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Clinical Impact of Re-irradiation with Carbon-ion Radiotherapy for Lymph Node Recurrence of Gynecological Cancers

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Abstract. *Background/Aim: To evaluate the safety and efficacy of re-irradiation with carbon-ion radiotherapy (C-ion RT) for lymph node recurrence of gynecological cancers after definitive radiotherapy. Patients and Methods: Data regarding patients with unresectable and isolated recurrent lymph node from gynecological cancer after definitive radiotherapy were analyzed. Total dose of C-ion RT was 48-57.6 Gy (RBE) in 12 or 16 fractions. Results: Sixteen patients received re-irradiation by C-ion RT were analyzed. Median follow-up was 37 months. Median tumor size was 27 mm. None developed Grade 1 or higher acute toxicities and Grade 3 or higher late toxicities. The 3-year overall survival, local control and disease-free survival rates after C-ion RT were 74%, 94% and 55%, respectively. Conclusion: Re-irradiation with C-ion RT for lymph node recurrence of gynecological cancers after definitive radiotherapy can be safe and effective. This result suggested that C-ion RT could be a curative treatment option for conventionally difficult-to-cure patients.*

Gynecological cancers after definitive radiotherapy (RT) often recur. The first choice of treatment for a pelvic recurrence in the irradiated area has been surgery (1), but some of the patients could not undergo surgery for reasons such as location of the recurrence, being technically unresectable or refusing extirpative surgery. Radiotherapy was considered one of the treatment options for these patients. However, most of these patients need to take into consideration the possibility that normal tissues such as bowel might receive a high cumulative dose. Thus, these patients could not receive curative local treatment, instead selecting chemotherapy or best supportive care (1). Chemotherapy and best supportive care would not be expected to result in long-term survival. Kitagawa *et al.* reported median survival of stage IVB cervical cancer patients treated with paclitaxel plus cisplatin of 18 months, and that with paclitaxel plus carboplatin of 17 months (2). In addition, previous studies revealed that the response rate of recurrent tumor in the irradiated field for cervical cancer treated with chemotherapy was still approximately 30%, so it was difficult to cure with chemotherapy alone (3-5).

Carbon-ion (C-ion) beams improve the dose localization properties because their Bragg peak results in a distal-tail off and a sharp lateral penumbra. This property of C-ion beams provides a highly conformal dose distribution, and enables the delivery of a high dose to tumors while minimizing normal tissue damage. Moreover, C-ion beams possess a biological advantage due to their high linear energy transfer (LET) in the Bragg peak (6-9). Therefore, even for re-irradiation cases, C-ion RT was considered to deliver a sufficient dose to the tumor while normal tissues received a tolerable dose. Until now, there have only been a few reports

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of re-irradiation after definitive RT for lymph node recurrence (10). The current study analyzed re-irradiation with C-ion RT for lymph node recurrence of multiple cases of gynecological cancer after definitive RT. Thus, this retrospective study reported the safety and efficacy of re-irradiation with C-ion RT for lymph node recurrence of gynecological cancers after definitive RT.

Materials and Methods

Patients. The eligibility criteria of this retrospective study were as follows. 1) The patient had recurrent tumor from gynecological cancer after definitive radiotherapy. 2) There was only one lesion of recurrence within or at the edge of the previously irradiated field. 3) In principal, the distance between tumor and nearest intestinal tract was more than 10 mm. 4) The tumor was unresectable. 5) The patient had no other active malignancy.

Pretreatment evaluation for C-ion RT consisted of an assessment of the patient's history, routine blood cell counts, chemistry profile and chest X-ray, and computed tomography (CT) scans of the pelvis and abdomen were also performed for all patients. Magnetic resonance imaging (MRI) and positron emission tomography (PET) were performed if considered necessary. The treatment protocol for the current study was reviewed and approved by the National Institute of Radiological Sciences Ethics Committee of Human Clinical Research, and all patients signed an informed consent form before the initiation of therapy.

Carbon-ion radiotherapy. Carbon-ion beams were generated using the synchrotron at the National Institute of Radiological Sciences. Tailor-made fixation cushions and thermoplastic shells were used for the immobilization of patients for acquiring treatment-planning CT. After immobilization, respiratory-gated CT was performed. For targeting, the gross tumor volume (GTV) was identified as the obvious tumor by planning CT. The clinical target volume (CTV) was defined as GTV plus 5 mm. Bone, muscle and vessels were excluded from CTV. The planned target volume (PTV) was defined as CTV plus 3 mm. The radiation dose was calculated for the target volume and surrounding normal structures and was expressed in Gy (relative biological effect (RBE)), which was defined as the physical dose multiplied by RBE of C-ion (11). Total dose of C-ion RT was 48-57.6 Gy (RBE) in 12 or 16 fractions. This analysis was not a dose escalation study. The prescribed dose was changed in accordance with the time-line of C-ion RT, tumor size, and histological type. The patients registered between July 2008 and October 2009 were treated with 48 Gy (RBE) in 12 fractions, and those registered since April 2012 were treated with 52.8 Gy (RBE) in 12 fractions. Bulky tumors and radioresistant tumors such as mucinous adenocarcinoma and carcinosarcoma were treated with 57.6 Gy (RBE) in 12 or 16 fractions. As an exception, one squamous cell carcinoma 24 mm in size received 57.6 Gy (RBE) in 12 fractions because the dose to the intestinal tract could be reduced by insertion of a spacer. These doses were decided on the basis of other clinical trials and studies at that time (12-17). The dose to intestinal tracts was reduced as much as possible, setting on 20-30% or less of the prescribed dose.

Patients received C-ion RT once daily, 4 days per week (Tuesday to Friday). At every treatment session, the patient was positioned on the treatment couch with the tailored immobilization devices, and the patient's position was verified by computer-aided, on-line positioning system. Digital orthogonal X-ray images were taken and transferred to the positioning computer. These positioning images were compared with reference images that were digitally reconstructed from CT scans. If the difference in positioning was > 2 mm, the treatment couch was moved until an acceptable position was attained. Figure 1 shows the typical dose distribution for a patient with common iliac lymph node recurrence.

Assessment of toxicity and efficacy. After completion of C-ion RT, patients were followed up every 1-3 months for 2 years, and every 3-6 months thereafter. Acute toxicity was graded according to the Common Terminology Criteria for Adverse Events, version 4.0 (18), with the highest toxicity within 3 months from the initiation of C-ion RT. Late toxicity was graded according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme (19). Survival was measured from the date of initiation of C-ion RT to the date of death or most recent follow-up. Treatment effects were evaluated in terms of overall survival (OS), local control (LC) and disease-free survival (DFS). Local failure was evaluated as irradiated lymph node recurrence after C-ion RT. The effect of treatment was evaluated on the basis of tumor regrowth or recurrence according to CT, MRI and PET. OS, LC and DFS rates were calculated by Kaplan-Meier method. Log-rank test was used for statistical analyses performed with SPSS software, version 22 (SAS Institute, Tokyo, Japan). Statistical significance was defined as a p-value <0.05.

Results

Between July 2008 and October 2016, 16 patients were enrolled in this study. Patient characteristics were summarized in Table I. Median follow-up of all patients was 37 months (range= 3-104 months). The data of this study were analyzed in May 2017. Median age at the time of registration for C-ion RT was 57 years (range=35-79 years), and median tumor size was 27 mm (range=14-80 mm). Initial treatment consisted of surgery in 11 patients, RT alone in 1 patient, and concurrent chemoradiotherapy in 4 patients. All patients had received RT as part of the initial treatment or treatment of postoperative recurrence. Three patients received surgical spacer placement by open surgery to keep intestinal tracts apart from the tumor, as the distance between tumor and nearest intestinal tracts was not sufficient. Median distance between tumor and the nearest intestinal tract was 12 mm (range=10-27 mm) except for the 3 patients with inserted spacer. Total dose of C-ion RT was 48 Gy (RBE) in 12 fractions for 4 patients, 52.8 Gy (RBE) in 12 fractions for 8 patients, 57.6 Gy (RBE) in 12 fractions for 3 patients, and 57.6 Gy (RBE) in 16 fractions for 1 patient. The median D2cc of the intestinal tract was 7.3 Gy (RBE) (range=1.2-47.4 Gy (RBE)). There were some cases with evaluated D2cc of the intestinal tract. Their tumors were recurrences from the edge of the previously irradiated field. The intestinal tracts near the tumor had not been exposed to the full dose of prior radiotherapy. Additionally, their follow-up duration was more than 60 months, and none of these 4 cases developed

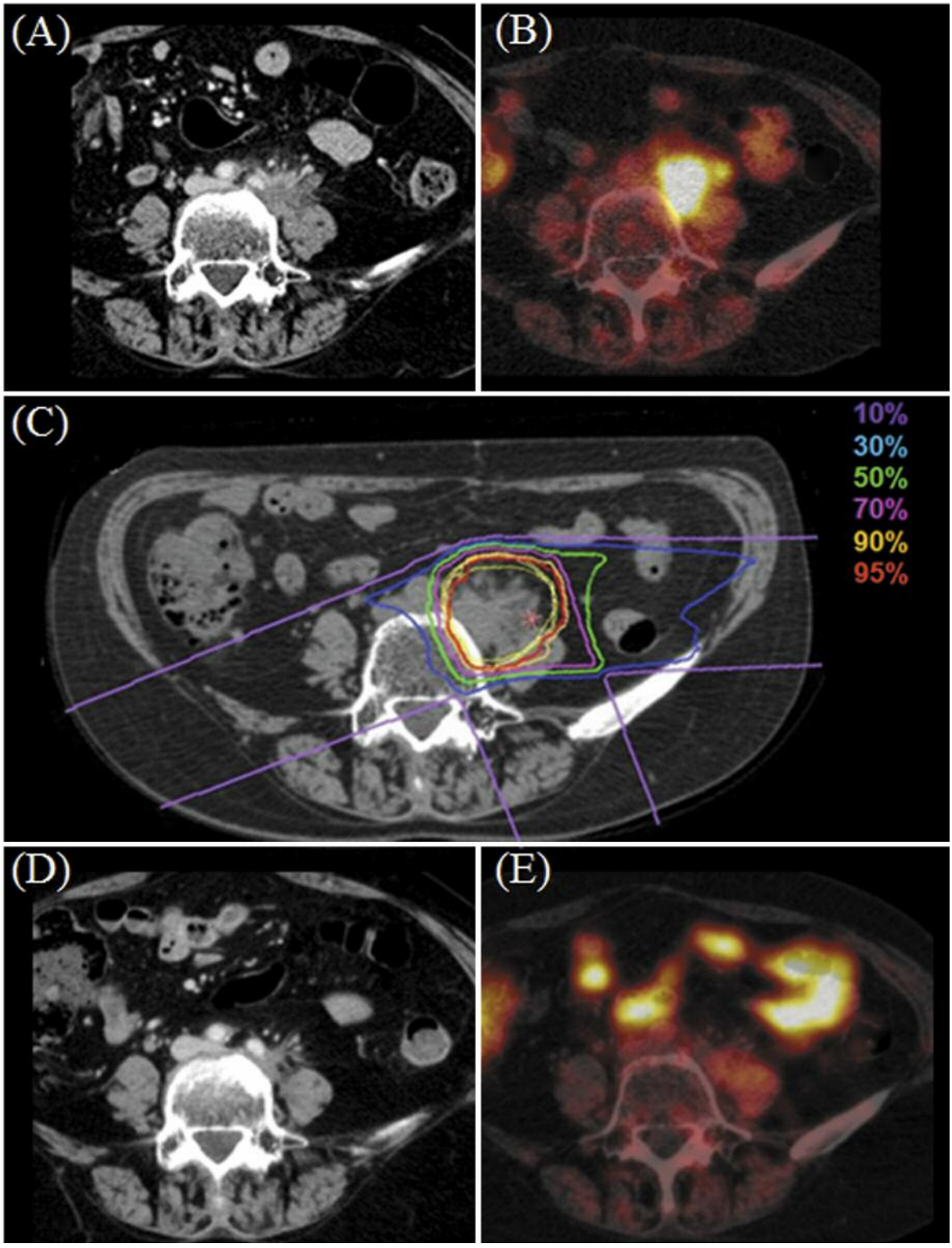

Figure 1. *Common iliac lymph node recurrence with cervical cancer. (A) Enhanced axial CT image shows enlarged lymph node in left iliac area. (B) Axial FDG-PET image shows abnormal FDG uptake corresponding to enlarged common iliac lymph node. (C) Dose distribution of C-ion RT for common iliac lymph node recurrence. Isodose curves of C-ion RT are superimposed on an axial CT image for the total irradiation plan. Highlighted are 95% (red), 90% (orange), 70% (pink), 50% (green), 30% (blue), 10% (purple) isodose curves (100% was 52.8 Gy (RBE)). (D) Enhanced axial CT image 18 months after C-ion RT. (E) Axial FDG-PET image 12 months after C-ion RT shows no abnormal FDG uptake.*

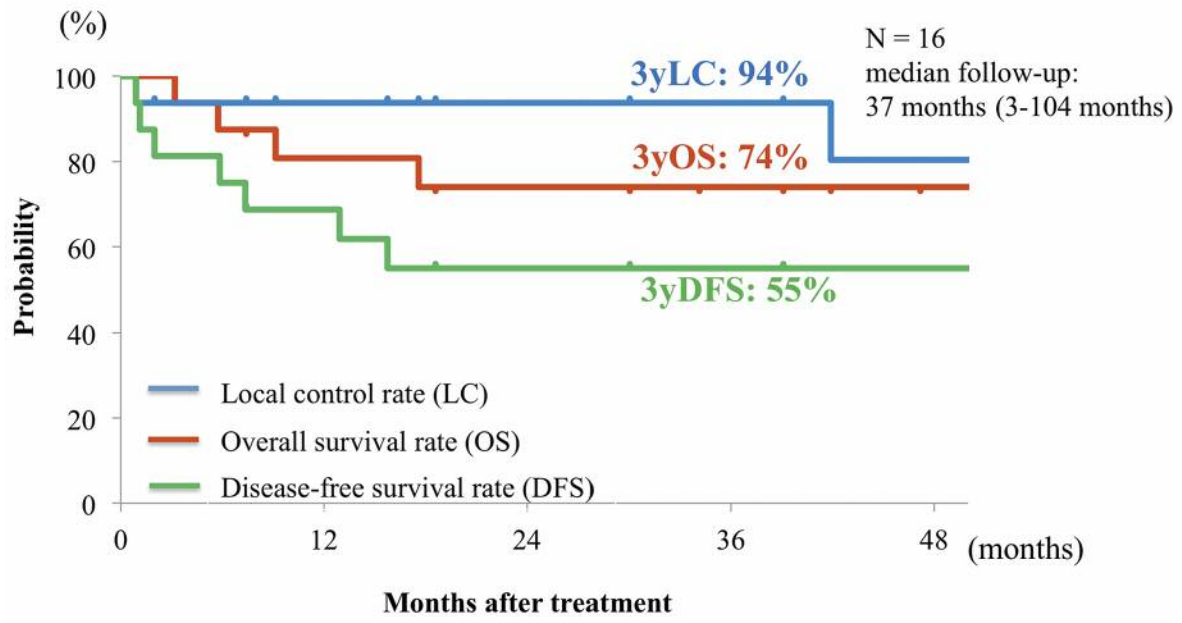

Figure 2. *Overall survival, local control, and disease-free survival curves. Overall survival (red line), local control (blue line), and disease-free survival (green line) of all patients treated with C-ion RT are shown.*

severe toxicities. All patients completed the treatment and no acute toxicities were observed. All observed late toxicities are listed in Table II. No patients developed Grade 3 or higher late toxicities. The 3-year OS, LC and DFS rates and 95% confidence interval (CI) after C-ion RT were 74% (95%CI, 48-90%), 94% (95%CI, 66-99%) and 55% (95%CI, 31-77%), respectively (Figure 2). Two patients had local recurrence, and 7 patients had distant metastases (Table I).

Discussion

The current study showed no severe toxicities and good local control with C-ion RT for lymph node recurrence of gynecological cancers after definitive RT. Thus, C-ion RT appears to be a safe and effective treatment, and could be expected to represent a curative treatment option for these patients.

Recurring tumors of the pelvic or para-aortic lymph node area within or at the edge of a previously irradiated field were often in close proximity to the intestinal tract. Severe toxicities could result if the initial and second radiation fields were overlapped on normal tissues such as the bowel, as the cumulative dose surpasses the tolerance dose. Park *et al.* reported stereotactic body RT (SBRT) for recurrent or oligometastatic cervical cancer (20). They reported that 68 of 100 sites were re-irradiation cases, and that the 2-year local progression-free survival rate was 60.2% in the re-irradiation group. Re-irradiation was related to inferior local control, but the dose of SBRT for the re-irradiation group was far less than the dose for other groups. As for toxicities, 5 patients developed Grade 3 or higher. It was considered that normal tissues were exposed to higher than tolerance doses. This result suggested that, in some re-irradiation of recurrent or oligometastatic tumor cases, SBRT with X-rays could not deliver a curative dose.

In terms of dose constraints for initial RT, in the 50-Gy irradiated small bowel, late toxicities of obstruction or perforation rates were reported to be 2% to 9% (21). Furthermore, to reduce Grade 3 or higher late rectal toxicity, rectal V50, V60, V65, V70 and V75 were limited to less than 50%, 35%, 25%, 20% and 15%, respectively (22). Although standard-dose constraints for re-irradiation with C-ion RT had not been established, it was considered that the cumulative dose should not exceed the dose constraint of initial RT. In cases of tumor and intestinal tract being in close proximity, staying within the dose constraint was difficult, and therefore such patients were treated with chemotherapy or best supportive care. In the current study, even though the tumor was near the intestinal tract, all patients completed the treatment course safely, and there were no acute toxicities or Grade 3 or higher late toxicities by re-irradiation with C-ion RT. Thus, C-ion RT could be considered a safe and effective treatment for cases with re-irradiation of conventionally difficult curative RT because of overlapped initial and second radiation fields.

Recently, the concept of oligometastases was proposed. It was shown that a few distant metastases, as the concept of oligometastases, given adequate local treatment, resulted

Table I. *Patient characteristics and clinical outcomes.*

Case	Primary site, Stage	Histology	Initial treatment	Dose of prior RT	Duration of prior RT to C-ion RT (months)	Tumor size (mm)	Dose of C-ion RT	Recurrence
1	Cervical cancer, T2bN1M0	Squamous cell carcinoma	CCRT	50 Gy/25 fr.	26	33	48 Gy (RBE)/12 fr.	NER
2	Cervical cancer, T2aN0M0	Squamous cell carcinoma	RT alone	50 Gy/25 fr.	25	28	48 Gy (RBE)/12 fr.	NER
3	Endometrial cancer, T1N0M0	Endometrioid adenocarcinoma	Surgery	50 Gy/25 fr.	68	25	48 Gy (RBE)/12 fr.	NER
4	Cervical cancer, T4N0M0	Squamous cell carcinoma	CCRT	50 Gy/25 fr.	26	14	48 Gy (RBE)/12 fr.	LN metastasis
5	Cervical cancer, T1b1N0M0	Squamous cell carcinoma	Surgery	66 Gy/33 fr.	11	33	52.8 Gy (RBE)/12 fr.	NER
6	Endometrial cancer, T3aN0M0	Carcinosarcoma	Surgery	60 Gy/30 fr.	12	20	57.6 Gy (RBE)/12 fr.	LN metastasis
7	Cervical cancer, T3bN1M0	Squamous cell carcinoma	Surgery	50 Gy/25 fr.	17	15	52.8 Gy (RBE)/12 fr.	Local recurrence, LN and Lung metastases
8	Cervical cancer, T2bN1M0	Squamous cell carcinoma	CCRT	50.6 Gy/27 fr.	33	24	57.6 Gy (RBE)/12 fr.	LN metastasis
9	Endometrial cancer, T3bN1M0	Endometrioid adenocarcinoma	Surgery	50 Gy/25 fr.	20	80	57.6 Gy (RBE)/16 fr.	Local recurrence
10	Cervical cancer, T2aN0M0	Squamous cell carcinoma	CCRT	46 Gy/23 fr.	77	30	52.8 Gy (RBE)/12 fr.	NER
11	Ovarian cancer, T1bN0M0	Serous adenocarcinoma	Surgery	56 Gy/28 fr.	40	18	52.8 Gy (RBE)/12 fr.	Lung metastasis
12	Endometrial cancer, T3aN0M0	Endometrioid adenocarcinoma	Surgery	50 Gy/25 fr.	130	22	52.8 Gy (RBE)/12 fr.	NER
13	Endometrial cancer, T1bN0M0	Small cell carcinoma	Surgery	54 Gy/27 fr.	17	75	52.8 Gy (RBE)/12 fr.	Lung metastasis
14	Cervical cancer, T1bN0M0	Mucinous adenocarcinoma	Surgery	50.4 Gy/28 fr.	21	38	57.6 Gy (RBE)/12 fr.	NER
15	Endometrial cancer, T1bN0M0	Endometrioid adenocarcinoma	Surgery	58.6 Gy/32 fr.	29	42	52.8 Gy (RBE)/12 fr.	Liver metastasis
16	Cervical cancer, T1bN1M0	Squamous cell carcinoma	Surgery	50 Gy/25 fr.	64	20	52.8 Gy (RBE)/12 fr.	NER

CCRT, Concurrent chemoradiotherapy; C-ion RT, carbon-ion radiotherapy; fr., fractions; LN, lymph node; NER, no evidence of recurrence; RT, radiotherapy.

in longer survival. Niibe *et al*. reported the clinical outcomes of initial RT for para-aortic lymph node recurrence of uterine cervical cancer as single-site tumor progression, and they had 3-year and 5-year OS rates of 50% and 31%, respectively (23). They suggested that initial RT for isolated para-aortic recurrence in uterine cervical cancer could achieve longer survival. However, there was no evidence that re-irradiation for isolated lymph node recurrence achieves longer survival. In the current study, with a limited the number of 16 patients, the 3-year OS and LC rates were 74% and 94%. This result was comparable or better than that of initial RT for oligometastases (24-26). The current study suggested that better local control of re-irradiation with C-ion RT for isolated lymph node recurrence achieved longer survival.

Table II. *Late toxicities by RTOG/EORTC scoring scheme (N=16).*

Organs involved	G0	G1	G2	G3	G4
Gastrointestinal tract	14	2	0	0	0
Urinary tract	15	1	0	0	0
Leg edema	15	0	1	0	0
Lower extremity nerve	14	2	0	0	0

RTOG/EORTC, Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer.

Several studies reported X-ray-induced radioresistance in various cancer cell lines (27-31). It was considered that recurrent tumors after RT possibly developed due to X-ray-

induced resistance to RT. C-ion RT was expected to achieve a better therapeutic effect than X-rays against radioresistant tumors, as C-ion beams possess a biological advantage due to their higher LET, which is considered to have contributed to a better LC (32, 33).

The distance between tumor and nearest intestinal tract was one of the limitations of the current study. Kato *et al.* and Matsushita *et al.* reported that a dose over 60 Gy (RBE) had a high risk of intestinal perforation (12, 34). The prescribed dose in the current study was 48-57.6 Gy (RBE). If the intestinal tract would be exposed to the full dose of C-ion RT, this dose added to that of prior RT would exceed the tolerable dose for the intestinal tract. Thus, an eligibility criterion of the current study was a distance between tumor and nearest intestinal tract of more than 10 mm. This distance setting of 10 mm was based on the properties of C-ion beams reported by Kanai *et al.* (7) and Sihver *et al.* (35). Kanai *et al.* measured the size of the penumbra and reported that the distance from the position of 80% dose level to that of 20% level was around 2-3 mm in a water phantom in 60 mm SOBP of 290 MeV/u C-ion beams. Sihver *et al.* measured the dose as a function of depth, reporting that the fragment tail attenuated to about 10% of the Bragg peak 2 mm on the distal side of the Bragg peak in a water phantom in a monoenergetic primary beam of 270 MeV/u C-ion. As a result, the median D2cc of the intestinal tract was 7.3 Gy (RBE), and there were no severe toxicities within the follow-up duration. Hence, the safety of the present study was confirmed by DVH parameter when the distance between tumor and nearest intestinal tract was set to 10 mm.

Recently, a gore-tex patch was surgically placed as spacer to cover the distance between intestinal tract and tumor. Fukumoto *et al.* reported the clinical benefit of surgical spacer placement for advanced abdominal leiomyosarcoma treated with particle beam therapy (35). In the case of re-irradiation and/or after surgery, it is sometimes difficult to place a spacer because of wide intestinal adhesion. However, if patients could receive surgical spacer placement, it would be possible to create a sufficient distance between intestinal tracts and tumor. This means that a sufficient dose of C-ion RT could be delivered to the tumor without causing severe toxicities. In this way, although the distance between the tumor and the nearest intestinal tract is close, the patient might become treatable with C-ion RT.

In conclusion, re-irradiation with C-ion RT could meet expectations as a curative treatment option for conventionally difficult-to-cure patients. Although re-irradiation with C-ion RT for LN recurrence of gynecological cancers after definitive RT showed favorable results, the present study has several limitations, including its retrospective nature with the small number of patients analyzed, as well as the short follow-up period. Further research is required to identify the long-term safety and efficacy for a larger number of patients.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

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