

Single fraction carbon ion radiotherapy for colorectal cancer liver metastasis: A dose escalation study

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Prognosis is usually grim for those with liver metastasis from colorectal cancer (CRC) who cannot receive resection. Radiation therapy can be an option for those unsuitable for resection, with carbon ion radiotherapy (CIRT) being more effective and less toxic than X-ray due to its physio-biological characteristics. The objective of this study is to identify the optimal dose of single fraction CIRT for colorectal cancer liver metastasis. Thirty-one patients with liver metastasis from CRC were enrolled in the present study. Twenty-nine patients received a single-fraction CIRT, escalating the dose from 36 Gy (RBE) in 5% to 10% increments until unacceptable incidence of dose-limiting toxicity was observed. Dose-limiting toxicity was defined as grade ≥ 3 acute toxicity attributed to radiotherapy. The prescribed doses were as follows: 36 Gy (RBE) (3 cases), 40 Gy (2 cases), 44 Gy (4 cases), 46 Gy (6 cases), 48 Gy (3 cases), 53 Gy (8 cases) and 58 Gy (3 cases). Dose-limiting toxicity was not observed, but late grade 3 liver toxicity due to biliary obstruction was observed in 2 patients at 53 Gy (RBE). Both cases had lesions close to the hepatic portal region, and, therefore, the dose was escalated to 58 Gy (RBE), limited to peripheral lesions. The 3-year actuarial overall survival rate of all 29 patients was 78%, and the median survival time was 65 months. Local control improved significantly at ≥ 53 Gy (RBE), with a 3-year actuarial local control rate of 82%, compared to 28% in lower doses. Treatment for CRC liver metastasis with single-fraction CIRT appeared to be safe up to 58 Gy (RBE) as long as the central hepatic portal region was avoided.

KEYWORDS

carbon ion therapy, colorectal cancer, dose escalation study, liver metastasis, particle therapy

1 | BACKGROUND

Liver metastasis from colorectal cancer (CRC) is a commonly seen event in the treatment and care of CRC patients and usually follows a

lethal course. Liver resection is now the current standard treatment for local therapy of liver metastases.¹ Whereas survival after liver metastasis resection is favorable,²⁻⁵ prognosis is usually grim for those who cannot receive resection.⁶ Radiation therapy is an option for those

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who are unfit for hepatectomy. Promising results have been reported from stereotactic body radiation therapy (SBRT),⁷⁻⁹ although treating larger tumors becomes increasingly challenging. Radiofrequency ablation (RFA) has also shown promising results; however, large tumors and those close to vessels are prone to incomplete treatment, and, thus, increased local recurrence and higher toxicity.^{10,11}

Charged particle therapy, in particular carbon ion radiotherapy (CIRT), has a distinctive dose distribution due to the nature of charged particle beams.¹²⁻¹⁴ Delivering high doses to the tumor while sparing surrounding organs at risk is possible even in larger tumors using charged particle beams.¹⁵ Utilizing this advantage, we have been successfully treating primary liver tumors in 2 fractions with minimal toxicity.¹⁶ CIRT is also a high linear energy transfer (LET) modality and is known to have a higher biological effect compared to low-LET beams as in X-ray/ γ -ray.^{14,17} Our previous study on locally recurrent rectal cancer showed exceptional local control,¹⁸ as was the case for other radio-resistant tumors.^{19,20}

Based on these experiences, we have been conducting a prospective single-arm dose escalation study since 2006 for CRC liver metastasis using single fraction CIRT. We herein show the initial results of this study.

2 | MATERIALS AND METHODS

2.1 | Patient eligibility

This phase I clinical trial was approved by the National Institutes for Quantum and Radiological Sciences and Technology (also known as National Institute of Radiological Sciences [NIRS] at the time of approval) institutional review board.

This study included patients who: (i) had colorectal cancer liver metastasis diagnosed by radiological and clinical findings; (ii) had Eastern Cooperative Oncology Group performance status (ECOG PS) 0 to 2; (iii) had primary colorectal lesions and lymph node metastasis removed totally by surgery (R0 resection) at least 4 weeks prior to enrollment and primary lesions to be histologically proven as CRC; and (iv) had not received chemotherapy for at least 4 weeks prior to enrollment.

The present study excluded patients who: (i) had evident vascular invasion; (ii) had prior treatment to the specific lesion, (iii) had lesions close to the intestine (less than 5 mm), (iv) had uncontrollable ascites, (v) had severe liver damage, (vi) had active coexisting malignancy; (vii) had extra-hepatic lesions including local recurrence; and (viii) were pregnant.

No therapy other than carbon ion radiotherapy was administered until evidence of recurrence of any kind was observed. Any salvage treatment was allowed in cases of recurrence. Candidate patients were fully informed about the study and treatment.

2.2 | Carbon ion radiotherapy

The carbon ion beam used for radiotherapy was generated by the Heavy Ion Medical Accelerator in Chiba developed by NIRS in 1993.

The accelerator system and the biophysical characteristics of the carbon ion beam have been previously described.^{12,17,21} For modulation of the Bragg peak of the beam to conform to the target volume, the beam lines in the treatment room are equipped with a pair of wobbler magnets, beam scatterers, ridge filters, multi-leaf collimators and a compensation bolus.

Before therapeutic planning, all patients had metallic markers (iridium seeds, .5 mm in diameter and 3 mm in length, in-house made) implanted near the tumor to ensure precise treatment positioning. The irradiation fields were established with a 3-D therapy plan based on computed tomography (CT) images. The clinical target volume (CTV) was defined as equal to gross tumor volume. Planning target volume (PTV) was defined as CTV plus 10 mm margin. Dose constraint for intestines was set to 10 Gy (RBE) at D_{2cc} and the minimum volume of unirradiated liver was 500 cm³. To reproduce the target position accurately, a low-temperature thermoplastic sheet (Shellfitter, Kuraray, Osaka, Japan), a customized cradle (Moldcare, Alcare, Tokyo, Japan) and a respiratory gated irradiation system²² were used in the CT planning and radiotherapy. The radiation field was confirmed and corrected by orthogonal fluoroscopy and radiography immediately before the treatment session. Both bone and metallic markers were considered, with a tolerance up to 2 mm. In any case with larger deviations, radiation oncologists re-evaluated the treatment plan and whether it was robust enough.

Irradiation doses were expressed in Gray relative biological effectiveness (Gy (RBE) = carbon physical dose [in Gray] \times relative biologic effectiveness). The relative biologic effectiveness value of carbon ions was assumed to be 3 at the distal part of the spread-out Bragg peak.²³

2.3 | Dose escalation and toxicity criteria

Starting at 36 Gy (RBE), we escalated the dose in close communication with the protocol evaluation committee, which included surgeons, radiation oncologists and other physicians, all of whom were liver specialists. Outcomes from co-existing trials with similar site and dose fractionations were also taken into account. Increments were set generally to 5% after evaluating acute toxicity in 3 or more patients per cohort. The initial plan was to increase the dose up to 44 Gy (RBE) or until dose limiting toxicity (DLT) was observed. No specific dose constraint was specified in the planning of this trial: the dose to the intestine should not be an issue because cases close to the intestine were excluded. Clinically, however, the dose to intestines was confirmed to be below 15 Gy (RBE) at maximum dose. Dose limiting toxicity was set to treatment-related grade 3 or higher acute toxicity within the first 90 days after CIRT using the Radiation Therapy Oncology Group (RTOG) Acute Radiation Morbidity Scoring System or National Cancer Institute - Common Toxicity Criteria (NCI-CTC) for toxicity not related to liver functions and the following for liver function toxicities. Grade 4 was assigned for aspartate transaminase, alanine transaminase and prothrombin time, and grade 3 and higher for albumin and total bilirubin based on NCI-CTC. Late

toxicity was evaluated using the RTOG/European Organization for Research and Treatment of Cancer Late Radiation (EORTC) Morbidity Scoring System. Any toxicity with an onset of 91 days after the treatment was considered as late toxicity.

2.4 | Tumor response and local control criteria

All patients were assessed according to a predetermined schedule. After carbon ion radiotherapy, patients were evaluated based on physical examinations and blood tests once a month for the first year, once every 3 months for the following year, and once every 3-6 months thereafter. Contrast-enhanced CT or MRI was performed every 3 months for the first 2 years and every 6 months thereafter. Local control was defined as no sign of regrowth or new tumor in the treatment volume per imaging studies. Local recurrence was defined as failure of local control. Initial tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors 1.0 at 6 months after carbon ion radiotherapy.

2.5 | Endpoints

As a dose escalation study, primary endpoints were acute toxicity and initial tumor response. Secondary endpoints were late toxicity, local control and overall survival.

2.6 | Statistics

Statistical analysis was performed using R software (<http://www.r-project.org/>). Overall survival was calculated using Kaplan-Meier analysis. The local recurrence rate was calculated using Fine analysis, accounting for death and distant metastasis as competing risks. Risk factor analysis was done by Fine-Gray analysis with the same competing risk factors. Cut-off value calculation was done by receiver operating characteristic curve analysis. A *P*-value of <.05 was considered statistically significant.

3 | RESULTS

3.1 | Patient enrollment

A total of 31 patients consented to and were enrolled in the study. Two patients, however, were not treated due to emergence of other lesions. A total of 29 evaluable patients underwent carbon ion radiotherapy. The median tumor size was 2.5 cm, ranging from 1.2 cm to 10.2 cm, with 5 cases larger than 4 cm. Patients' characteristics for the treated cases are shown in Table 1. Figure S1 shows a representative treatment plan.

3.2 | Dose escalation and adverse events

Three patients received 36 Gy (RBE), 2 received 40 Gy (RBE), 4 received 44 Gy (RBE), 6 received 46 Gy (RBE), 3 received 48 Gy (RBE), 8 received 53 Gy (RBE) and 3 received 58 Gy (RBE). The

TABLE 1 Patient and tumor characteristics

Characteristic	Value
Median age in years (range)	69 (46-84)
ECOG performance status	
0	23
1	6
Sex	
Male	20
Female	9
Primary site	
Colon	15
Rectum	14
Median time from operation to primary until CIRT in months (range)	26 (8-137)
Number of lesions	
Solitary	26
Multiple	3
Median tumor diameter in mm (range)	25 (12-102)
Observation Period in months (range)	46 (8-116)

CIRT, carbon ion radiotherapy; ECOG, Eastern Cooperative Oncology Group.

dose was escalated up to 44 Gy (RBE) as planned, but 3 out of 4 patients developed in-field recurrence. Because no severe acute toxicities were observed, it was decided by the protocol evaluation committee that the dose should be escalated further. In close communication with the protocol evaluation committee and interpreting outcomes from other ongoing single/2 fraction protocols, the dose was escalated up to 53 Gy (RBE). Still, no dose limiting toxicity was reached, although 2 temporary grade 3 liver toxicity cases due to biliary obstruction were observed at 9 months and 21 months after the treatment as late toxicity at 53 Gy (RBE) (Table 2). Although the PTV did not include the second-order branches of the portal vein, both cases had lesions close to the hepatic portal region, with high dose areas overlapping, and, therefore, dose escalation to 58 Gy (RBE) was limited to peripheral lesions where treatment volumes did not overlap with second-order branches and larger portal veins. No DLT was observed at 58 Gy (RBE), although the final dose was 58 Gy (RBE).

3.3 | Tumor response

Initial tumor responses are shown in Table 3. Immediate tumor regrowth was not seen after escalating the dose to 44 Gy (RBE). Three-year actuarial overall survival was 78%, with a median survival time of 65 months (Figure 1). Local control improved significantly at doses ≥ 53 Gy (RBE) (specificity .67, sensitivity .82), with a 3-year actuarial local recurrence rate of 18%, compared to 72% in lower doses (Figure 1, *P* = .025). Risk factor analysis for local recurrence showed dose being the only contributing factor among age, sex,

TABLE 2 Carbon ion radiation-related acute and late toxicities

Grade	Acute			Late						
	0	1	2	3	4	0	1	2	3	4
Liver	23	5	1	0	0	17	6	0	2 ^b	0
Skin	0	27	2 ^a	0	0	0	27	2	0	0
Lung	26	3	0	0	0	14	15	0	0	0
Others	25	4 ^c	0	0	0	29	0	0	0	0

Acute toxicities are scored using the RTOG Acute Radiation Morbidity Scoring System and late toxicities are scored using the RTOG/EORTC Late Radiation Morbidity Scoring System.

^aG2 acute toxicity was seen in 1 patient at 48 Gy (RBE) and 2 at 53 Gy (RBE).

^bG3 late toxicity was seen in 2 patients at 53 Gy (RBE), both fully recovered.

^cG1 fever: all recovered shortly after the treatment.

performance status, tumor size, operability of the metastatic lesion, CEA level and dose in a univariate analysis with a hazard ratio of .88 ($P = .025$; .79-.98 95% CI).

4 | DISCUSSION

Approximately 20% of patients with CRC have metastases at the time of diagnosis,^{24,25} which also occurs in around 50% of patients with CRC over the course of their lifetime.²⁶ Improvements in diagnostic imaging, perioperative management and systemic chemotherapy have made liver resection the current standard treatment for local therapy of liver metastases.¹ The 5-year overall survival after liver metastasis resection is reported to be 30%-60%,²⁻⁵ but for those who cannot receive resection, chances of survival are slim.⁶

Radiation therapy is an option for those who are unfit for hepatectomy for multiple reasons. Local control by SBRT has been reported to be very good, with a 2-year local control rate ranging from 60% to 90%, and toxicity to be minimal.⁷⁻⁹ Although reports demonstrate that results for SBRT are promising, SBRT has limitations due

TABLE 3 Initial tumor responses at 6 mo after carbon ion radiotherapy evaluated as per Response Evaluation Criteria in Solid Tumors 1.0

Dose in Gy (RBE) (n)	CR	PR	SD	PD
36.0 (3)	0	0	0	3
40.0 (2)	1	0	0	1
44.0 (4)	2	2	0	0
46.0 (6)	0	5	1	0
48.0 (3)	0	3	0	0
53.0 (8)	1	4	3	0
58.0 (3)	1	2	0	0
Total (29)	5	16	4	4

CR, complete response; Gy, Gray; RBE, relative biological effectiveness; PD, progressive disease; PR, partial response; SD, stable disease.

to the nature of X-ray/ γ -ray beams, being a low-LET beam and less effective in hypoxic and radio-resistant tumors, which generally colorectal cancers are, and its physical characteristics, where dose deposition does not "stop." Although the physical dose distribution in SBRT is better compared to conventional radiotherapy, and that has made it possible to treat CRC liver metastasis, it is still limited by the physical properties of photons, making treating larger tumors increasingly challenging.²⁷

Radiofrequency ablation is another option for those who are unfit for hepatectomy. Results are also promising, with high local control rates and minimal toxicity, although larger lesions (>2 cm) and lesions close to major vessels, the gall bladder and the diaphragm are difficult to control, and are associated with a higher toxicity rate.^{10,11,28,29}

Charged particle therapy, in particular CIRT, has a distinctive dose distribution due to the nature of charged particle beams.¹²⁻¹⁴ This enabled us to deliver high doses to the target while sparing doses to the surrounding organs at risk.^{15,27} Given these advantages, we have successfully treated hepatocellular carcinomas with minimal toxicity.³⁰ In addition, we used extreme hypofractionation of 2 fractions with successful outcomes.¹⁶ CIRT is also a high-LET beam and generally has a stronger biological effect compared to low-LET beams as in X-ray/ γ -ray.^{14,17} Locally recurrent rectal cancer, which is typically considered as radio-resistant, showed exceptional local control using carbon ion radiotherapy.¹⁸ Other radio-resistant tumors like bone and soft tissue sarcomas also responded to carbon ion radiotherapy.^{19,20} Based on these experiences, we planned this prospective single-arm dose-escalation study.

It took us approximately 10 years to recruit patients. This was mainly because our source of patient referral was from surgeons, and the de-facto sole standard treatment for solitary liver metastasis is surgery. Thus, those who are fit for surgery for the primary lesion but not fit enough for a hepatectomy, and those who refused hepatectomy were the only patients that were referred.

Although the initially planned dose target was not enough to control the disease, we successfully escalated the dose to 58 Gy (RBE) without severe adverse events. Initial tumor response improved after 48 Gy (RBE), and while the number of cases is limited, local control improved at 53 Gy (RBE) and over (Table 3 and Figure 1B). DLT was not observed, although we did see grade 3 liver toxicity due to biliary obstruction at 53 Gy (RBE) as late toxicity. While biliary obstruction is not reported as a common toxicity in X-ray SBRT, the 2 cases had elevated levels of bilirubin and/or gamma-glutamyl transpeptidase, with peripheral bile duct dilation. These 2 cases had high dose areas overlapping with the hepatic portal region. Therefore, while late toxicity was not determined as a DLT, a decision was made to terminate dose escalation for lesions close to the hepatic portal region. Thus, dose escalation to 58 Gy (RBE) was limited to peripheral lesions. Although 3 cases were successfully treated with no DLT, considering the 2 grade 3 late toxicities at 53 Gy (RBE), further escalation was considered high risk and the trial was closed.

Median tumor size was 2.5 cm, with a PTV volume of 50 cm³, which was larger compared to other reports using SBRT which report a median PTV size of 25 to 35 cm^{3,8,9,15,16,31-35}. Although this

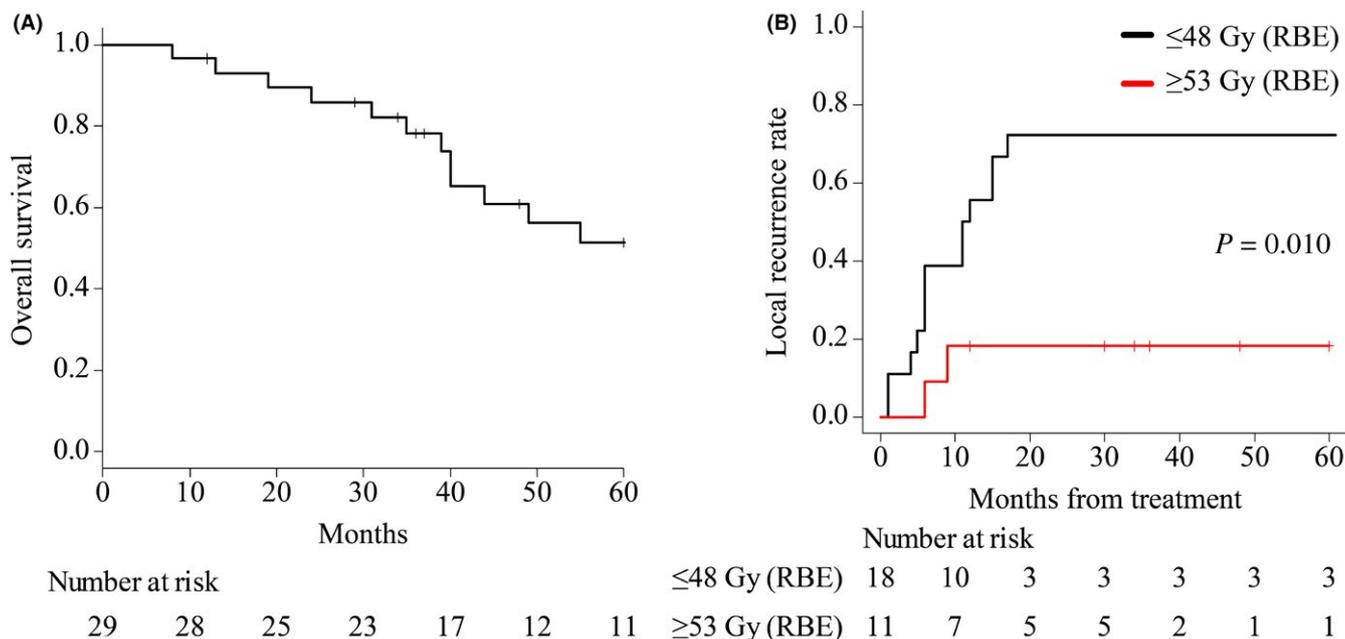


FIGURE 1 Kaplan-Meier curves showing overall survival of all 29 cases (A) and cumulative local recurrence between 2 dose groups (B). Significant difference in local recurrence was observed between those receiving 48 Gy (RBE) and less, compared to 53 Gy (RBE) and more

is not an phase-II trial and it is difficult to evaluate the efficacy of this treatment without a matched control group, an actuarial 3-year overall survival of all dose levels at 78% without severe toxicity or treatment-related deaths is promising, considering the fact that even those who are “fit” for hepatectomy are under a burden of a morbidity rate of 20%-45% and mortality rate of 1%-3%.^{2-5,36}

In this study, we discovered that a substantial dose is required to control CRC liver metastasis. As shown in Figure 1, 53 Gy (RBE) or more was required to achieve a satisfactory local control, which is approximately 6 times more, after accounting for the difference in fractionation, than required in locally recurrent rectal cancer which was treated at 73.6 Gy (RBE) in 16 fractions.^{18,37} The dose required for lung metastases from CRC cancer (60 Gy (RBE) in 4 fractions) falls somewhere in between these 2 studies.³⁸ The same phenomenon has been seen in single fraction high dose rate brachytherapy where patients suffered low local control rates, although estimations through the linear quadrant model predicted otherwise.³⁹ The same was also seen in single fraction carbon ion therapy for early stage lung cancer where 44 to 50 Gy (RBE) was required to achieve satisfactory local control.⁴⁰ One reason may be related to the heterogeneity of the tumor. Because the calculation of an equivalent dose between different fractionation is based on radio-sensitivity, heterogeneity of radio-sensitivity within a tumor will severely impact the calculation. In previous reports from our institute, while increased heterogeneity did not affect 50% tumor control probability, the dose required for 90% tumor control probability increased dramatically.¹⁷

The fact that an extremely high dose is required makes treatment difficult when any organ at risk is in close contact with the target. To overcome this, it is necessary to lower the dose to the organ at risk by re-planning multiple times for each patient. This is not possible

if we choose to treat in 1 fraction using passive scattering methods but is still possible using scanning beams and inverse planning (intensity modulated particle therapy). With all the challenges we face, we believe that single fraction treatments are important to achieve the cost-effectiveness and sustainability of particle therapy, and, moreover, shorter treatment courses are more convenient for our patients, because they are easier to integrate with other treatments such as surgery for the primary lesion and adjuvant chemotherapy. To broaden the application, while this study set the DLT as acute grade 3 or severe toxicity, a carefully designed phase 1 dose escalation study focusing on dose to major vessels, duodenum, colon and other nearby organs reflecting not just acute but also late toxicities is required, especially in cases where the target is close to the portal region.

This study, with its limitations of a long recruitment period and a predefined DLT not being observed in the dose escalation process, suggests that carbon ion therapy is a treatment with low toxicity, enabling those who cannot receive hepatectomy to have a potential better chance of survival. Doses up to 58 Gy (RBE) were shown to be safe if limited to peripheral lesions. We are currently working on a phase II trial to further confirm the efficacy of this treatment. In addition, this study revealed the necessity for further exploration to determine the tolerance dose for Glisson’s capsule to safely treat lesions close to the portal region.

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CONFLICTS OF INTEREST

There are no conflicts of interest pertaining to this work for any of the authors.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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