Comparison of dose distributions when using carbon ion radiotherapy versus intensity-modulated radiotherapy for hepatocellular carcinoma with macroscopic vascular invasion: A retrospective analysis

Shintaro Shiba (✉ shiba4885@yahoo.co.jp)

Gunma University Graduate of Medicine

Kei Shibuya

Gunma University

Motohiro Kawashima

Gunma University

Naoko Okano

Gunma University

Takuya Kaminuma

Gunma University

Masahiko Okamoto

Gunma University

Yoshiki Kubota

Gunma University

Takashi Nakano

Gunma University

Tatsuya Ohno

Gunma University

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Abstract

Background. Studies comparing the dose distributions of carbon ion radiotherapy (C-ion RT) and intensity-modulated radiotherapy (IMRT) in patients with locally advanced hepatocellular carcinoma (LAHCC) are lacking. This study aimed to investigate the dose distributions of these modalities and identify any advantages to using C-ion RT. **Methods.** Patients with LAHCC who had undergone C-ion RT between June 2010 and November 2018 were retrospectively analyzed. From among 210 patients with hepatocellular carcinoma who received C-ion RT, 10 consecutive patients with LAHCC were included. The dose-volume histogram parameters of clinical plans using C-ion RT at 60 Gy (relative biological effectiveness [RBE]) and simulated plans using IMRT at 60 Gy and 50 Gy were compared. We evaluated the three plans in terms of the following parameters: the percentage of the minimum dose that covered 95% of the target volume (D95); mean liver dose (MLD); and percentage of the normal liver volume that received at least 5 Gy (V5), 10 Gy (V10), 20 Gy (V20), 30 Gy (V30), 40 Gy, and 50 Gy. Patients at high risk of developing radiation-induced liver disease (RILD) were those with MLD and V30 of >23 Gy and >28%, respectively. **Results.** The V5, V10, V20, and MLD were significantly lower in patients who received 60 Gy (RBE) of C-ion RT than in those who received 60 Gy of IMRT, although the D95 values were not significantly different. The V5, V10, and V20 were also significantly lower in patients who received 60 Gy (RBE) of C-ion RT than in those who received 50 Gy of IMRT; moreover the D95 was significantly superior in the former group. The numbers of high-risk patients who developed RILD when administered 60 Gy (RBE) of C-ion RT, 60 Gy of IMRT, and 50 Gy of IMRT were 1, 7, and 6, respectively. **Conclusions.** C-ion RT exhibits a better dose distribution to the liver than does IMRT when treating patients with LAHCC. C-ion RT made it possible to treat patients with LAHCC who otherwise could not be treated using IMRT because of the high risk of RILD.

Background

Hepatocellular carcinoma (HCC) involving a major branch of the portal or hepatic vein, including portal vein tumor thrombosis (PVTT) or inferior vena cava tumor thrombosis (IVCTT), are locally advanced-stage tumors that are difficult to treat despite the availability of multidisciplinary therapies. In a randomized controlled trial, Yoon et al. found that the clinical outcomes of patients with locally advanced HCC (LAHCC) who underwent transarterial chemoembolization (TACE) combined with X-ray radiotherapy (RT) were more favorable than those of patients only treated with sorafenib [1], and that TACE combined with X-ray RT improved survival compared to sorafenib alone. Accordingly, TACE combined with X-ray RT could potentially be a standard treatment for patients with LAHCC.

Conventional X-ray RT is of limited use owing to the poor radiation tolerance of the liver; therefore, a curative dose to the tumor is usually not feasible. More recently, stereotactic body RT (SBRT) and intensity-modulated RT (IMRT), which can deliver high radiation doses to the target with much better precision, have become widely used to treat patients with HCC [2-4]. Particle therapy has since improved radiation dose distributions further still [5, 6]. In particular, carbon ion RT (C-ion RT) has produced favorable clinical outcomes for patients with HCC [7-11], as this modality reduces the dose to the liver

while ensuring good target coverage [12, 13] owing to its physical characteristics that include distal tail-off because of a high and narrow Bragg Peak as well as a sharp lateral penumbra [14]. Abe et al.'s dosimetric comparison between C-ion RT and SBRT for HCC treatment found that the former has better sparing of the liver [5]. However, their study investigated patients with HCC that exhibited no macroscopic vascular invasion; there have been no studies comparing the dose distributions of C-ion RT and IMRT in patients with LAHCC. Nevertheless, it is important to compare the dose distributions of C-ion RT and IMRT for patients with LAHCC (which have large and/or irregular shapes), as the dose to the liver may increase for the patients with LAHCC than the patients with HCC who have no macroscopic vascular invasion. As such, we conducted a simulation analysis to compare the dose distributions of C-ion RT and IMRT in patients with LAHCC.

Methods

Patients

Data from patients with HCC who had undergone C-ion RT at Gunma University Heavy Ion Medical Center between June 2010 and November 2018 were retrospectively collected. A total of 210 HCC patients received C-ion RT during the study period; 10 patients with LAHCC (i.e., HCC involving a major branch of the portal or hepatic vein, including the PVTT or IVCTT) were investigated. The diagnoses of all patients were confirmed by the presence of typical hallmarks of HCC using four-phase multi-detector-row computed tomography (CT) or dynamic contrast-enhanced magnetic resonance imaging. This study complied with the standards set forth in the Declaration of Helsinki and current ethical guidelines, and was reviewed and approved by our Institutional Review Board.

Treatment planning

Target delineation

Treatment-planning CT with respiratory-gated CT, as well as four-dimensional CT images were acquired. Treatment-planning and contrast-enhanced CT images were merged to precisely delineate the gross tumor volume (GTV). The clinical target volume (CTV) was defined as the GTV plus least a 5 mm margin in all directions to encompass any microscopic disease progression. The internal target volume (ITV) was defined as the sum of CTV from the four-dimensional CT images. The planning target volume (PTV) was defined as the sum of the ITV and an additional margin for patient setup discrepancies [8].

C-ion RT

At our facility, the C-ion RT dose distribution was calculated using the XiO-N, software, which is based on the XiO treatment planning system (Elekta, Stockholm, Sweden) and incorporates an ion beam RT dose

engine (K2 dose) developed by the National Institute of Radiological Sciences [15] as well as a source management tool developed by Mitsubishi Electric (Tokyo, Japan). C-ion RT doses were expressed in Gy (relative biological effectiveness [RBE]), which was defined as the physical dose multiplied by the RBE of C-ions [16]. The heavy ion accelerator at our facility generated C-ion beams; the passive scattering technique was applied for the treatment of HCC. The beam energy selections were 290 MeV/u, 380 MeV/u, or 400 MeV/u depending on the depth of the tumor. Prescribed doses were 60 Gy (RBE), with the aim of covering the PTV with at least 95% of this dose. C-ion RT plans used two or three coplanar ports to avoid the gastrointestinal (GI) tract. The maximum dose to 1 mL (D_{1cc}) was <40 Gy (RBE) administered to the GI tract [8]. Figure 1 shows the typical dose distribution of C-ion RT; all treatment plans were made by medical physicists.

IMRT

IMRT treatment plans were calculated using the X-ray RT treatment-planning system (Eclipse, Varian Medical Systems, Inc. California, USA). All IMRT treatment plans were simulated using the treatment-planning CT images of patients who received C-ion RT; moreover, all the contours were the same as those used for C-ion RT. The prescribed doses were 60 and 50 Gy; the aim was to cover the PTV with at least 95% of the prescribed dose. IMRT plans used five or six coplanar 6 MV X-rays with gantry angles to avoid the GI tract and spinal cord. The dose constraints were D_{1cc} <40 Gy administered to the GI tract. The weights of each field were also arranged to cover the PTV with at least 95% of the prescribed dose while minimizing the dose to the liver and GI tract. Figure 2 shows the typical IMRT dose distribution in the same patient as that shown in Figure 1; again, all IMRT treatment plans were made by medical physicists.

Dose-volume histogram (DVH) parameters and statistical analyses

We assessed the percentage of the minimum dose that covered 95% of the target volume (D_{95}) based on the DVH for the PTV. To compare normal tissue sparing achieved with C-ion RT versus IMRT, we assessed the mean liver dose (MLD) as well as the percentage of the normal liver volume that received at least 5, 10, 20, 30, 40, and 50 Gy using both C-ion RT (RBE) and IMRT (the V_5 , V_{10} , V_{20} , V_{30} , V_{40} , and V_{50} , respectively) for the normal liver (i.e., total liver volume minus GTV). Additionally, we defined patients at high risk for developing radiation-induced liver disease (RILD) as those with MLD >23 Gy and V_{30} values >28% [17].

The DVH parameters when using both modalities were analyzed. Normal distributions were compared using t-tests (the V_5 , V_{10} , V_{20} , V_{30} , V_{40} , V_{50} , and MLD), and non-normal distributions were compared using Wilcoxon's test (PTV D_{95}), after testing for normality with the Shapiro–Wilk test. Statistical significance was defined as a *P*-value less than 0.05. All statistical analyses were performed using the SPSS 22.2.0 software (IBM Corp, Armonk, NY, USA).

Results

Patient characteristics

The median tumor size was 53 mm (range; 27–119 mm). The median PTV and liver volume were 363.2 cm³ (range; 77.1–1331.2 cm³) and 1113.3 cm³ (range; 782.6–1854.6 cm³), respectively.

DVH parameters

Table 1 shows the DVH parameters used in the clinical plans of C-ion RT (60 Gy [RBE]) versus those used in the simulated IMRT using 60 Gy, while Table 2 shows the same C-ion RT plan compared to the simulated IMRT using 50 Gy.

There was no significant difference in the PTV D₉₅ between 60 Gy (RBE) with C-ion RT and 60 Gy with IMRT ($P = 0.24$). In contrast, the difference in the PTV D₉₅ between 60 Gy (RBE) with C-ion RT and 50 Gy with IMRT was significant ($P < 0.01$).

There were also significant differences in the liver V₅, V₁₀, and V₂₀ between the 60 Gy (RBE) C-ion RT plan and each of the 60 Gy and 50 Gy IMRT plans ($P < 0.05$ for both comparisons). In contrast, there were no significant differences in the V₃₀, V₄₀, and V₅₀ values, indicating high-dose areas. Thus, the median MLD was also significantly different between C-ion RT at 60 Gy (RBE) and IMRT at 60 Gy.

The numbers of patients who exceeded an MLD of 23 Gy and V₃₀ of 28% in the C-ion RT 60 Gy (RBE) group were 1 and 4, respectively, those in the IMRT 60 Gy group were 7 and 8, respectively, and those in the IMRT 50 Gy group were 6 and 7, respectively. Therefore, the numbers of patients at high risk of developing RILD in three groups were 1, 7, and 6, respectively. Scatterplots of the MLD and tumor sizes when comparing these modalities are shown in Figure 3.

Discussion

Our study demonstrated that C-ion RT has a more favorable dose distribution than IMRT when treating LAHCC, and also produces a lower dose to the liver. Additionally, there was a significant difference in PTV dose coverage between C-ion RT at 60 Gy (RBE) and IMRT at 50 Gy.

A number of studies have investigated the relationships between liver DVH parameters and RILD given that this organ has poor tolerance for radiation. One such study found that an MLD >23 Gy and V₃₀ >28% were risk factors for RILD [17]. In the present study, 70–80% of patients would be difficult to treat with IMRT at 60 Gy owing to the high risk of developing RILD. Moreover, 60–70% of patients risked developing RILD even with IMRT at 50 Gy. Lowering the prescribed dose would decrease the target D₉₅, which would likely worsen the local control rate. In contrast, when administering 60 Gy (RBE) of C-ion RT, 10% of

patients exceeded an MLD of 23 Gy and 40% exceeded a V_{30} of 28%; the D_{95} of the dose coverage to the PTV using this method was significantly better than that when using 50 Gy of IMRT. These data indicate that C-ion RT ought to be preferable to IMRT in terms of delivering a sufficient radiation dose to the LAHCC while simultaneously avoiding the risk of RILD. Additionally, adopting C-ion RT created the possibility of treating patients with LAHCC who were ineligible for IMRT, thereby expanding the treatment indication for LAHCC.

There was no significant difference in the PTV D_{95} between the C-ion RT at 60 Gy (RBE) and IMRT at 60 Gy groups. However, the lowest PTV D_{95} among the patients who received C-ion RT was 49.1 Gy (RBE) which was below the lowest PTV D_{95} observed in the simulated IMRT at 60 Gy. This may be because C-ion RT plans used fewer ports than did IMRT plans. In the present study, C-ion RT treatment plans made by a maximum of three ports to avoid the GI tract maintain the planned constraints while irradiating the PTV to the greatest extent possible, especially when the PTV is surrounded by the GI tract. As such, the dose distribution with C-ion RT could be further improved with the use of additional ports (as is done with IMRT).

Liver functional status is a critical prognostic factor [18, 19]. A higher radiation dose-concentration directed at the tumor might maintain liver function status and consequently survival. Yoon et al. reported that TACE combined with X-ray RT resulted in improved overall and progression-free survival than did sorafenib treatment in patients with LAHCC. Hence, TACE combined with C-ion RT might further improve survival over TACE combined with X-ray RT, particularly as C-ion RT can help maintain liver function.

There were some limitations in our study. First, we performed a retrospective simulation with a small number of patients. Second, the dose of C-ion RT to the liver (Gy [RBE]) might not be equal to that of IMRT (Gy). Because Gy (RBE) is calculated based on the survival response of human salivary gland cells after C-ion beam irradiation, and not of liver cells, a direct comparison between Gy (RBE) and Gy for the liver can be problematic; moreover, the dose constraints of C-ion RT and those of IMRT for the liver might be different. However, the dose constraints of C-ion RT for the liver used in our study are considered safe, as previous clinical studies of C-ion RT used the same dose constraints, and no severe toxicities were observed [7-11].

Conclusions

We demonstrated that C-ion RT for treating LAHCC provides a better dose distribution than IMRT; a clinical-use dose of 60 Gy (RBE) using C-ion RT showed a superior dose distribution to the PTV and liver than did 50 Gy of IMRT. Additionally, our results suggest adopting C-ion RT may enable the treatment of patients with LAHCC who cannot be treated with IMRT owing to the high risk of RILD; hence, C-ion RT may expand the treatment indication of LAHCC.

Abbreviations

C-ion RT	Carbon ion radiotherapy
CT	Computed tomography
CTV	Clinical target volume
DVH	Dose-volume histogram
D ₉₅	The percentage of the minimum dose that covered 95% of the target volume
GI tract	Gastrointestinal tract
GTV	Gross tumor volume
HCC	Hepatocellular carcinoma
IMRT	Intensity-modulated radiotherapy
ITV	Internal target volume
IVCTT	Inferior vena cava tumor thrombosis
LAHCC	Locally advanced hepatocellular carcinoma
MLD	Mean liver dose
PTV	Planning target volume
PVTT	Portal vein tumor thrombosis
RBE	Relative biologic effectiveness
RILD	Radiation-induced liver disease
RT	Radiotherapy
SBRT	Stereotactic body radiotherapy
TACE	Transarterial chemoembolization
V _{5–50} Gy (RBE)	The percentage of the normal liver volume that received at least 5–50 Gy and 5–50 Gy (RBE)

Declarations

Ethics approval and consent to participate

This study complied with the standards of the Declaration of Helsinki and current ethical guidelines and was reviewed and approved by the Institutional Review Board (approval number1608).

Consent for publication

All patients signed a consent form for publication before the initiation of therapy.

Availability of data and material

The datasets generated and/or analyzed during the current study are not publicly available because they contain personal information but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

S.S., K.S., M.K., T.N. and T.O. made substantial contributions to the conception and design of the study. S.S., K.S., N.O., T.K., Y.K., and T.O. treated and followed the patients. S.S., K.S, N.O., and T.O. collected the data. S.S., K.S., M.K., and T.O. drafted the manuscript and performed the statistical analysis. N.O., T.K., M.O., Y.K., and T.N. were involved in revising the manuscript critically for important intellectual content. S.S., K.S., and T.O. participated in the acquisition and interpretation of the data. All authors read and approved the final manuscript.

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Tables

Table 1. DVH parameters of C-ion RT (60 Gy [RBE]) and simulated IMRT (60 Gy)

		Median (range) for C-ion RT at 60 Gy (RBE)	Median (range) for IMRT at 60 Gy	P=
PTV D ₉₅		58.5 Gy (RBE) (range, 49.1–60.0 Gy [RBE])	58.9 Gy (range, 55.6–60.0 Gy)	P = 0.29
Liver	V ₅	41.0% (range, 12.1–76.2%)	85.3% (range, 52.5–99.8%)	P < 0.01
	V ₁₀	34.5% (range, 10.6–71.2%)	72.6% (range, 32.9–96.7%)	P < 0.01
	V ₂₀	30.7% (range, 9.0–51.6%)	53.3% (range, 17.3–75.0%)	P < 0.01
	V ₃₀	27.3% (range, 7.5–49.3%)	40.9% (range, 10.8–61.2%)	P = 0.05
	V ₄₀	22.9% (range, 5.8–46.4%)	31.2% (range, 7.7–53.8%)	P = 0.27
	V ₅₀	19.8% (range, 4.8–42.2%)	22.4% (range, 5.9–47.4%)	P = 0.63
	Mean dose	17.6 Gy (RBE) (range, 5.1–30.1 Gy [RBE])	28.8 Gy (range, 11.4–41.0 Gy)	P < 0.05

N = 10. Abbreviations: C-ion RT = carbon ion radiotherapy, D₉₅ = the percentage of the minimum dose that covered 95% of the target volume, DVH = dose volume histogram, IMRT = intensity-modulated radiotherapy,

PTV = planning target volume, RBE = relative biological effectiveness, V₅₋₅₀ = the percentage of the normal liver volume that received at least 5-50 Gy (RBE) or 5-50 Gy.

Table 2. DVH parameters of C-ion RT (60 Gy [RBE]) and simulated IMRT (50 Gy)

		Median (range) for C-ion RT at 60 Gy (RBE)	Median (range) for IMRT at 50 Gy	P-value
PTV D ₉₅		58.5 Gy (RBE) (range, 49.1–60.0 Gy [RBE])	49.1 Gy (range, 46.6–50.0 Gy)	<i>P</i> < 0.01
Liver	V ₅	41.0% (range, 12.1–76.2%)	82.6% (range, 47.2–99.7%)	<i>P</i> < 0.01
	V ₁₀	34.5% (range, 10.6–71.2%)	68.1% (range, 29.1–91.9%)	<i>P</i> < 0.01
	V ₂₀	30.7% (range, 9.0–51.6%)	47.9% (range, 13.7–70.2%)	<i>P</i> < 0.05
	V ₃₀	27.3% (range, 7.5–49.3%)	35.3% (range, 8.7–56.5%)	<i>P</i> = 0.32
	V ₄₀	22.9% (range, 5.8–46.4%)	23.9% (range, 6.2–49.0%)	<i>P</i> = 0.95
	V ₅₀	19.8% (range, 4.8–42.2%)	14.4% (range, 3.6–35.2%)	<i>P</i> = 0.23
	Mean dose	17.6 Gy (RBE) (range, 5.1–30.1 Gy [RBE])	24.0 Gy (range, 9.5–34.2 Gy)	<i>P</i> = 0.15

N = 10. Abbreviations: C-ion RT = carbon ion radiotherapy, D₉₅ = the percentage of the minimum dose that covered 95% of the target volume, DVH = dose volume histogram, IMRT = intensity-modulated radiotherapy, PTV = planning target volume, RBE = relative biological effectiveness, V₅₋₅₀ = the percentage of the normal liver volume that received at least 5-50 Gy (RBE) or 5-50 Gy

Figures

Figure 1

Axial computed tomography images of a locally advanced hepatocellular carcinoma. Shown is the dose distribution when treated with 60 Gy (relative biologic effectiveness [RBE]) of carbon-ion radiotherapy. The area within the red outline is the gross target volume. Highlighted are the 95% (red), 90% (yellow), 70% (light green), 50% (green), 30% (light blue), 10% (blue) isodose curves (100% was 60 Gy [RBE]).

Figure 2

Axial computed tomography images of a locally advanced hepatocellular carcinoma. Shown is the dose distribution when treated with 60 Gy with IMRT. The area within the red outline is the gross target volume. Highlighted are the 95% (red), 90% (yellow), 70% (light green), 50% (green), 30% (light blue), 10% (blue) isodose curves (100% was 60 Gy). The tumor is from the same patient as that shown in Figure 1.

Figure 3

Scatter plots of the mean liver dose (MLD) and tumor size. (A) Comparing 60 Gy (relative biological effectiveness [RBE]) of carbon-ion radiotherapy (C-ion RT) and 60 Gy of intensity-modulated radiotherapy (IMRT). (B) Comparing 60 Gy (RBE) of C-ion RT and 50 Gy of IMRT.