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Five-year outcomes in carbon-ion radiotherapy for postoperative pelvic recurrence of rectal cancer: A prospective clinical trial (GUNMA 0801)

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ABSTRACT

Introduction: Carbon-ion radiotherapy (C-ion RT) is associated with favorable clinical outcomes for the pelvic recurrence of rectal cancer. However, few long-term follow-up studies after C-ion RT have been conducted. Hence, we performed an updated analysis of a prospective clinical trial of C-ion RT for the postoperative pelvic recurrence of rectal cancer.

Materials and methods: The study included 28 patients. Inclusion criteria were patients with confirmed pelvic recurrence of rectal cancer without distant metastasis; those who underwent curative resection of their primary disease and regional lymph nodes without gross or microscopic residual disease; and those who had radiographically measurable tumors. The total dose of C-ion RT for all the patients was 73.6 Gy (relative biological effectiveness) administered in 16 fractions.

Results: The median follow-up duration in all patients and those who survived were 51.2 and 69.2 months, respectively. The follow-up rate at the time of analysis was 96.4%. The 5-year overall survival and local control rates were 50% and 83%, respectively. Four patients had local recurrence, and 17 died of rectal cancer. Regarding late toxicities, two patients developed grade 3 pelvic infection, and nine developed grade 2 peripheral neuropathy.

Conclusion: Our updated analysis of a prospective clinical trial of C-ion RT for postoperative pelvic recurrence of rectal cancer confirmed its long-term efficacy and safety. These results suggest that C-ion RT may be a safe and effective treatment option for the postoperative pelvic recurrence of rectal cancer.

1. Introduction

The global incidence and mortality rates of rectal cancer in 2020 were estimated to be 732,210 and 339,022, respectively [1]. Although surgery results in favorable clinical outcomes in patients with resectable rectal cancer, 4–15% of the patients develop local recurrence after curative resection [2,3]. While surgery is the first-line treatment for a pelvic recurrence of rectal cancer, the R0 resection rate is 55–80% [4–6]. In addition, many patients are unsuitable candidates for curative resection, which is often highly invasive in terms of loss of function. X-ray radiotherapy (RT), including stereotactic body radiotherapy (SBRT) is one of the treatment options as a less invasive curative treatment for patients with pelvic recurrence of rectal cancer who refuse surgery or are not eligible. However, clinical outcomes of X-ray RT including SBRT were 16–41% in 5-year overall survival (OS) and 56–74% in 4- and 5-year local control (LC), respectively, and we considered that these clinical results were insufficient [7–10]. In contrast, carbon-ion radiotherapy (C-ion RT), which has higher dose localization and cytotoxic effects than X-ray RT, has shown favorable clinical outcomes, with 5-year OS and LC rates of 51% and 88%, respectively [11]. Therefore, the clinical results of C-ion RT suggest its potential role in the curative treatment for unresectable pelvic recurrence of rectal cancer, which the national insurance has covered in Japan since April 2022.

Generally, 5-year survival is an important landmark in cancer treatment, during which it is necessary to confirm treatment efficacy and safety. Our group reported the clinical outcomes of a prospective clinical trial (GUNMA0801) of C-ion RT for the pelvic recurrence of rectal cancer, in which the 3-year OS and LC rates were 92% and 86%, respectively, over a median follow-up duration of 38.9-months [12]. This report showed favorable results regarding treatment efficacy and

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safety; however, the follow-up duration was only approximately 3 years, and the long-term efficacy and safety of this report were insufficient. Hence, we performed an updated analysis of a prospective clinical trial of C-ion RT for postoperative pelvic recurrence of rectal cancer over a 5-year observation period to confirm its long-term efficacy and safety.

2. Materials and methods

2.1. Patient eligibility

As previously described [12], eligible patients (i) had a pelvic recurrence of rectal cancer without distant metastasis, as confirmed by histology or diagnostic imaging; (ii) underwent curative resection of their primary disease and regional lymph nodes, without gross or microscopic residual disease; (iii) had radiographically measurable tumors; (iv) had an Eastern Cooperative Oncology Group performance status ≤ 2; and (v) were aged 20–80 years. Patients with direct invasion of the bladder and/or gastrointestinal (GI) tract, chemotherapy within 4 weeks, prior RT to the target area, intractable infections in the target area, or another active malignancy were excluded.

Before patient registration, medical history, physical examination, routine testing of blood cell counts, chemistry, urine analysis, computed tomography (CT), magnetic resonance imaging (MRI), and fluorodeoxyglucose positron emission tomography (FDG-PET) were acquired as pretreatment evaluations. Cystoscopy and/or proctoscopy were performed to exclude direct invasion of the bladder or GI tract when indicated.

The treatment protocol for this study was reviewed and approved by the Gunma University Institutional Review Board, and all patients signed an informed consent form prior to treatment initiation. This study was registered with the University Hospital Medical Information Network in Japan (UMIN000009719, prospectively registered on January 8, 2013).

2.2. Carbon-ion radiotherapy

A heavy-ion accelerator at the Gunma University Heavy Ion Medical Center was used to generate C-ion beams. Beam energies of 290, 380, or 400 MeV/u were selected according to the depth of the tumor from the skin per beam angle. Doses of C-ion RT were expressed as the relative biological effectiveness (RBE)-weighted doses [Gy (RBE)], which was defined as the physical dose multiplied by the RBE of the C-ions [13]. Preparation for C-ion RT, target delineation, treatment planning, and evaluation during follow-up have been reported elsewhere [12]. Patients received C-ion RT once daily, four days a week (Tuesday to Friday). C-ion RT was performed with 73.6 Gy (RBE) in 16 fractions for 4 weeks [4.6 Gy (RBE) per fraction]. A representative case of the dose distribution and diagnostic images before and after C-ion RT is shown in Fig. 1. Patients were followed up for 1 month after C-ion RT completion and every 3 months thereafter. Acute and late toxicities were graded using the Common Terminology Criteria for Adverse Events (version 4.0) of the National Cancer Institute [14]. Acute and late toxicities were evaluated as the highest grade of toxicity that occurred within three months and after three months, respectively, from the initiation of C-ion RT. For patients in which re-irradiation was performed for recurrence after C-ion RT, toxicities were counted until re-irradiation was performed.

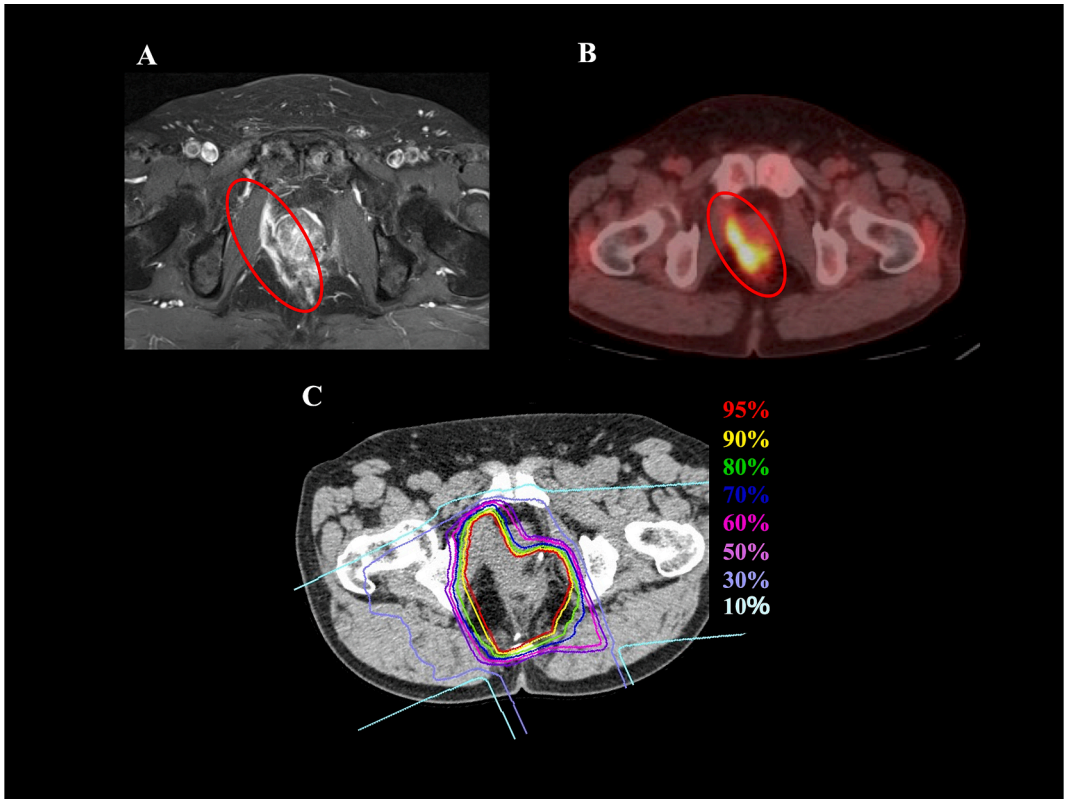

Fig. 1. A 62-year-old male patient with pelvic recurrence of rectal cancer treated with C-ion RT. (A) Gadolinium enhanced MRI taken before treatment. The red circle indicates the tumor with contrast enhancement. (B) FDG-PET taken before treatment. The red circle shows the tumor with abnormal FDG uptake. (C) Dose distribution on an axial CT image. Highlighted areas represent 95% (red), 90% (yellow), 80% (green), 70% (dark blue), 60% (magenta), 50% (purple), 30% (blue), and 10% (light blue) isodose curves (100% is 73.6 Gy [RBE]). C-ion RT, Carbon-ion radiotherapy; CT, computed tomography; FDG-PET, fluorodeoxyglucose positron emission tomography; MRI, magnetic resonance imaging; RBE, relative biological effectiveness. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Patient characteristics (n = 28).

Characteristics		Value
Age, years	Median (Range)	63 (40–76)
PS, n	0	12
	1	16
Sex, n	Male	16
	Female	12
Primary tumor surgery, n	Abdominoperineal excision	16
	Low anterior resection	9
	Hartmann's resection	1
	Intersphincteric resection	2
Histology, n	Well-differentiated adenocarcinoma	10
	Moderately differentiated adenocarcinoma	15
	Mucinous adenocarcinoma	3
Pathological stage	I	6
	II	7
	III	15
Duration from the date of surgery to initiation of C-ion RT, months	Median (Range)	25.6 (2.6–117.6)
Tumor site, n	Presacral	7
	Side wall	17
	Perineal	4
Tumor size, mm	Median (Range)	44 (16–84)
Gross tumor volume, cm^3	Median (Range)	16.6 (1.0–213.2)
Serum CEA level before C-ion RT, ng/mL	Median (Range)	10.7 (0.3–617.3)
Spacer placement	Yes	6
	No	22
Dose fraction of C-ion RT, n	73.6 Gy (RBE) in 16 fractions	28

Abbreviations: CEA, carcinoembryonic antigen; C-ion RT, carbon-ion radiotherapy; PS, performance status; RBE, relative biological effectiveness.

2.3. Statistical analysis

This study of the prospective clinical trial, GUNMA0801, was designed to detect an increase in the 3-year LC from 50% (based on X-ray RT with chemotherapy data) to 85%, with α error of 0.05 and β error of 0.20. The number of patients required to detect this difference with normal approximation of the binomial distribution was 32. Considering the dropout rate, we aimed for a total of 35 patients. The primary endpoint was the 3-year LC rate, and the secondary endpoints were the rates of OS, progression-free survival (PFS), and acute and late toxicities. All statistical analyses were performed using JMP Pro 12.2.0 software (SAS Institute, Inc., Cary, NC, USA). OS was measured from the date of C-ion RT initiation to the date of death or most recent follow-up. LC was defined as no evidence of tumor regrowth on CT, MRI, or PET in the irradiated tumor bed, with or without a continuous elevation of blood levels of tumor markers, including carcinoembryonic antigens (CEA). LC was measured from the date of C-ion RT initiation to the date of local failure or most recent follow-up. PFS was defined as the absence of progression of both local and distant metastases. PFS was measured from the date of C-ion RT initiation to the date of observation of tumor progression or death from any cause. The probabilities of OS, LC, and PFS were calculated using the Kaplan–Meier method. Variable risk was expressed as a hazard ratio with a corresponding 95% confidence interval (CI). Additionally, Fisher's exact test was used to evaluate the prognostic factors for PFS by differentiation of pathology, pathological stage at the time of surgery, duration from the date of surgery to initiation of C-ion RT, CEA level before C-ion RT, gross tumor volume (GTV), and bone invasion before C-ion RT. The cut-off values of the duration from the date of surgery to initiation of C-ion RT, GTV, and CEA levels in the analysis of prognostic factors for PFS were defined according to the nearest point from the coordinates (0, 1) on the receiver operating characteristic (ROC) graph. Statistical significance was set at $P < 0.05$.

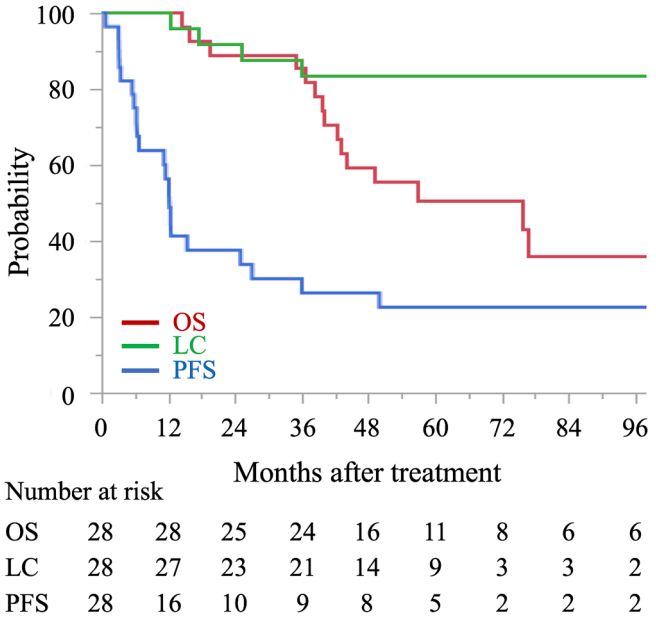

Fig. 2. Kaplan–Meier curves and number at risk for overall survival (OS), local control (LC), and progression-free survival (PFS).

3. Results

3.1. Patient characteristics

As previously described [12], 28 patients were enrolled between October 2011 and July 2017. Patient enrollment was terminated before the completion of the planned enrollment with 35 patients because another multicenter prospective trial for evaluating the efficacy and safety of C-ion RT for postoperative pelvic recurrence of rectal cancer with the same eligibility criteria was initiated. The characteristics of the study sample are summarized in Table 1. The diagnosis of recurrence was prompted by tumor-induced pain in 10 patients, paralysis of the lower extremities in 2 patients, and radiological imaging abnormalities for postoperative follow-up purposes without symptoms in 16 patients. Six patients underwent spacer-related surgery prior to C-ion RT; three of these six underwent Gore-Tex sheet spacer-inserted surgery, two underwent pelvic floor reconstruction, and another underwent mesenteric covering surgery of the tumor. All patients received 73.6 Gy (RBE) in 16 fractions and completed C-ion RT, as scheduled. No patient received chemotherapy after C-ion RT as an adjuvant treatment. The median follow-up durations in all patients and surviving patients were 51.2 (range; 14.3–121.6) and 69.2 (range; 46.3–121.6) months, respectively. The follow-up rate at the time of analysis was 96.4%.

3.2. Clinical results

The median survival, local control, and progression-free times after C-ion RT were 75.6 months (95% CI 40.0–98.7 months), not reached, and 12.2 months (95% CI 6.4–27.1 months). The 3- and 5-year OS, LC, and PFS rates were 89% and 50% (95% CI 71–96% and 32–69.0%), 88% and 83% (95% CI 68–96% and 63–94%), and 30% and 23% (95% CI 16–49% and 10–42%), respectively (Fig. 2). Although the number of enrolled patients was smaller than planned, the hypothesis used to determine the number of patients who were enrolled in the current study was consistent with the results of the 3-year LC.

A total of 17 patients died during the follow-up period; of the 16 patients who died of rectal cancer, the cause of death in another patient was unknown. Four patients had local recurrence, and one patient had local recurrence with lymph node metastasis. Local recurrence was observed within three years after the initiation of C-ion RT. Sixteen

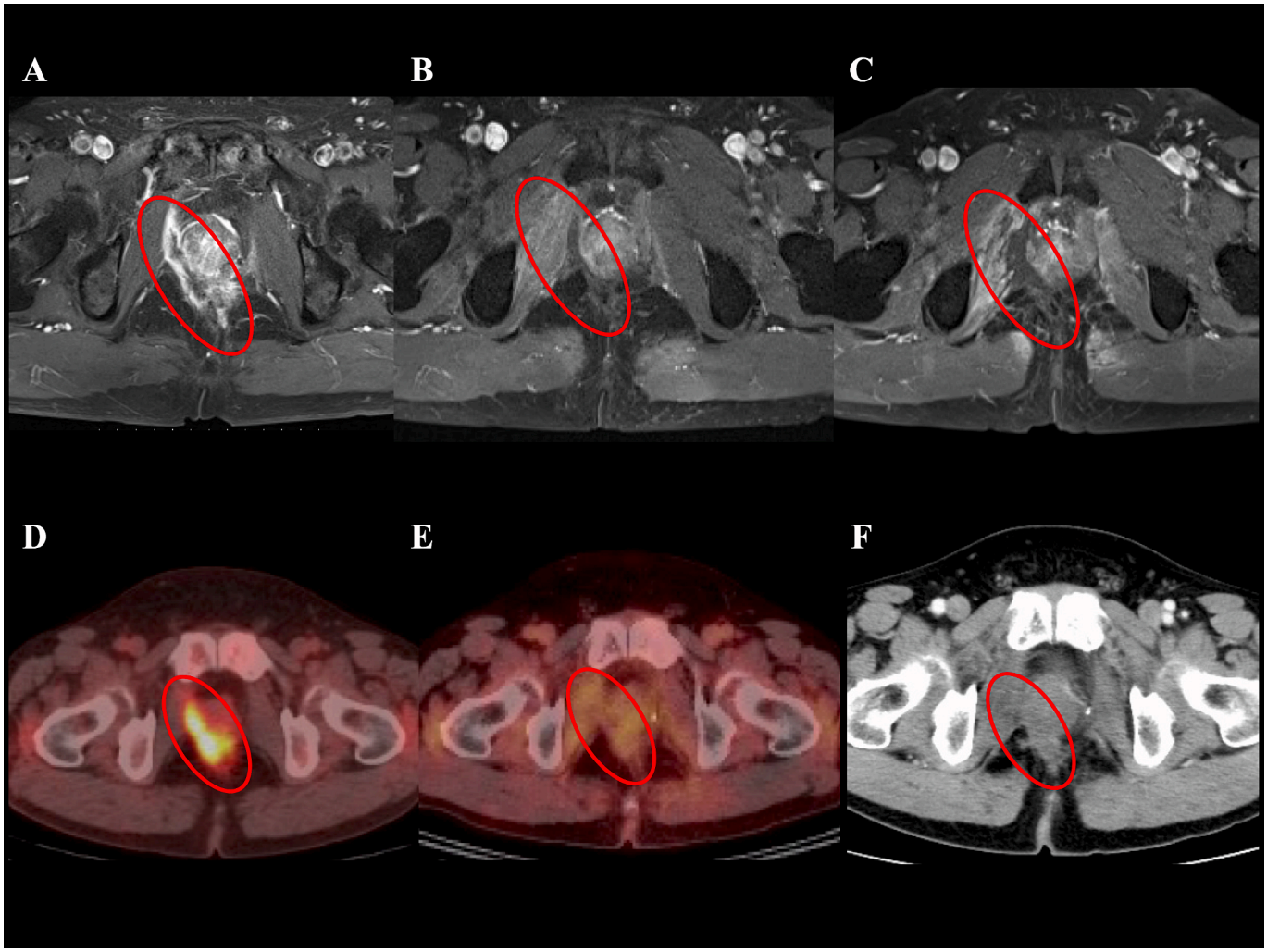

Fig. 3. The radiological image changes before and after C-ion RT for the same patient as in Fig. 1. (A) Gadolinium enhanced MRI before C-ion RT. The red circle shows the tumor with contrast enhancement. (B) Gadolinium enhanced MRI six months after C-ion RT. The red circle indicates the disappearance of the tumor. (C) Gadolinium enhanced MRI 12 months after C-ion RT. The red circle shows the continued disappearance of the tumor. (D) FDG-PET before C-ion RT. The red circle shows the tumor with abnormal FDG uptake. (E) FDG-PET six months after C-ion RT. The red circle shows the disappearance of abnormal FDG uptake. (F) CT 45 months after C-ion RT. The red circle shows the absence of tumor recurrence. C-ion RT, Carbon-ion radiotherapy; CT, computed tomography; FDG-PET, fluorodeoxyglucose positron emission tomography; MRI, magnetic resonance imaging. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

patients had lymph node or distant organ metastasis without local recurrence, and 12 patients developed lymph node or distant organ metastasis within one year after the initiation of C-ion RT. Fig. 3 shows the treatment response to C-ion RT in the case of postoperative perineal recurrence of rectal cancer. All patients who had pain and paralysis were able to control their symptoms with C-ion RT and medication (e.g., opioids, nonsteroidal anti-inflammatory drugs, and/or pregabalin).

3.3. Management of post-carbon-ion radiotherapy recurrences

Three of the four patients with local recurrence received salvage C-ion RT, and two of them received cytotoxic chemotherapy with molecular targeted therapy after salvage C-ion RT for local recurrence. The other patient underwent X-ray SBRT. Eleven of the 16 patients had lymph node or distant organ metastasis and received cytotoxic chemotherapy with or without molecular targeted therapy. Three patients received salvage C-ion RT for lymph node oligometastases, and one patient underwent surgery. Three patients received cytotoxic chemotherapy with or without molecular targeted therapy after salvage C-ion RT for lymph node oligometastases. A total of 16 patients received cytotoxic chemotherapy with or without molecular targeted therapy for recurrence after C-ion RT.

3.4. Toxicity

All acute toxicities have been previously reported [12]. All the

Table 2
Late toxicities graded by CTCAE, version 4.0 (n = 28).

	Grade, n				
Late non-hematological toxicities	0	1	2	3	4
Dermatitis	21	7	0	0	0
GI tract	27	1	0	0	0
Urinary	28	0	0	0	0
Neuropathy	10	9*	9**	0	0
Infection	26	0	0	2	0

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; GI, gastrointestinal tract.
*Three patients had peripheral neuropathy prior to carbon-ion radiotherapy.
**Four patients had peripheral neuropathy before the carbon-ion radiotherapy.

Table 3
Evaluation of prognostic factors for PFS.

Prognostic factors	Number			*P* value
	All	Tumor control	PFS failure	
Differentiation of pathology				
Well-differentiated	10	5	5	0.06
Moderately differentiated, mucinous	18	2	16	
Pathological stage				
I, II	13	5	8	0.20
III	15	2	13	
Duration from the date of surgery to initiation of C-ion RT				
<37 months	17	6	11	0.19
≥37 months	11	1	10	
CEA level before C-ion RT				
<10 ng/mL	13	4	9	0.67
≥10 ng/mL	15	3	12	
GTV				
<6 cm^3	9	5	4	0.02
≥6 cm^3	19	2	17	
Bone invasion before C-ion RT				
Negative	23	5	18	0.57
Positive	5	2	3	

Abbreviations: CEA, carcinoembryonic antigen; C-ion RT, carbon-ion radiotherapy; GTV, gross tumor volume; PFS, progression-free survival.

observed late toxicities are shown in Table 2. Two patients developed grade 3 pelvic infections six and 17 months after the initiation of C-ion RT. The details of both patients have been described [12]. Nine patients developed grade 2 peripheral neuropathy, four of whom had peripheral neuropathy before initiating C-ion RT. All patients who developed grade 2 peripheral neuropathy were symptomatic with neuralgia and were treated with medication.

One patient who received salvage C-ion RT for local recurrence after C-ion RT developed grade 3 toxicities, although these toxicities were not counted because the onset of these toxicities developed after re-irradiation had been performed. This patient was a 51-year-old man who experienced a sidewall in-field recurrence of rectal cancer 36 months after C-ion RT. Local recurrence occurred as the recurrent tumor was unresectable, and the patient received re-irradiation with C-ion RT of 57.6 Gy (RBE) in 12 fractions. After 83 months of re-irradiation with C-ion RT, the patient developed a pelvic abscess due to a rectal perforation in the irradiated area without local recurrence, requiring drainage and intravenous antibiotics.

3.5. *Prognostic factor analysis for progression-free survival*

We evaluated prognostic factors for PFS. The cut-off values for the duration from the date of surgery to initiation of C-ion RT, GTV, and CEA levels defined by the ROC graph were 37 months, 6 cm^3, and 10 ng/mL, respectively. Table 3 shows the results of the Fisher's exact test. GTV was the only significant prognostic factor for PFS.

4. Discussion

We performed an updated analysis from a prospective clinical trial of C-ion RT for postoperative pelvic recurrence of rectal cancer (GUNMA 0801) over a 5-year observation period with a 96.4% follow-up rate. The 5-year OS and LC rates were 50% and 83%, respectively. In addition, the current study found minimal toxicity. These results demonstrated the long-term efficacy and safety of C-ion RT for the postoperative pelvic recurrence of rectal cancer and the reproducibility of treatment effect and safety with C-ion RT was confirmed [11,15].

The present study showed no local recurrence three years after C-ion RT. A previous study by Yamada et al. reported similar local efficacy in the 70 Gy (RBE) or higher irradiation groups [15]. Therefore, three years after, C-ion RT would be a landmark for local effects. The clinical results of PFS were unsatisfactory, and many patients developed lymph node or distant organ metastases relatively early (i.e., within one year). We believe that systemic therapy after C-ion RT may be an option to improve PFS. According to the National Comprehensive Cancer Network guidelines, perioperative chemotherapy is recommended for pelvic recurrence of rectal cancer [16]. Furthermore, there have been reports of favorable clinical outcomes with X-ray RT combined with chemotherapy compared to X-ray RT alone; however, reports of combined treatment with RT and chemotherapy are limited [17]. There are no reports of systemic therapy after C-ion RT as an adjuvant treatment improving PFS or OS. Therefore, there is no established method of combining C-ion RT and chemotherapy for pelvic recurrence of rectal cancer. Still, adjuvant chemotherapy might improve the clinical results of C-ion RT for pelvic recurrence of rectal cancer. Further studies on the combination of C-ion RT and chemotherapy are required.

In the current study, there were two cases of grade 3 late toxicities, both of which have been described previously [12]. One patient who received salvage C-ion RT for local recurrence after C-ion RT developed rectal perforation and pelvic abscess, although these were not counted as toxicities in the current study. The site of perforation was the postoperative anastomotic rectum, which was irradiated twice with a summed maximum point dose of 93.5 Gy (RBE). Since we considered the rectal perforation as a result of re-irradiation, it was not directly related to the safety of the initial C-ion RT for pelvic recurrence of rectal cancer in this clinical trial. Similar to our prior research, our conclusion remains the same: initial C-ion RT can be safely performed for the pelvic recurrence of rectal cancer [12]. Therefore, other reports of C-ion RT for pelvic recurrence of rectal cancer with grade 3 or higher toxicity rates of 2–5% are comparable to the current study [11]. In contrast, further studies on re-irradiation with C-ion RT for recurrent pelvic tumors of post-C-ion RT are needed to determine its safety.

Factor analysis showed that only GTV (GTV ≥ 6 cm^3 showed worse PFS than GTV < 6 cm^3) was a significant prognostic indicator of PFS. In a previous study, tumor size was a prognostic factor for OS [11]. We believe that early detection before recurrent tumor size increases and early therapeutic intervention for recurrent tumors is necessary. There was also a trend toward worse PFS with the differentiation of pathology, with moderately differentiated or mucinous carcinoma compared to the well-differentiated type, but the difference was not statistically significant (Table 3). Patients with these exacerbating factors of a large GTV or pathological type with moderately differentiated or mucinous carcinoma may be considered for adjuvant therapy after C-ion RT as adjuvant chemotherapy.

A spacer may be surgically inserted between the tumor and GI tract to physically separate them if they are in close proximity. In the current study, six patients underwent spacer insertion surgery before C-ion RT, and three of them underwent Gore-Tex sheet spacer insertion. These three patients were followed up for a long period after C-ion RT, and were safely treated without spacer-related toxicities. In contrast, Shinoto et al. reported spacer-related pelvic infection [11], and there is a risk of infection when a device such as Gore-Tex sheets is implanted in the body for a long period of time after treatment. However, a bioabsorbable polyglycolic acid (PGA) spacer, which was reduced to less than 10% of the thickness or volume within 32 weeks after insertion, was recently developed, and the mainstream spacer-placement options shifted from Gore-Tex sheets to PGA spacers in Japan to reduce the risk of infection [18]. Therefore, it would be preferable to treat cases in close proximity to the tumor and GI tract with PGA spacer insertion for safer treatment.

The current study has some limitations. First, we planned to analyze 35 patients, but only 28 were ultimately enrolled because another multicenter prospective trial evaluating the efficacy and safety of C-ion RT for postoperative pelvic recurrence of rectal cancer with the same eligibility criteria had been initiated. Additionally, the current study was a single-institution analysis with a small number of patients. Therefore, the safety and efficacy of postoperative C-ion RT may not have been sufficiently evaluated. Second, although the patients were observed for up to 5 years, it is possible that the follow-up duration was insufficient for some toxicities. However, we believe that the current study is valuable because it is one of the few studies that have reported on the long-term follow-up of patients who received C-ion RT.

In conclusion, we performed an updated analysis of a prospective clinical trial of C-ion RT for postoperative pelvic recurrence of rectal cancer and confirmed favorable long-term clinical outcomes. These results suggest that C-ion RT may be a safe and effective treatment option for the postoperative pelvic recurrence of rectal cancer.

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CRediT authorship contribution statement

Shintaro Shiba: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Visualization, Funding acquisition. **Masahiko Okamoto:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Visualization, Project administration. **Kei Shibuya:** Writing – review & editing. **Daijiro Kobayashi:** Writing – review & editing. **Yuhei Miyasaka:** Writing – review & editing. **Tatsuya Ohno:** Conceptualization, Methodology, Writing – original draft, Funding acquisition.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Tatsuya Ohno received research funding from Hitachi. All other authors declare no conflict of interest.

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