design and patients

This was a single-centre retrospective analysis of 21 patients whose pancreatic cancers recurred after C-ion RT and who were then re-treated with C-ion RT between December 2010 and November 2016. Patients provided informed consent authorizing the use of their personal information for research purposes. This study was approved by our institutional review board (16-017, QST Hospital, National Institutes for Quantum and Radiological Sciences and Technology) and was performed pursuant to the Declaration of Helsinki. The inclusion criteria were as follows: (1) patients underwent repeat C-ion RT for pancreatic cancer that recurred after initial C-ion RT, (2) the initial and second planning target volume (PTV) overlapped, (3) the tumours were unresectable or medically inoperable, (4) patients had non-metastatic or controlled oligo-metastatic disease, (5) Eastern Cooperative Oncology Group performance status scores were 0–1, and (6) all tumours were at least 3 mm away from the gastrointestinal tract.

2.2. Study endpoints

The primary endpoints were OS (calculated from the start date of re-irradiation) and LC (defined as no evidence of tumour regrowth within the PTV) rates. "In-field central" and "marginal" recurrences after initial C-ion RT were defined as recurrent lesions inside or outside the 90% isodose covered PTV. In case 100% of the recurrent tumour appeared outside the 90% isodose covered PTV, it was dealt as marginal recurrence. The secondary endpoints were acute and late toxicities, which were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Toxicity data was obtained from the patients' charts.

2.3. Treatment protocol

As a rotating gantry for irradiating pancreatic cancers was not available at our institute in 2016 [16], all patients were immobilised in the supine and/or prone positions in customised cradles (Moldcare; Alcare, Tokyo, Japan) using thermoplastic shells (Shellfitter; Kuraray, Osaka, Japan). A respiratory gating system using pressure monitoring under thermoplastic shell was used for conducting planning computed tomography (CT) and for delivering C-ion RT. The peak exhalation ±10% respiratory phase was used for both planning CT and treatment execution to mitigate the respiratory movement of the tumour and surrounding organs. Non-contrast CT images with a slice thickness of 2 mm were obtained for treatment planning. Planning CT images were fused with those obtained using contrast-enhanced CT, gadolinium-enhanced magnetic resonance imaging (MRI), and 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) for accurate gross tumour volume (GTV) delineation. The clinical target volume (CTV) was defined as the GTV plus a 0–5 mm margin and was reduced in size if it lay close to the gastrointestinal tract. The PTV was defined as the CTV plus a 5-mm margin to account for set-up errors. The goals for target volume coverage were that 95% of the GTV and 90% of the PTV should be covered by 95% of the prescribed dose. All doses of initial and repeat C-ion RT were both administered in 12 fractions by passive beam, 4 times a week for 3 weeks.

We followed our institutional protocol concerning dose constraints to the organs at risk. The total dose of the initial and repeat C-ion RT to the gastrointestinal tract covering 2 cc (D2cc) was $\leq$60 Gy (RBE), while that to the spinal cord was $\leq$40 Gy (RBE). Three-dimensional treatment planning was performed using the in-house HIPLAN (NIRS, Chiba, Japan) and Xio-N (ELEKTA, Stockholm, Sweden; Mitsubishi Electric, Tokyo, Japan) planning software. To reduce the gastrointestinal and spinal doses, personalised separate angles including a beam originating from the oblique dorsal side were used. Biological treatment plan optimisation that took into account a clinical RBE value of 3 at the distal part of the Bragg peak was used. A representative case is shown in Fig. 1.

With respect to chemotherapy, 10 patients received concurrent chemotherapy with intravenous gemcitabine 1000 mg/m^2 on days 1, 8, and 15. Three patients received S-1 (a combination of tegafur, gimeracil, and oteracil) 80 mg/m^2 twice daily for 2 weeks, followed by 1 week of rest as one course. There were 13 and 10 patients who received induction chemotherapy and adjuvant chemotherapy, respectively.

2.4. Follow-up

Clinical follow-up visits were scheduled every 3 months, and assessments included contrast-enhanced CT, 18F-FDG-PET, and MRI of the pancreatic region at 3–6-month intervals. The follow-up time was calculated from the date of commencing re-irradiation to that of the last follow-up visit.

2.5. Statistical analysis

LC, OS, and progression-free survival (PFS) were calculated using the Kaplan-Meier method. Univariate analysis using the log-rank test was performed to compare parameters among different subgroups; these included tumour and treatment-related factors such as age, sex, T-stage of the recurrence tumour, total

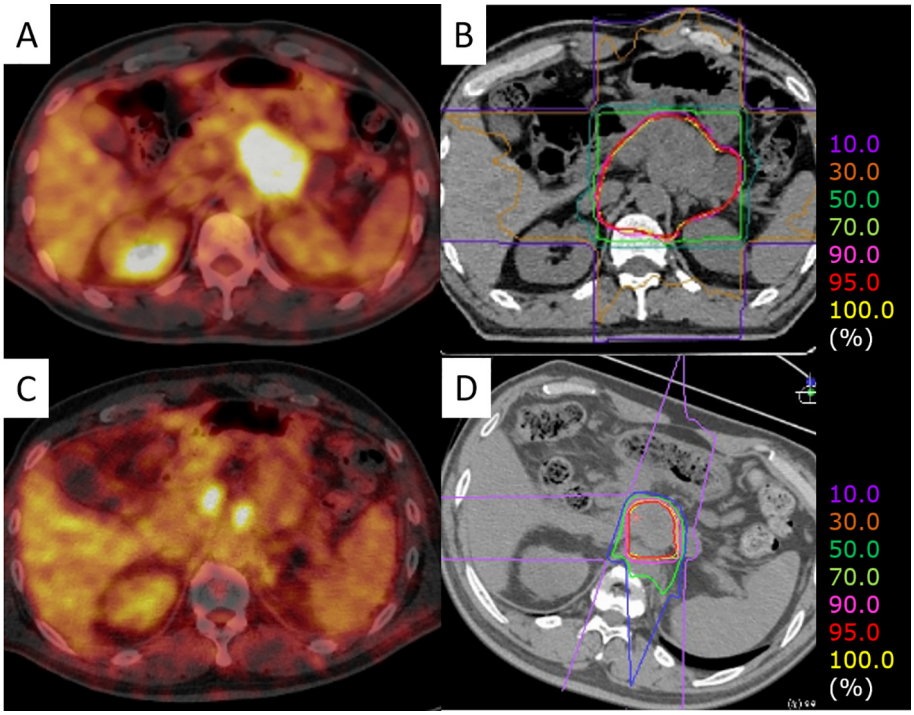

Fig. 1. A representative patient with pancreatic body cancer. The initial carbon-ion radiotherapy (C-ion RT) was 50.4 Gy (RBE)/12 fraction/3 weeks. Moreover, gemcitabine was administered as bridging and concurrent chemotherapy. The patient developed in-field local failure 13 months after initial C-ion RT. S-1 was delivered as bridging chemotherapy, and re-irradiation with 55.2 Gy (RBE)/12 fraction/3 weeks was delivered 17 months after the initial C-ion RT. The patient received a third round of C-ion RT following marginal recurrence at the site of initial C-ion RT 29 months after that initial treatment. Furthermore, the patient received intensity-modulated radiotherapy for recurrence at the para-aortic lymph node more than 5 years after the initial C-ion RT. However, the patient developed septic shock for unknown reasons and died 75 months after the initial C-ion RT. (A) An 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) image of the pancreas before initial C-ion RT. (B) Dose distribution of the initial C-ion RT. (C) An 18F-FDG-PET image showing in-field local failure. (D) Dose distribution for re-irradiation.

doses of repeat C-ion RT, duration between the 2 treatments, receipt of concurrent chemotherapy, and receipt of adjuvant chemotherapy. A P-value of <0.05 was considered significant. Multivariate analysis was not performed due to the limited number of cases. All statistical analyses were performed using R software, version 3.4.4.

3. Results

3.1. Baseline characteristics

The median age of all patients at re-irradiation was 67 years; the male-to-female ratio was 15:6. Most primary tumours (n = 16) were located in the pancreatic body and the remaining (n = 5) in the pancreatic head. The majority of patients (85.7%) initially presented with locally advanced T4 stage, while 52.4% had this same stage at recurrence. Moreover, 76.2% of the patients had in-field central recurrences. The median interval between initial irradiation and re-irradiation was 17 (6–95) months. The median doses of initial and repeat C-ion RT were both 52.8 Gy (RBE). The cumulative dose was 105.6 Gy (RBE). All patients received initial C-ion RT as initial radical treatment. The baseline characteristics of the patients are shown in Table 1.

3.2. Treatment outcomes

The median follow-up durations for all patients and survivors were 11 months (range, 3–58 months) and 12 months (range, 4–37 months), respectively. The actuarial LC rates at 12 months was 53.5% (95% CI: 17.2–80.0). The median OS was 11 months. The OS rates at 12 was 48.7% (95% CI: 25.6–68.4). The 12-month PFS rates was 24.5% (95% CI: 7.9–45.9). Kaplan-Meier curves for LC, OS, and PFS are shown in Fig. 2.

3.3. Patterns of failure

In total, 17 patients developed recurrences, among whom 6 developed local recurrences and 15 had distant metastases. Among the 6 patients with local recurrences, 2 patients had only local recurrences, 1 patient had local recurrence 3 months after distant metastasis, 1 patient had local recurrence followed by distant metastasis 22 months later, and 2 patients had concurrent local recurrence and distant metastasis. The local recurrences in all 6 patients were in-field only within the 90% isodose lines; there were no marginal recurrences. The median times to local failure and distant metastasis was 11 and 6 months, respectively.

3.4. Analysis of prognostic factors

Univariate analyses were used to compare LC and OS according to various factors (Table 2). Patients who underwent adjuvant chemotherapy had longer LC than those who did not (1-year LC: 80.0% vs. 0.0%; P = 0.0469).

3.5. Acute and late toxicities

All the patients were compliant with their treatments. There was 1 patient (4.8%) who experienced grade 3 duodenal stenosis and received endoscopic stent treatment 1 month after re-irradiation. No patient developed grade 3 or higher late toxicities.

Table 1
Baseline patient characteristics.

Characteristics		Number (%)
Number of patients		21 (100.0)
Sex	Male/female	15 (71.4)/6 (28.6)
Age at re-irradiation	Median/range, years	67/49–88
Performance status	Score 0/1	17 (81.0)/4 (19.0)
Histologic type	Adenocarcinoma/no analysis*	12 (57.1)/9 (42.9)
Primary site in pancreas at initial irradiation	Head/body	5 (23.8)/16 (76.2)
TNM staging at initial irradiation	cT4N0M0	18 (85.7)
	cT2N1M0	1 (4.8)
	cT2N0M0	1 (4.8)
	cT1N0M0	1 (4.8)
Site of failure at re-irradiation	In-field	16 (76.2)/5 (23.8)
	central/marginal	
TNM staging at re-irradiation	rT4N0M0	11 (52.4)
	rT3N0M0	3 (14.3)
	rT2N1M0	1 (4.8)
	rT2N0M0	6 (28.6)
Interval between initial and re-irradiation	Median/range, months	17/6–95
Total dose of initial irradiation	48.0 Gy (RBE)	2 (9.5)
	50.4 Gy (RBE)	5 (23.8)
	52.8 Gy (RBE)	5 (23.8)
	55.2 Gy (RBE)	9 (42.9)
Total dose of re-irradiation	50.4 Gy (RBE)	1 (4.8)
	52.8 Gy (RBE)	15 (71.4)
	55.2 Gy (RBE)	5 (23.8)
Induction chemotherapy for re-irradiation	GEM	5 (23.8)
	S-1	5 (23.8)
	GEM + S-1	2 (9.5)
	CDDP + CPT-11	1 (4.8)
Concurrent chemotherapy for re-irradiation	GEM	10 (47.6)
	S-1	3 (14.2)
Adjuvant chemotherapy for re-irradiation	GEM	3 (14.3)
	S-1	7 (33.3)
	GEM + nab-PTX	1 (4.8)

Abbreviations: * = diagnosed using imaging findings; RBE = relative biological effectiveness; GEM = gemcitabine; S-1 = tegafur, gimeracil, and oteracil potassium; nab-PTX = nanoparticle albumin-bound paclitaxel; CDDP = cisplatin; CPT-11 = irinotecan

4. Discussion

This study investigated the feasibility and efficacy of carbon-ion re-irradiation for patients with pancreatic cancer who experienced recurrence after initial C-ion RT. The 1-year LC and OS rates were 53.5% and 48.7%, respectively. Only 4.8% developed grade 3 acute toxicities, and none developed grade ≥3 late toxicities. Collectively, these findings support that repeating C-ion RT may be a reasonable option with tolerable toxicity for patients with recurrent pancreatic cancers. To our best knowledge, this is the first study to examine the efficacy and the feasibility of re-irradiation using C-ion for recurrent pancreatic cancer after initial C-ion RT.

Several studies have demonstrated the efficacy and feasibility of re-irradiation using stereotactic body RT (SBRT) after photon external beam RT (EBRT) [17–19]. Comparison with these studies and current study are summarised in Table 3.

Despite the current study showing median OS rates that were superior to those of other studies, LC at 12 months post-re-irradiation appeared to be low. This may be due to patients having received initial RT as part of a treatment plan that included surgery, as described in previous studies [17–19]. Our findings indicate that re-irradiation with C-ion RT may be an acceptable treatment with respect to both efficacy and toxicity. Another potential reason for lower LC rates in our study is that we used CT and 18F-FDG-PET to detect local recurrence after C-ion RT. Notably, Shinoto et al. [9–10] discovered dissimilarities in evaluations when using CT versus 18F-FDG-PET criteria, as the latter can assess tumour viability more reliably.

Patients with inoperable recurrent pancreatic cancers receive systemic therapy as a salvage intervention after C-ion RT. Burris et al. [20] reported that the median survival of patients treated with gemcitabine and 5-fluorouracil were 5.65 and 4.41 months, respectively; the corresponding 12-month survival rates were 18% and 2%, respectively. Okusaka et al. [21] reported that the median OS of patients treated with gemcitabine, S-1, and gemcitabine plus S-1 (GS) were 8.8 months, 9.7 months, and 9.9 months, respectively. The 12-month OS rates of patients on these regimens were 35.0%, 38.4%, and 40.4%, respectively. Von Hoff et al. [22] reported the median survival times of patients administered nanoparticle albumin-bound paclitaxel plus gemcitabine or gemcitabine alone as 8.5 months and 6.7 months, respectively; the corresponding 12-month survival rates were 35% and 22%, respectively. In the current study, the 12-month OS rate for the 11 patients (52.4%) who underwent re-irradiation with adjuvant chemotherapy was 48.7%. These chemotherapy studies including many distant metastasis cases, so it is difficult to compare with current study. To reveal which treatment procedure would be better for local recurrent pancreatic cancer after C-ion RT we need randomized control study.

Our univariate analysis revealed that patients with adjuvant chemotherapy showed significantly better LC than did patients without adjuvant chemotherapy. Previous studies of SBRT re-

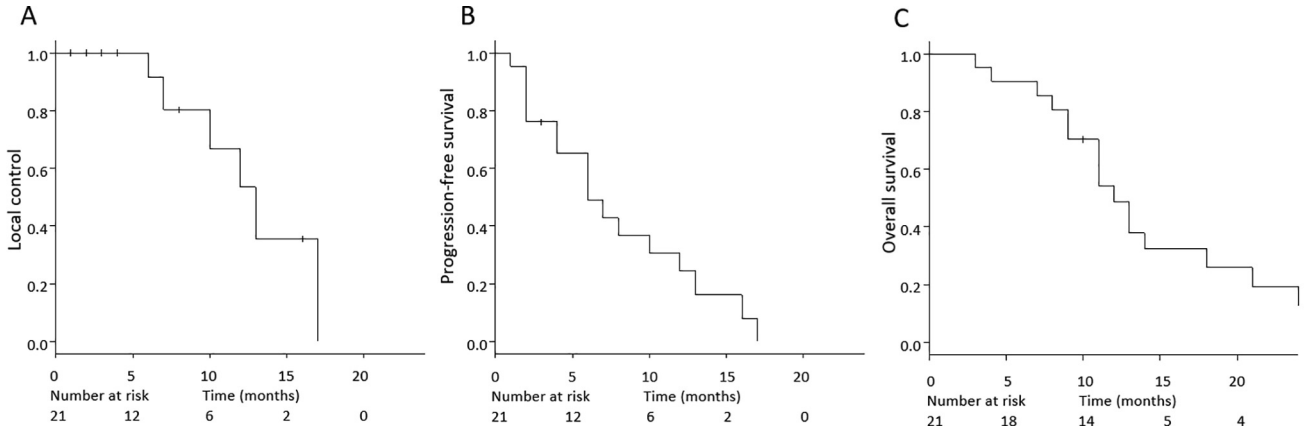

Fig. 2. Local control (A), progression-free survival (B), overall survival from the time of repeat carbon-ion radiotherapy (C), and overall survival from the time of initial carbon-ion radiotherapy (D) for the 21 patients.

Table 2
Univariate analysis of potential prognostic factors.

Factor	Category	No. of patients	1-year OS (%)	P-value	1-year local control (%)	P-value
Age (years)	<67	9	25	0.624	66.7	0.261
	≥67	12	65.6		45.7	
Sex	Male	15	37	0.313	37	0.382
	Female	6	80		100	
Duration between C-ion RT (months)	<17	9	51.9	0.483	20	0.092
	≥17	12	46.3		100	
Recurrence T staging	rT2–3	10	60	0.153	60	0.957
	rT4	11	34.6		41.7	
Total dose of re-irradiation (Gy [RBE])	<55.2	16	47.1	0.253	50	0.953
	≥55.2	5	53.3		75	
CCRT	Yes	13	38.5	0.424	62.5	0.321
	No	8	72.9		37.5	
Adjuvant chemotherapy	Yes	11	54.5	0.439	80	0.0469
	No	10	39.4		0	

Abbreviations: OS = overall survival; RBE = relative biological effectiveness; C-ion RT = carbon-ion radiotherapy; CCRT = concurrent chemoradiotherapy.

Table 3
Comparison with other series of re-irradiation of pancreatic cancer.

Author	No. of patients	Initial RT	Modality of second RT	Median follow-up	Grade ≥ 3 toxicity	Local control	Median OS
Wild et al 2013 [17]	18	Radical 17%* Postoperative 83%*	SBRT†	34.3 months from initial RT	6%	78% at 6 months 62% at 12 months	8.8 months
Lominska et al 2012 [18]	28	Radical 71%* Postoperative 29%*	Boost SBRT 39%† Salvage SBRT 61%†	5.9 months from second RT	7%	70% at 12 months	5.9 months
Koong et al 2017 [19]	23	Radical 48%* Postoperative 52%*	SBRT†	28 months from initial RT	9%	86.4% at 6 months 81% at 12 months	8.5 months
Current study	21	Radical 100%‡ Postoperative 0%	C-ion RT‡	28 months from initial RT 11 months from second RT	4.8%	91.7% at 6 months 53.5% at 12 months	11 months

Abbreviations: No. = Number; RT = radiotherapy; OS = overall survival; * = photon radiotherapy; † = Stereotactic body radiotherapy; ‡ = C-ion RT = carbon-ion radiotherapy.

irradiation showed no significant impact of adjuvant chemotherapy on LC [17–19]; hence, we hypothesise that the extent of tumour radioresistance differs between patients described in SBRT re-irradiation studies and those in our current study. In previous SBRT studies, the initial RT modalities used conventional photons with low LET. In contrast, the initial RT in our study was high-LET C-ion RT. Hayashi et al. [15] reported that the 2-year LC following re-irradiation with C-ion RT in patients with head and neck malignancies whose tumours recurred after initial C-ion RT was 40.5%. This was inferior to the 2-year LC rates following initial C-ion RT reported by Koto et al. [23] (83.9%). These findings may indicate that recurrent tumours that were initially treated with C-ion RT has radioresistance even against high-LET RT. This would also explain the significant effect of adjuvant chemotherapy on LC.

Concerning dose constraints, the combined total D2cc to the gastrointestinal tract in both the initial and repeat C-ion RT was ≤60 Gy (RBE), while the Dmax to the spinal cord was ≤40 Gy (RBE). However, we were unable to accurately calculate the total dose distributions of initial and repeat C-ion RTs in the digestive tract organs. In patients with LAPC, the positions of the pancreas, main arteries (such as the celiac or superior mesenteric arteries), and spinal cord did not markedly change, although those of the digestive tract organs such as the stomach and duodenum did. Therefore, it was critical to avoid overlapping beam delivery to the gastrointestinal tract, and our rule during repeat C-ion RT was to avoid directing the beam through the gastrointestinal tract to the greatest extent possible. As such, patients were placed in multiple positions such as prone, spinal, and certain angled oblique poses. This was facilitated by the unique physical character of C-ions and the sharpness of the lateral penumbra [7]. In the future, utilizing a rotating gantry will enable the delivery of all beams while the patient is in a single position; this will also enable the accurate estimation of gastrointestinal toxicities and dose-volume relationships.

Only 1 patient (4.8%) in our study experienced grade 3 duodenal stenosis and received endoscopic stent treatment 1 month after re-irradiation. No patient developed grade 3 or higher late toxicities. This indicated that the basic strategy of avoiding overlapping beam delivery to the gastrointestinal tract was effective even though the location of the gastrointestinal tract remained uncertain. The small number of grade ≥3 toxicities does not imply that re-irradiation using C-ion RT is acceptable for every patient. Rather, careful adaptation and avoiding overlapping beams to the gastrointestinal tract are critical when considering whether a patient is a candidate for a repeat procedure.

This study was limited by its retrospective nature and small sample size; therefore, there remains a possibility of selection bias. However, to our best knowledge, ours was the first clinical study to show the efficacy and feasibility of re-irradiation using C-ion RT for radioresistant pancreatic cancers that recurred after initial C-ion RT. We are now performing a prospective registry study of a 12-fraction re-irradiation procedure using C-ion RT for recurrent pancreatic cancers.

5. Conclusion

Re-irradiation with C-ion RT may benefit patients who experienced pancreatic cancer recurrence after initial C-ion RT. Moreover, adjuvant chemotherapy can improve the LC.

Declaration of Competing Interest

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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Data availability

The datasets generated and/or analyzed during this study are not publicly available due to the risk of research participant privacy but are available from the corresponding author on reasonable request.

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