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Original Article

# Carbon-ion radiotherapy for locally recurrent rectal cancer: Japan Carbon-ion Radiation Oncology Study Group (J-CROS) Study 1404 Rectum

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ABSTRACT

*Purpose:* We investigated the efficacy and safety of carbon-ion radiotherapy (C-ion RT) for locally recurrent rectal cancer (LRRC).

*Patients and methods:* Data from patients with LRRC treated with C-ion RT from November 2003 to December 2014 at three institutions were retrospectively analyzed. The endpoints of this clinical trial were overall survival (OS), local control (LC), and acute/late toxicity.

*Results:* A total of 224 patients' data were collected. The prescribed dose was 70.4 Gy (relative biological effectiveness [RBE]-weighted absorbed dose) or 73.6 Gy (RBE) in 16 fractions. The median follow-up period from the initiation of C-ion RT was 62 months (range 6–169 months). The OS rates were 73% (95% confidence interval [CI], 67%–79%) at 3 years and 51% (95%CI 44%–58%) at 5 years. The LC rates were 93% (95%CI 88%–96%) at 3 years, and 88% (95%CI 82%–93%) at 5 years. Grade 3 acute toxicity was observed in three patients: gastrointestinal toxicity ($n = 1$) and pelvic infection ($n = 2$). Grade 3 late toxicity was observed in 12 patients: skin reaction ($n = 2$), gastrointestinal toxicity ($n = 2$), neuropathy ($n = 1$), and pelvic infection ($n = 7$). There was no grade 4 or 5 acute or late toxicity.

*Conclusions:* This first multi-institutional analysis of C-ion RT for LRRC indicated relatively favorable outcomes with limited toxicities.



The incidence of locally recurrent rectal cancer (LRRC) has decreased due to the progression of surgical techniques and the use of preoperative radiotherapy for rectal cancer. However, 5%–11% of patients with rectal cancer still develop LRRC after primary surgery [1]. Although a small number of patients develop LRRC, their prognosis is poor, with 5-year survival rates of <10% if curative surgery is not performed [2]. Surgery has been the only treatment with curative potential, but less than one-sixth of patients with LRRC can undergo R0 resection [3]. LRRC is often associated with severe symptoms, some of which may be alleviated by palliative radiotherapy. Unlike primary rectal cancer, LRRC is relatively radioresistant due to its large hypoxic cell fraction [4,5]. In addition, the proximity of LRRC to nearby radiosensitive organs such as the gastrointestinal tract and bladder precludes the administration of effective high radiation doses to the tumor.

With the development of current radiation techniques such as intensity-modulated radiotherapy (IMRT), stereotactic body radiotherapy (SBRT), and proton and carbon-ion radiotherapy (C-ion RT), higher radiation doses can be delivered with precision to tumors. Several studies have shown a positive relationship between the radiation dose and clinical outcomes [6–9]. The possibility of escalating the dose to LRRC without increasing the dose to surrounding normal tissues should therefore be explored.

Compared to photon therapy and proton therapy, C-ion RT offers unique physical and biological advantages that deliver a more conformal dose distribution to the tumor and a better biological effect due to a higher linear energy transfer [10,11]. A dose-escalation clinical trial of C-ion RT for LRRC was conducted in 2016 and showed excellent clinical results with limited toxicities [12]. As the number of facilities worldwide that could conduct C-ion RT was very small at that time, only that single report on C-ion RT for LRRC from a single institution has been available. However, the current number of C-ion RT facilities has increased slightly; five such institutions are now in operation in Japan, which

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led to the creation of the Japan Carbon-ion Radiation Oncology Study Group (J-CROS). Here we report the results of the first multi-institutional retrospective study evaluating the efficacy and safety of C-ion RT for LRRC.

## Patients and methods

### *The Japan Carbon-ion Radiation Oncology Study Group (J-CROS)*

The J-CROS is a study group including all five C-ion RT institutions currently operating in Japan. The following three institutions participated in this multi-institutional study on LRRC: the National Institute of Radiological Sciences (NIRS, Chiba), the Gunma University Heavy Ion Medical Center (GHMC, Gunma), and the Ion Beam Therapy Center, SAGA HIMAT Foundation (HIMAT, Saga). The other two institutions were not part of this study because a carbon-ion beam was not used for LRRC at the institutions due to accelerator specification issues and because the treatment had not yet started during the study period (Nov. 2003 to Dec. 2014). This study was conducted with the approval of Institutional Review Board of each C-ion RT facility and carried out in accordance with the Declaration of Helsinki.

### *Patient eligibility*

Patients with LRRC treated with C-ion RT during the period November 2003 to December 2014 at one of the three institutions were eligible for this retrospective study. The eligibility criteria were as follows: (1) confirmed localized recurrence of a pelvic lesion after surgery for primary rectal cancer, (2) had rectal adenocarcinoma or adenosquamous cell carcinoma, (3) a radiographically measurable tumor, $\leq$15 cm, (4) a performance status $\leq$2, (5) having preserved organ functions, (6) no contact between the recurrent tumor and the digestive tract or bladder, and (7) no active infection at the tumor site. Patients who received prior radiotherapy were also considered as candidate for C-ion RT if the dose of organ at risk did not exceed the limitation of dose constrain. Chemotherapy before and after C-ion RT was not prohibited.

### *Carbon-ion radiotherapy*

The details of C-ion RT techniques were approximately the same as those described [12]. Each patient was positioned in a customized cradle and immobilized with a low-temperature thermoplastic sheet. A set of 2.0- to 5.0-mm-thick CT images was taken for three-dimensional treatment planning using a HiPLAN or Xio-N system. Irradiation was performed daily, 4 days a week (Tuesday through Friday) for a total of 16 fractions in 4 weeks. The radiation dose was expressed as the photon-equivalent dose in Gy (i.e., the relative biological effectiveness [RBE]-weighted absorbed dose) and was defined as the physical dose multiplied by the carbon-ion RBE [13].

The clinical target volume (CTV) included a 5-mm margin around the gross tumor volume and a prophylactic internal iliac node area in some cases of pelvic sidewall recurrence. The planning target volume (PTV) had a margin of 3–5 mm added around the CTV. Dose constraints for the bladder and intestines were 60 Gy (RBE) and 50 Gy (RBE), respectively. All treatments were performed with only C-ion RT, and concurrent chemotherapy was not used.

### *Follow-up and statistical analyses*

Patients were seen approx. every 3–4 months after their C-ion RT. The follow-up consisted of a physical examination, CT, MRI, and PET. Local recurrence was defined as the enlargement of the tumor inside the full-dose irradiation field. 'Regional recurrence' was defined as a new tumor in the pelvic region other than the full-dose irradiation field. The endpoints of this study were overall survival (OS), local control (LC), and acute/late toxicity. The regional control (RC) and distant metastasis-free survival (DMFS) rates were also calculated. The OS, LC, RC, and DMFS rates were calculated from the initiation date of C-ion RT and were determined by the Kaplan–Meier method.

The log-rank test was used for the univariate analyses. All factors with significant associations in the univariate analysis were included in the multivariate analysis using the Cox proportional hazards regression model. Values of $p < 0.05$ were considered significant. Statistical calculations were performed using Prism 5 (GraphPad Software, San Diego, CA) and JMP 8 software (SAS, Cary, NC). Toxicity was graded according to the Common Terminology Criteria for Adverse Events (ver. 4.0).

## Results

### *Patient characteristics*

The total number of enrolled patients from all three institutions was 224 (NIRS: $n = 200$, GHMC: $n = 21$, HIMAT: $n = 3$). The treatment of eligible patients for this study started since November 2003 in NIRS, October 2011 in GHMC, and May 2014 in HIMAT. This analysis included the phase 2 data (n = 143) in the previous clinical trial reported from NIRS [12]. All patients in this analysis had completed the scheduled C-ion RT. The patients' characteristics are summarized in Table 1. Their median age was 62 years (range 28–80 years). The median tumor size was 30 mm (range 10–100 mm). The median disease-free time from surgery for primary rectal cancer was 29 months (range 3–131 months). Of the 224 patients, 220 received 73.6 Gy (RBE) in 16 fractions; the other four patients received 70.4 Gy (RBE) in 16 fractions. In 43 patients (19%), surgical spacer placement was performed to spare the tumor from the organs at risk before the C-ion RT. Three patients had undergone previous radiotherapy of 50 Gy for the relevant recurrent tumors.

### *Treatment outcomes*

The median follow-up period form the initiation of C-ion RT was 62 months (range 6–169 months). Recurrence after C-ion RT was

**Table 1**
Characteristics of the 224 patients with LRRC.

| Characteristic | |
|---|---|
| Gender | |
| Male | 159 (71%) |
| Female | 65 (29%) |
| Age, years; median (range) | 62 (28–80) |
| Pathologic subtype: | |
| Adenocarcinoma | 217 (97%) |
| Mucinous adenocarcinoma | 6 (3%) |
| Adenosquamous cell carcinoma | 1 (0%) |
| Tumor size, mm; median (range) | 30 (10–100) |
| CEA, U/mL; median (range) | 6.1 (0.3–456.2) |
| Disease-free time from surgery, months; median (range) | 29 (3–131) |
| Spacer placement: | |
| Yes | 43 (19%) |
| No | 181 (81%) |
| Prescribed dose: | |
| 70.4 Gy (RBE) in 16 fractions | 4 (2%) |
| 73.6 Gy (RBE) in 16 fractions | 220 (98%) |

UICC: Union for International Cancer Control.

observed in 152 patients (68%), of whom 18 (8%) had a local recurrence, 72 (32%) had a regional recurrence, and 114 (51%) had distant metastases. The LC and regional control rates were 93% (95% confidence interval [CI], 88%–96%) and 63% (95%CI 56%–70%) at 3 years, and 88% (95%CI 82%–93%) and 49% (95%CI 40%–57%) at 5 years, respectively (Fig. 1). The OS rate was 73% (95%CI 67%–79%) at 3 years, and 51% (95%CI 44%–58%) at 5 years, respectively (Fig. 2). The distant metastasis free survival rate was 40% (95%CI 34%–48%) at 3 years and 27% (95%CI 21%–35%) at 5 years, respectively. The 2-year LC and OS in 3 institutions were 94% and 88%, 94% and 94%, and 94% and 100%, respectively. There was no significant difference among the institutions.

Our analysis of the patients' prognoses revealed that in the univariate analysis for LC, no factors had a significant effect on the LC rate, including gender, age, tumor size, CEA, disease-free time, pathologic subtype, spacer placement, and prescribed dose. However, the tumor size and the disease-free time were significant factors affecting the patients' OS. In the multivariate analysis of these two factors using a Cox proportional hazards model, both smaller size of tumor, i.e., <30 mm ($p = 0.014$) and longer disease-free period, i.e., ≥12 months ($p = 0.007$) were associated with significantly better OS (Table 2).

### *Toxicities*

Grade 3 acute toxicities were observed in three (1%) of the 224 patients: gastrointestinal reaction ($n = 1$) and pelvic abscess ($n = 2$). The two patients with pelvic abscesses had infections due to surgical spacer placement before C-ion RT. Grade 3 late toxicities were observed in 12 patients (5%): skin reaction ($n = 2$), gastrointestinal reaction ($n = 2$), peripheral nerve reaction ($n = 1$), and pelvic abscess ($n = 7$). The seven patients who had a pelvic abscess had also undergone a spacer insertion before C-ion RT. There was no grade 4 or more acute or late toxicity (Table 3).

## Discussion

This was the first multi-institutional retrospective study to investigate the clinical results of C-ion RT for LRRC. Our retrospective analyses revealed that the effectiveness and toxicity of C-ion RT for LRRC were comparable to those reported in the 2016 single-institutional study by Yamada et al. [12]. They reported that the post-C-ion RT LC rate of LRRC patients at 5 years was 88% at 73.6 Gy (RBE) in 16 fractions, and the 3-year and 5-year OS rates were 78% and 59% with the median follow-up time of 53.5 months. The clinical outcomes of our present patient series demonstrated that comparable data were obtained in a nationwide multi-institutional retrospective study in Japan even with longer follow up time than that in previous report. However, these results should be verified in large number of the patients in each institution.

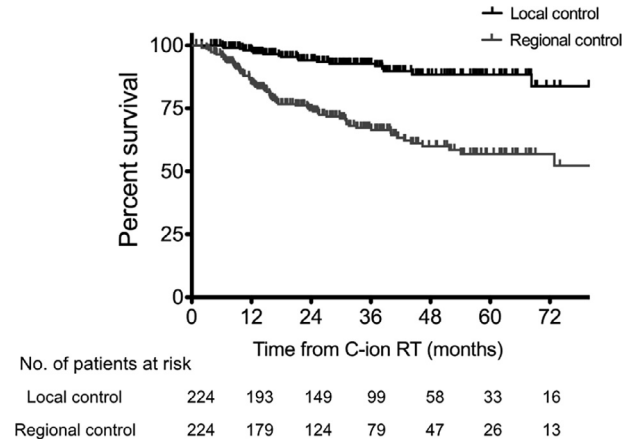


**Fig. 1.** Kaplan–Meier's estimates of local control and regional control rates calculated from the initiation of carbon-ion radiotherapy.

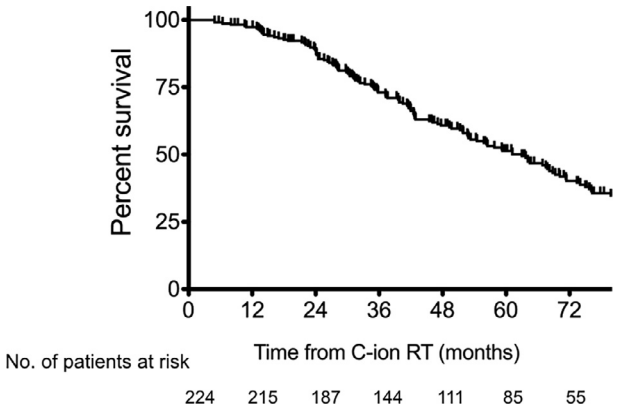


**Fig. 2.** Kaplan–Meier's estimates of the overall survival (OS) rate calculated from the initiation of carbon-ion radiotherapy.

Although rectal cancer is common worldwide, solitary LRRC after surgery is relatively rare. Patients undergoing R0 resection have the greatest survival advantage after surgery for recurrent rectal cancer [14,15]. However, the optimal treatment for this rare disease in patients who may not be good candidates for surgery has not been established. In most of these cases, systemic chemotherapy or chemoradiotherapy is chosen for palliative treatment. Unfortunately, local recurrence is resistant to conventional treatments and is often fatal.

Westberg et al. reported in a nationwide population-based study that (1) less than one-sixth of all patients with LRRC had a curative surgical tumor resection; (2) R0 resections were signifi-

**Table 2**
Univariate analysis for local control and overall survival.

| Factor | *n* | Local control UVA *p* | Overall survival UVA *p* | MVA *p* |
|---|---|---|---|---|
| Gender | | 0.142 | 0.687 | |
| Male | 159 | | | |
| Female | 65 | | | |
| Age | | 0.264 | 0.145 | |
| ≧62 | 122 | | | |
| <62 | 102 | | | |
| Tumor size | | 0.060 | 0.017 | 0.014 |
| ≧30 | 128 | | | |
| <30 | 96 | | | |
| CEA | | 0.813 | 0.473 | |
| ≧6.1 | 111 | | | |
| <6.1 | 110 | | | |
| Data missing | 1 | | | |
| Disease-free time (month) | | 0.572 | 0.002 | 0.007 |
| ≧12 | 193 | | | |
| <12 | 28 | | | |
| Data missing | 1 | | | |
| Pathologic subtype | | 0.830 | 0.133 | |
| Adenocarcinoma | 217 | | | |
| Others | 7 | | | |
| Spacer placement | | 0.206 | 0.447 | |
| Yes | 43 | | | |
| No | 181 | | | |

UVA: univariate analysis, MVA: multivariate analysis, RBE: relative biological effectiveness.

**Table 3**
Treatment-related acute and late toxicities.

| | Acute toxicity | | | Late toxicity | | |
|---|---|---|---|---|---|---|
| | Grade 2 *n* (%) | Grade 3 *n* (%) | Grade 4/5 *n* (%) | Grade 2 *n* (%) | Grade 3 *n* (%) | Grade 4/5 *n* (%) |
| Skin | 7 (3.1) | 0 | 0 | 1 (0.4) | 2 (0.9) | 0 |
| GI tract | 3 (1.3) | 1 (0.4) | 0 | 1 (0.4) | 2 (0.9) | 0 |
| Bladder | 2 (0.9) | 0 | 0 | 2 (0.9) | 0 | 0 |
| Pain | 0 | 0 | 0 | 17 (7.6) | 0 | 0 |
| Neuropathy | 2 (0.9) | 0 | 0 | 10 (4.5) | 1 (0.4) | 0 |
| Pelvic infection | 0 | 2 (0.9) | 0 | 2 (0.9) | 7 (3.1) | 0 |

GI: gastrointestinal.

cantly more common in centrally located tumors, and (3) R0 resection of the LRRC was the single most important factor influencing prognosis [16]. It can be difficult to achieve clear resection margins in tumors that have invaded the pelvic sidewall or posterior wall (i.e., at a non-central location). Centrally located LRRC tends to invade organs at risk such as the gastrointestinal tract and bladder. As a result, a centrally located LRRC with a good indication for surgery tends to be contraindicated for C-ion RT, because the higher dose exceeding the tolerance dose of organs at risk should be concentrated against the tumor in C-ion RT for LRRC. On the other hand, a non-central tumor tends to be apart from organs at risk, and it can therefore be a good candidate for C-ion RT. Considering the risks of mortality and morbidity following extensive surgical procedures, it would be reasonable to select C-ion RT for these non-centrally located tumors.

For comparisons of the anti-tumor effect of these prescribed doses by C-ion RT with those of other RT modalities, the prescribed doses can be converted to the biological effective dose with $\alpha/\beta = 10$ ($BED_{10}$). The prescribed doses of 70.4 Gy (RBE) and 73.6 Gy (RBE) in 16 fractions converted to $BED_{10}$ of 101.4 Gy (RBE) and 107.5 Gy (RBE), respectively. The equivalent dose in 2 Gy fractions ($EQD_2$) of the prescribed doses were also calculated as 84.5 Gy (RBE) and 89.5 Gy (RBE). Cai et al. reported that the 3-year LC and OS rates of patients who underwent IMRT with 45 Gy in 25 fractions ($BED_{10}$ of 53.1 Gy) for LRRC were 33.9% and 36.5%, respectively. This radiation dose intensity was almost one-half that of C-ion RT.

Tanaka et al. reported that the 3-year LC and OS rates of LRRC patients who underwent various dose fractions of radiotherapy ($BED_{10}$ at 48.0–95.2 Gy) were 19.6% and 45.2%, respectively. In their subset analysis, the LC rate was significantly higher in the high $BED_{10}$ group ($\geq$75 Gy) compared to the lower $BED_{10}$ group ($p = 0.0243$), and the 3-year OS rate for high $BED_{10}$ group was 64%. The radiation dose intensity would affect the LC and OS; however, dose escalation in this pelvic lesion with conventional photon therapy is not a simple matter because LRRC is always located close to critical organs. The most notable advantage of C-ion RT is that carbon ion beams can deliver a higher dose of $BED_{10}$ $\geq$100 Gy (RBE) to the tumor with a minimal dose to surrounding normal tissues due to the unique physical characteristics of C-ion RT. Regarding the difference between 70.4 Gy (RBE) and 73.6 Gy (RBE), there was no significance in LC in our cohort.

Cases in which the tumor is close to both critical organs and the pelvic wall can sometimes be contraindicated for surgery and C-ion RT. Surgical spacer placement using polytetrafluoroethylene and silicon has been reported as a procedure for separating the tumor from the bowel loop and safely increasing the delivered dose to the tumor and thus provide high doses to ensure adequate tumor control [17–19]. In our present series, 43 patients were able to benefit from the curative intent of C-ion RT by the insertion of a spacer. This type of surgical spacer placement is considered very helpful not only for C-ion RT but also for IMRT and SBRT, in which high doses are concentrated at the tumor.

With regard to toxicity, several patients in our study experienced grade 3 toxicities (including nine pelvic abscesses). Surgeons should be aware of the possibility of the development of infection after spacer insertion. In our patient series, the spacer insertion was performed in the limited number of cases in which the tumor contacted gastrointestinal tract. In cases of postoperative severe adhesion or a direct invasion of the tumor to the bowel, a bowel injury could occur during the surgical procedure, and this might cause pelvic infection. Among our patients, peripheral neuropathy and pain (especially related to the ischiatic nerve) were the most common treatment-related toxicities, though most of these cases were grade 1 or 2. When patients have already reported such symptoms due to tumor invasion before the initiation of C-ion RT, the symptom(s) and the injury of neurons by tumor invasion would not recover even after the tumor is cured. These patients might have to continue the use of analgesic drugs.

There are several limitations in this study. First, this was a retrospective analysis using observational data. Information regarding the status of the patients' initial stage and adjuvant chemotherapy at the first operation for primary rectal cancer was unavailable. Additionally, information related to the exact chemotherapy type and the duration for LRRC was unavailable. The patients' postoperative status and use/non-use of adjuvant chemotherapy, and the patients' sensitivity to chemotherapy could have influenced the OS and/or LC.

Second, this study lacked information on the patients' treatment after C-ion RT. It is also possible that adjuvant chemotherapy after C-ion RT and surgery or radiotherapy for the new/recurrent disease might have influenced the clinical outcomes. To validate our retrospective results, we are conducting a prospective multi-institutional clinical trial. That trial is expected to provide valuable information of the C-ion RT for LRRC.

In conclusion, the results of this multi-institutional study indicate that C-ion RT can provide LC and OS rates that are comparable to those of the prior single-institutional study of C-ion RT. The incidence of acute and late toxicities was also tolerable. C-ion RT should be considered as a definitive treatment, especially in unresectable LRRC cases.

## Conflict of interest statement

None.

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