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Original Article

A feasibility study of high-dose hypofractionated carbon ion radiation therapy using four fractions for localized hepatocellular carcinoma measuring 3 cm or larger

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ABSTRACT

Background and purpose: To evaluate the safety of carbon-ion radiotherapy (C-ion RT) using 60 Gy (relative biological effectiveness, RBE) in four fractions for patients with hepatocellular carcinoma (HCC).
Materials and methods: The primary outcome was acute toxicities within 90 days. The secondary outcomes were late toxicities, local control, and progression-free survival and overall survival rates. The key inclusion criteria were as follows: (1) 3 cm or larger HCC without major vascular invasion and not adjacent to the alimentary tract; (2) Child–Pugh's grade A/B; and (3) without extrahepatic metastasis.
Results: A total of 21 cases were analyzed between October 2012 and April 2016. The median follow-up period among the 17 survivors was 24.2 (range: 6.3–43.7) months. Grade 3 or higher acute toxicity was not observed, while three (14.3%) of the 21 patients experienced grade 3 late toxicities. The 1- and 2-year local control, progression-free survival, and overall survival rates were 100% and 92.3%, 81.0% and 50.0%, and 90.5% and 80.0%, respectively.
Conclusion: C-ion RT using 60 Gy (RBE) in four fractions was safe and achieved promising local tumor control.

Hepatocellular carcinoma (HCC) is one of the most common causes of cancer-related deaths worldwide [1,2]. Surgical resection and liver transplantation are potentially curative; however, these treatment methods are restricted to select patients because of tumor extension, poor hepatic function, and a shortage of graft donors. Although excellent local control can be achieved via local ablation therapies, including radiofrequency ablation, microwave ablation, and percutaneous ethanol injection therapy, these are not suitable for patients with large HCCs, unfavorable anatomic locations, and bleeding tendencies [3–6]. Thus, an effective and less invasive local treatment modality that can be applied to various patients and can be used on tumors of any size or location within the liver is needed.

Charged particle radiotherapy, including proton beam therapy (PBT) and carbon-ion radiotherapy (C-ion RT), has unique properties that allow the delivery of high radiation doses to the anatomical target while sparing surrounding normal tissues. Several studies on charged particle radiotherapy for HCC patients have reported promising results [7–13]. C-ion RT has the advantages of superior dose localization and higher relative biological effectiveness (RBE) than X-ray and protons. Previous studies of C-ion RT from the National Institute of Radiological Sciences in Japan have produced encouraging results within relatively short overall treatment courses by four fractions [12,14]. While the toxicities reported in these studies were acceptable, radiation doses were limited up to 52.8 Gy (RBE) by four fractions, and there were local recurrences in some patients. Another previous study suggested that tumor size was a significant risk factor for local recurrence after charged particle radiotherapy; however, dose-escalation studies of short-course C-ion RT are lacking, and the appropriate dose level has not been established, particularly for large tumors [8]. Therefore, we believe that a feasibility study of high-dose C-ion RT is essential to obtain clinical data to establish treatment guidelines and ultimately improve local control rates and survivals.

The purpose of this study was to evaluate the safety and initial treatment effect of high-dose C-ion RT using 60 Gy (RBE) by four fractions for HCC.

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Methods

Study design

Dose escalation to 60 Gy (RBE) in four fractions was based on the result of a phase I clinical trial conducted at Gunma University Heavy Ion Medical Center (GHMC). This single-arm, prospective clinical trial was registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR trial number: 000020344, http://www.umin.ac.jp/ctr/index.htm). The patients in the phase I trial and the follow-up cohort treated according to the same eligibility criteria and treatment protocol were included in the analyses. These studies were conducted in accordance with the Declaration of Helsinki and all of its amendments and was approved by the local institutional review board. Written informed consent was obtained from all individuals before initiation of any protocol procedures.

Patients

We enrolled consecutive patients based on the following eligibility criteria: (1) pathologically proven or clinically diagnosed HCC based on the guidelines proposed by the Japan Society of Hepatology [15]; (2) tumor is measurable, and the tumor size is 3 cm or larger but less than 10 cm; (3) absence of major portal vein, hepatic vein, or bile duct invasion; (4) cN0M0 according to the 7th edition of the International Union Against Cancer TNM classification of malignant tumors; (5) at least one month had passed after previous treatment with local ablation therapy or trans-arterial chemoembolization. (6) Child–Pugh's score ranging from 5 to 9 points; (7) absence of uncontrolled ascites; and (8) Eastern Cooperative Oncology Group performance status of 0 to 2. Meanwhile, the exclusion criteria were: (1) history of radiation therapy to the lesion of interest; (2) the alimentary tract was adjacent to the target lesion (less than 1 cm); (3) presence of any other active malignancies; and (4) severe comorbidity.

Simulation, planning, and treatment

The patients underwent simulation and planning based on respiratory-gated computed tomography (CT). Patients were immobilized using fixation cushions and 3-mm-thick thermoplastic shells during the simulation CT and the treatment. Gross tumor volume was contoured based on the fusion image of respiratory-gated CT and contrast-enhanced CT. The clinical target volume was an expansion of 5 mm to all direction and was modified to exclude the digestive tract and portal vein by the treating physician. The planning target volume margin was decided based on the distance of internal movement during the respiratory gating and 3-mm setup margin.

C-ion RT dose is described herein in Gy (RBE), which is calculated by multiplying the carbon absorbed dose by an RBE of three. The prescribed dose was 60 Gy (RBE) delivered in four fractions. Carbon ion beams were accelerated using the synchrotron at GHMC [16]. The beam energies were determined individually for each patient based on tumor depth and delivered at 290 MeV/u, 380 MeV/u, and 400 MeV/u. The equivalent dose in 2 Gy fractions (EQD2) were calculated using α/β ratios of 10 Gy for targets and α/β ratios of 3 Gy for organs at risk (OARs) based on the linear quadratic model.

The dose constraints for OARs were as follows: liver volume receiving more than 20 Gy (RBE) (V20) <35%, maximum gastrointestinal tract (including the stomach, duodenum, small bowel, and large bowel) dose of 42 Gy (RBE), maximum skin dose of 45 Gy (RBE), and maximum porta hepatis (including the first branch of the portal vein and hepatic duct) dose of 52.8 Gy (RBE).

Outcomes and evaluation

The primary endpoint was acute toxicity described as the highest grade of all adverse events within 90 days. Toxicities were evaluated according to the Common Terminology Criteria for Adverse Events version 4.0. Dose-limiting toxicity, defined as grade 3 or more severe non-hematological toxicity or Grade 4 or more severe hematological toxicity, was evaluated in the phase I trial. The secondary endpoints were late toxicity starting from 91 days after C-ion RT, local control, and progression-free survival and overall survival rates. Late toxicities were defined as adverse events clearly related to C-ion RT excluding those caused by tumor progression. Liver toxicity was also assessed according to the changes in Child–Pugh's score; platelet count; and serum levels of albumin, total bilirubin, and the prothrombin time-international normalized ratio (PT-INR). Local control rate was calculated from the date of initiation of C-ion RT to the date of local treatment failure, which was defined as radiographic signs indicating increasing tumor size according to the Response Evaluation Criteria in Solid Tumors version 1.1 or as continuous increase in alpha-fetoprotein level following treatment without any radiographic disease progression outside of the primary site. Progression-free survival was calculated from the date of initiation of C-ion RT to the date of local treatment failure, disease progression outside of the primary site, or death from any cause. Overall survival was calculated from the initial treatment date of C-ion RT to the date of death from any cause. Patients visited the hospital for follow-up every three months after completion of C-ion RT and underwent dynamic contrast-enhanced CT or magnetic resonance imaging. The first three patients in the phase I trial were scheduled for follow-up visits every four weeks for the first six months.

Statistical analyses

Local control and overall survival rates were estimated using the Kaplan–Meier method. Data were censored in January 2017. Patients who were lost to follow-up were censored at the date of last contact. The Wilcoxon signed-rank test was used to analyze the changes in Child–Pugh's score and laboratory investigation data before and after C-ion RT. All statistical analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA) and statistical significance was set at $P < 0.05$.

Results

Patient characteristics

Between October 2012 and April 2016, a total of 21 patients with HCC underwent 60 Gy (RBE) C-ion RT by four fractions in the phase I trial and the following cohort study. Three patients were included in the phase I trial between October 2012 and May 2013. After six months of the observation period stipulated in the phase I trial, 18 patients were sequentially included in the cohort study between November 2013 and April 2016. The characteristics of the patients are given in Table 1. The median follow-up duration among the 17 survivors was 24.2 (range: 6.3–43.7) months.

Toxicity and impact of C-ion RT on liver function

Dose-limiting toxicity was not observed in the phase I trial. Acute and late toxicities during the follow-up period are shown in Table 2. No grade 3 or more severe acute toxicity was observed within 90 days after C-ion RT. Grade 2 toxicities were observed in four patients (19.0%).

Three (14.3%) of the 21 patients experienced grade 3 late toxicities. One patient who had cholelithiasis before C-ion RT experienced grade 3 acute cholecystitis eight months after C-ion RT

Table 1
Patient characteristics.

Characteristics	No. of patients	Proportion, %
Age, yrs		
<70	7	33
≥70	14	67
Median (range)	76 (58–88)	
Sex		
Male	14	67
Female	7	33
ECOG performance status		
0	13	62
1	6	29
2	2	9
Etiology		
HCV-Ag positive	11	52
HBs-Ab positive	1	5
NASH/NAFLD	4	19
Alcoholic	4	19
Unidentified	1	5
Child–Pugh's score		
5	13	62
6	8	38
ICG retention rate at 15 min,%		
<15%	13	62
≥15%	8	8
Median (range)	18.9 (2.3–62.2)	
Max. tumor diameter, cm		
<5	11	52
≥5	10	48
Mean (range)	4.8 (3.0–7.8)	
No. of target lesions		
Single	20	95
Multiple	1	5
UICC stage		
I	15	71
II	3	14
IIIa	1	5
IIIb	2	10
Pretreatment AFP (IU/ml)		
<200	19	90
200–400	1	3
>400	2	7
Previous treatment		
Naïve	14	67
Recurrent	7	33

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HCV-Ag, hepatitis C antibody; HBs-Ab, hepatitis B surface antibody; NASH/NAFLD, non-alcoholic fatty liver disease/non-alcoholic steatohepatitis; ICG-R15, Indocyanine green retention rate at 15 min; AFP, alpha-fetoprotein; UICC, Union for International Cancer Control.

that was managed via antibiotic therapy and percutaneous drainage. Although C-ion RT might have aggravated the acute cholecystitis, it was considered to have been caused by the cholelithiasis. Cognitive disorder (in one patient) and hepatic encephalopathy (in one patient) that required short-term hospitalization was observed, and these adverse events were manageable via medication and oral and intravenous nutrition. The patient who developed hepatic encephalopathy also had grade 2 bilirubin elevation. No patient developed grade 4 or 5 toxicities during the follow-up period.

Two (9.5%) of the 21 patients and three (15.7%) of the 19 patients had worsening Child–Pugh's score at three and six months, respectively. There was no significant difference in Child–Pugh's score at three and six months after C-ion RT compared to that before treatment ($p = 0.846$, Friedman test). The changes in laboratory values before and after C-ion RT are shown in Fig. 1. The median baseline values of platelet counts, PT-INR, serum bilirubin, and albumin were 143 (range: 68–272) $\times$ $10^3/\mu L$, 1.03 (range: 0.92–1.13), 0.9 (range: 0.5–1.7) mg/dL, and 3.7 (range: 2.9–4.4) mg/dL, respectively. There were no significant differences in platelet counts, serum bilirubin, and albumin at three or six months after C-ion RT compared to those before treatment. Significant ($p = 0.025$) and borderline significant difference ($p = 0.078$) in PT-INR were observed at three and six months compared to those before treatment. Among the 21 patients, the maximum increases in PT-INR and bilirubin levels within six months after treatment were 0.14 (from 1.13 to 1.27) mg/dL and 0.7 (from 1.7 to 2.4) mg/dL, respectively. The maximum increases in PT-INR and bilirubin were observed in the same patient whose Child–Pugh's score increased by 2 points six months after C-ion RT.

Local control, progression-free survival, and overall survival rates

The 1- and 2-year local control rates were 100% and 92.3%, respectively (Fig. 2). Local treatment failure was observed in one patient at 23.1 months after C-ion RT. The 1- and 2-year progression-free survival rates were 81.0% and 50.0%, respectively (Fig. 3). Seven patients (33.3%) experienced recurrence; five patients (23.8%) had intrahepatic recurrence outside of the planning target volume, and one (4.8%) had right adrenal metastasis. The 1-year and 2-year overall survival rates were 90.5% and 80.0%, respectively (Fig. 4). Two patients (9.5%) died of HCC progression, and another two patients died of other causes, specifically, myocardial infarction and idiopathic sudden death unrelated to tumor progression or liver failure.

Discussion

This study investigated the feasibility of hypofractionated high-dose C-ion RT for HCC. The results showed that C-ion RT with 60 Gy (RBE) in four fractions is a safe treatment modality with a high rate of local tumor control.

Previous studies of stereotactic body radiation therapy (SBRT) have proven that high-dose radiation reliably ablated small HCC

Table 2
Treatment-related toxicities after carbon ion radiation therapy.

Toxicities	Acute (Within 90 days)				Late (After 90 days)			
Grade	**≤1**	**2**	**3**	**4**	**≤1**	**2**	**3**	**4**
Skin	21	0	0	0	21	0	0	0
Respiratory	21	0	0	0	21	0	0	0
Musculoskeletal	21	0	0	0	21	0	0	0
Gastrointestinal	20	1	0	0	21	0	0	0
Hepatobiliary	21	0	0	0	19	0	**2**	0
Investigations	18	3	0	0	19	2	0	0
Others	21	0	0	0	20	0	**1**	0
Total	17	4	0	0	16	2	3	0
Details of toxicities	Gastrointestinal: Ascites Investigation: Elevation of gamma-glutamyltransferase, aspartate aminotransferase, and alkaline phosphatase				Hepatobiliary: Cholecystitis and encephalopathy Investigation: Elevation of gamma-glutamyltransferase and bilirubin Others: Cognitive disorder			

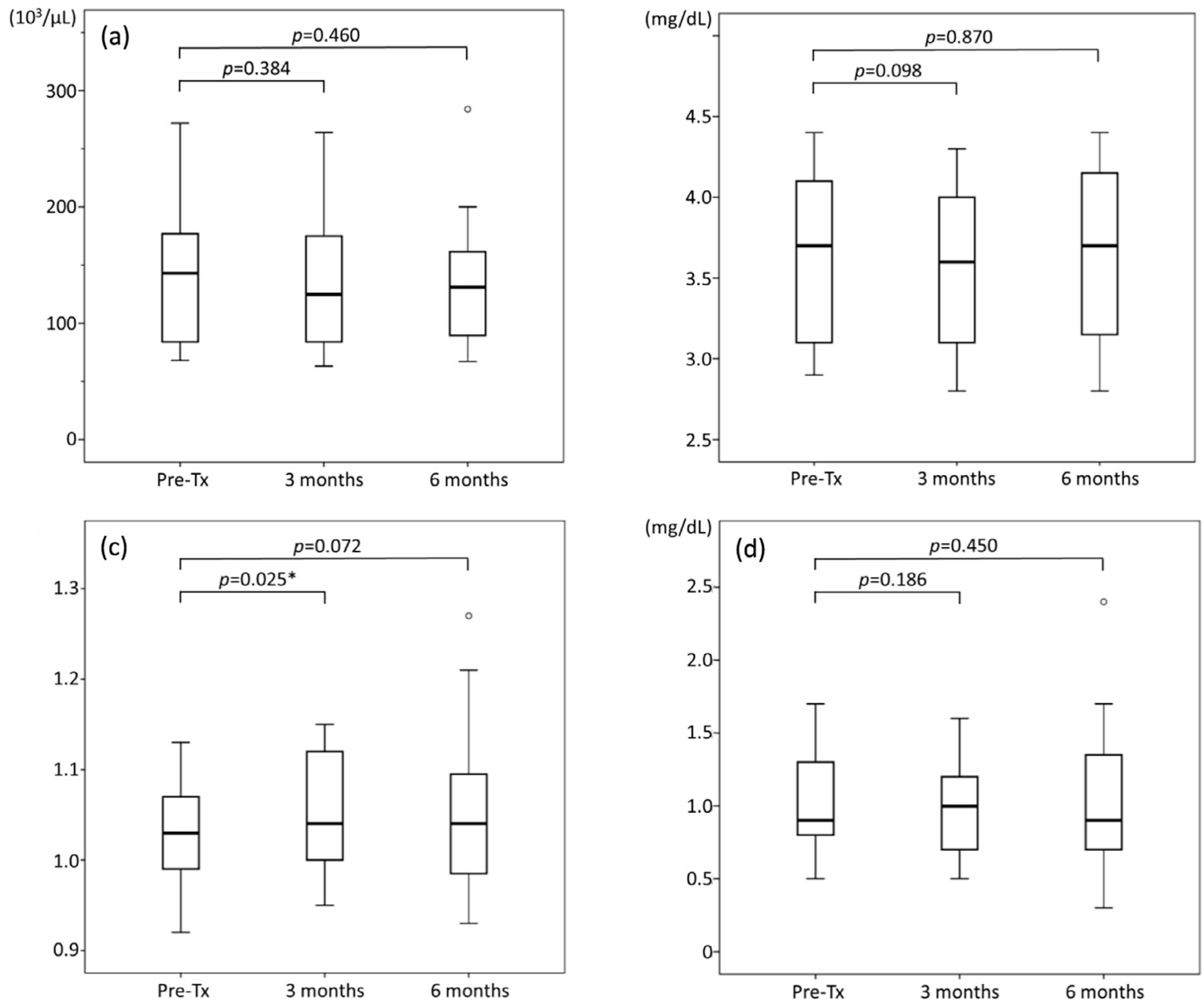

Fig. 1. Impact of C-ion RT on laboratory parameters. (a): Platelet counts; (b): PT-INR; (c): serum bilirubin; (d): serum albumin.

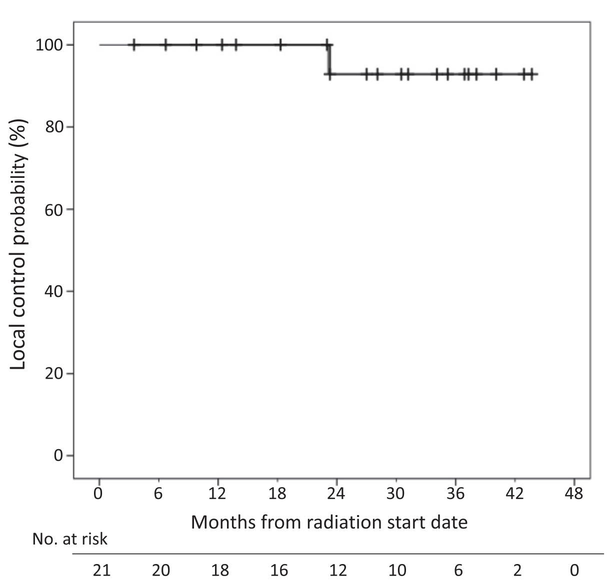

Fig. 2. Local control rates of all patients.

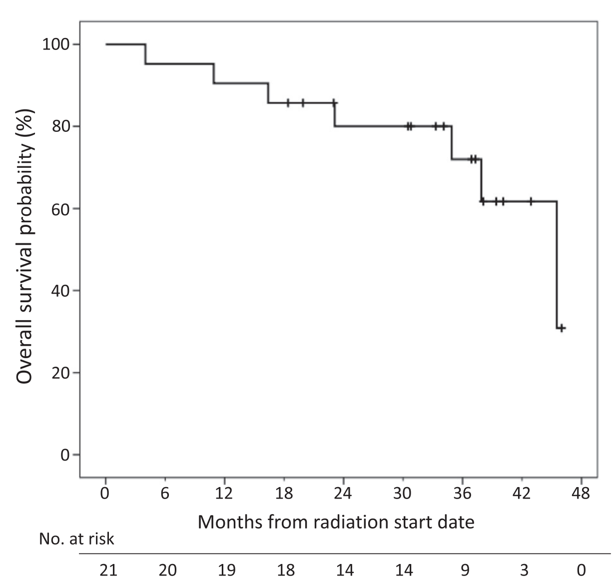

Fig. 3. Progression-free survival rates of all patients.

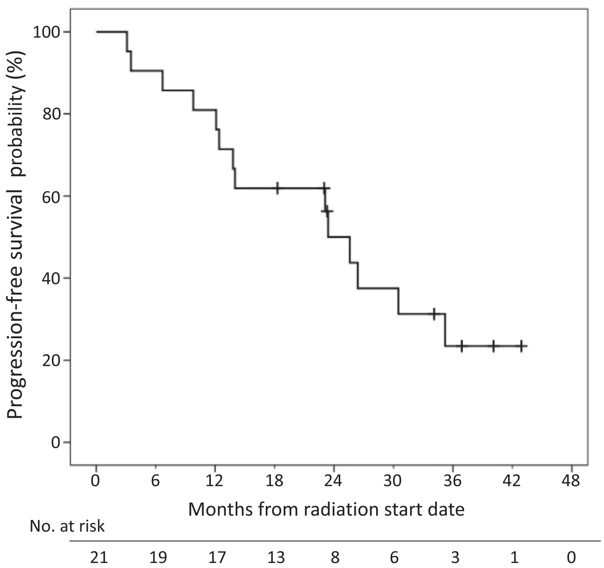

Fig. 4. Overall survival rates of all patients.

[17–21]. Meanwhile, the application of SBRT for large tumors is challenging due to the possibility of hepatic toxicity [22–24]. Charged particle radiotherapy including PBT and C-ion RT are attractive radiation modalities for large HCC. Some previous studies on PBT and C-ion RT reported encouraging outcomes using various total doses and fraction sizes that ranged from 50.6 to 80 Gy (RBE) with 2.0–3.9 Gy (RBE) per fraction in PBT and 52.8 to 76.0 Gy (RBE) with 4.0–13.2 Gy (RBE) per fraction in C-ion RT [7–9,12,13,25–31]. In these studies, EQD2 (α/β = 10 Gy) ranged from 62.5–102.1 Gy in PBT and 54.9–102.1 Gy in C-ion RT.

The most important clinical implication of the findings of this study is that the maximum tolerance dose of the liver should be increased up to 125 Gy in EQD2 (α/β = 10 Gy) using a short-course treatment protocol in four fractions. Kasuya et al. reported that tumor size was not a statistically significant factor for local control after C-ion RT by univariate analysis. However, the hazard ratios in patients with large tumors compared to the reference (tumor size $\leq$3 cm) were 4.850 (tumor size 3–5 cm) and 4.329 (tumor size $\geq$5 cm), and multivariate analysis was not performed due to the small number of events [31]. Komatsu et al. reported that tumor size was one of the significant prognostic factors for local control in a large study that included patients treated using 52.8 Gy (RBE) in four fractions [8]. Therefore, the recommended dose level of C-ion RT has not yet been established especially for large tumors, and dose escalation is required to improve the outcomes. The dose used in this study (60 Gy (RBE) in four fractions) is equivalent to 125 Gy in EQD2, and although it is the most intensive protocol reported to date for particle therapy in patients with liver tumors, we found that C-ion RT using 60 Gy (RBE) in four fractions can safely be used in the treatment of intrahepatic tumor without increasing treatment-related toxicity. Furthermore, the patients included in the present study had tumors measuring more than 3 cm in maximum diameter to which SBRT is hardly applicable. These results may be because the doses targeting critical risk organs (i.e., the alimentary tract, skin, and porta hepatis) were constrained within the dose limits predetermined based on our experience and previous studies about C-ion RT by four fractions [8,12,31].

In this study, the adverse effect of C-ion RT on laboratory parameters was generally considered to be acceptable; however, PT-INR significantly increased at 3 months after C-ion RT. PT-INR is a more sensitive and specific indicator than serum bilirubin, albumin, and platelet counts. Thus, it reflects liver damage induced by C-ion RT more sensitively, although the Child–Pugh's score and other laboratory data did not significantly change after C-ion RT. Further investigations, such as dose-volumetric analysis and evaluation using indocyanine retention test or technetium-99m-galactosyl human serum albumin liver scintigraphy, are required to determine the accurate effect of C-ion RT on liver function.

We achieved encouraging treatment responses and local control rates during the follow-up period, although the patients with relatively large tumors (maximum diameter >3 cm) were enrolled in this study. The preliminary results of intensive C-ion RT in the current study may be a strong rationale to evaluate this protocol in a larger population. Overall survival was also feasible, but it is impossible to directly compare these results with those obtained from different study populations because the overall survival of HCC patients largely depends on the co-existing hepatic disease and hepatic function impairment. Longer follow-up and larger studies are needed to evaluate the beneficial effect of C-ion RT on overall survival. Therefore, we had started a multi-institutional prospective study in partnership with other institutions in Japan in which the protocol of 60 Gy (RBE) in four fraction was adopted based on the results of the present study.

Several limitations of this study should be acknowledged. First, there were no severe treatment-related toxicities in this study; therefore, 60 Gy (RBE) in four fractions might not be the maximum tolerable dose in patients with liver tumor. To the best of our knowledge, 60 Gy in four fractions (EQD2, 125 GyE10) is the most intensive protocol in the entire field of radiation oncology including photons and protons, although the RBE of carbon ions varies for different physical and biological parameters including dose per fraction, and comparison of different regimens of photon and proton therapy to C-ion RT contains some uncertainty. There is the need for further dose escalation and the RBE issue in hypofractionated C-ion RT should be discussed after the long-term results of this intensive protocol have been determined. Second, because it was a safety study evaluating a relatively small number of patients during a short observation period, we could not evaluate the effects of dose escalation on long-term progression-free survival and overall survival. Although the local control rate of this study is promising, the long-term evaluation should be continued. Third, patients whose tumors were adjacent to the alimentary tract and who had major portal vein invasion were excluded in this study. We considered the 1 cm distance between the tumor and the alimentary tract to be the limitation in applying the protocol. However, the validity of the treatment protocol should be assessed according to the anatomic location of the target tumors and the dose constraints of the OARs.

In conclusion, our results suggested that C-ion RT with 60 Gy (RBE) in four fractions was safe and can achieve sufficient local tumor control in patients with HCC larger than 3 cm. Additional larger studies with and longer-term follow-up are needed to evaluate the clinical effects of such protocol to patient survival.

Conflict of interest

None.

Financial support statement

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2018.10.009.

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