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Carbon ion radiotherapy with pencil beam scanning for hepatocellular carcinoma: Long-term outcomes from a phase I trial

Zhengshan Hong[1,2,3] | Wenna Zhang[1,2,3] | Xin Cai[1,2,3] | Zhan Yu[1,2,3] | Jiayao Sun[2,3,4] | Weiwei Wang[2,3,4] | Lienchun Lin[2,3,4] | Jingfang Zhao[2,3,4] | Jingyi Cheng[2,3,5] | Guangyuan Zhang[2,3,6] | Qing Zhang[1,2,3] | Guoliang Jiang[1,2,3,7] | Zheng Wang[1,2,3,7]

[1]Department of Radiation Oncology, Shanghai Proton and Heavy Ion Center, Shanghai, China

[2]Shanghai Key Laboratory of Radiation Oncology (20dz2261000), Shanghai, China

[3]Shanghai Engineering Research Center of Proton and Heavy Ion Radiation Therapy, Shanghai, China

[4]Department of Medical Physics, Shanghai Proton and Heavy Ion Center, Shanghai, China

[5]Department of Nuclear Medicine, Shanghai Proton and Heavy Ion Center, Fudan University Cancer Hospital, Shanghai, China

[6]Department of Radiology, Shanghai Proton and Heavy Ion Center, Shanghai, China

[7]Department of Radiation Oncology, Shanghai Proton and Heavy Ion Center, Fudan University Cancer Hospital, Shanghai, China

Correspondence
Guoliang Jiang and Zheng Wang, Department of Radiation Oncology, Shanghai Proton and Heavy Ion Center, Fudan University Cancer Hospital, Shanghai Key Laboratory of Radiation Oncology (20dz2261000), Shanghai Engineering Research Center of Proton and Heavy Ion Radiation Therapy, No.4365 Kangxin Road, Pudong, Shanghai 201315, China.
Email: guoliang.jiang@sphic.org.cn and zheng.wang@sphic.org.cn

Abstract

This study evaluates the feasibility of the pencil beam scanning technique of carbon ion radiotherapy (CIRT) in the setting of hepatocellular carcinoma (HCC) and establishes the maximum tolerated dose (MTD) calculated by the Local Effect Model version I (LEM-I) with a dose escalation plan. The escalated relative biological effectiveness-weighted dose levels included 55, 60, 65, and 70 Gy in 10 fractions. Active motion management techniques were employed, and several measures were applied to mitigate the interplay effect induced by a moving target. CIRT was planned with the LEM-I-based treatment planning system and delivered by raster scanning. Offline PET/CT imaging was used to verify the beam range. Offline adaptive replanning was performed whenever required. Twenty-three patients with a median tumor size of 4.3 cm (range, 1.7–8.5 cm) were enrolled in the present study. The median follow-up time was 56.1 months (range, 5.7–74.4 months). No dose limiting toxicity was observed until 70 Gy, and MTD had not been reached. No patients experienced radiation-induced liver disease within 6 months after the completion of CIRT. The overall survival rates

Abbreviations: 3DCRT, 3-dimensional conformal radiotherapy; 4D-CT, 4-dimensional CT; ABC, active breath coordinator; AC, abdominal compression; BH, breath hold; CIRT, carbon ion radiotherapy; CP, Child-Pugh; CTCAE, Common Terminology Criteria for Adverse Events; CTV, clinical target volume; DLT, dose limiting toxicity; D_{RBE}, RBE-weighted dose; GI, gastrointestinal; GTV, gross tumor volume; HCC, hepatocellular carcinoma; HIT, Heidelberger Ion Therapy; IGTV, internal gross tumor volume; IMRT, intensity modulated radiotherapy; LEM-I, Local Effect Model version I; LET, linear energy transfer; LPFS, local progression-free survival; MDTNL, mean dose to normal liver; MKM, Microdosimetric Kinetic Model; MTD, maximum tolerated dose; OAR, organs at risk; OER, oxygen enhancement ratio; OS, overall survival; PFS, progression-free survival; PRT, proton radiotherapy; PTV, planning target volume; RBE, relative biological effectiveness; SBO, single beam optimization; SBRT, stereotactic body radiotherapy; TACE, transcatheter arterial chemoembolization.

Zhengshan Hong and Wenna Zhang contributed equally to this work.

at 1, 3, and 5 years were 91.3%, 81.9%, and 67.1% after CIRT, respectively. The local progression-free survival and progression-free survival rates at 1, 3 and 5 years were 100%, 94.4%, and 94.4% and 73.6%, 59.2%, and 37.0%, respectively. The raster scanning technique could be used to treat HCC. However, caution should be exercised to mitigate the interplay effect. CIRT up to 70 Gy in 10 fractions over 2 weeks was safe and effective for HCC.

KEYWORDS
carbon ion radiotherapy, dose escalation, hepatocellular carcinoma, pencil beam scanning, phase I trial

1 | INTRODUCTION

Chinese and US guidelines have proposed radiotherapy as a treatment option for unresectable or inoperable hepatocellular carcinoma (HCC) without distant metastases.[1,2] Since the 1990s, three-dimensional conformal radiotherapy (3DCRT), intensity-modulated radiotherapy (IMRT), and stereotactic body radiotherapy (SBRT) have been used for HCC and have yielded very good outcomes.[3–6] In the 1990s, new innovations—proton radiotherapy (PRT) and carbon ion radiotherapy (CIRT)—were introduced to irradiate HCC.[7,8] Although the physical properties of PRT and CIRT are deemed to be similar due to the Bragg-peak effect, which enables delivery of high radiation dose to the target while sparing the normal liver, CIRT leads to reduced lateral scattering and longitudinal straggling compared to PRT. In addition, CIRT possesses biological benefits as a high linear energy transfer (LET) beam with a high relative biological effectiveness (RBE) of 2–3 and a low oxygen enhancement ratio (OER) of around 2 in the target region, which makes it more attractive for the treatment of radioresistant and hypoxic tumors.[9,10]

Japanese clinical studies of CIRT using passive broad-beam delivery techniques for HCC have already shown encouraging outcomes.[11–13] Nevertheless, the pencil beam scanning technique has gone through a rapid development recently and is believed to be a better approach than passive beam with unsurpassed conformity and decreased secondary radiation, although there is a great challenge for it to treat moving targets caused by the interplay effects, which exacerbate uncertainties in dose delivery.[14,15] To date, no published studies have elaborated on the utilization of pencil beam scanning CIRT to treat HCC except for the initial 6 cases reported by Heidelberger ion therapy (HIT) in Germany with a short follow-up period of 11.0 months.[16] In addition to beam delivery techniques, biophysical models used for RBE-weighted dose (D_{RBE}) calculation and prescription in Japan (Microdosimetric Kinetic Model, MKM) and our center (Local Effect Model version I, LEM-I) are different, so we could not directly use their total dose and fractionation for our patients.[17,18]

Thus, we carried out this prospective dose escalation study to determine the maximum tolerated dose (MTD) calculated by LEM-I and evaluate the feasibility and safety of CIRT with raster scanning, one of the pencil beam scanning techniques, for HCC patients in the long term.

2 | MATERIALS AND METHODS

2.1 | Patient eligibility criteria

The patient eligibilities were as follows: HCC confirmed by cytology or histology or clinically diagnosed using the criteria proposed by the Chinese Society of Clinical Oncology[19] or the American Association for the study of Liver Diseases;[1] surgically unresectable, medical inoperable, or refusal of surgery; maximal tumor size is less than 12 cm; tumor located 10 mm away at least from the gastrointestinal (GI) tract; Child-Pugh (CP) class of A; and adequate renal and bone marrow function. This study was reviewed and approved by the ethical committee of our center and registered at ClinicalTrials.gov (NCT02802124). All patients signed an informed consent form before the initiation of CIRT. The patients were strongly recommended to have the transcatheter arterial chemoembolization (TACE) before and/or after CIRT, and an interval of at least 1 month was required between TACE and CIRT. The antiviral agent was prescribed during and after CIRT for patients with hepatitis B infection.

2.2 | Dose escalation and toxicity criteria

This was a phase I dose escalation study using a standard 3 + 3 design. It consisted of four CIRT dose levels: D_{RBE} of 55, 60, 65, and 70 Gy in 10 daily fractions and five fractions per week. Adverse events that occurred within 90 days from the initiation of CIRT were defined as acute toxicities, and those beyond 90 days as late toxicities, evaluated by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03). The dose-limiting toxicity (DLT) was defined as any grade 3 or higher non-hematological toxicities and any grade 4 or higher for hematological toxicities within 3 months from the start of CIRT. After CIRT, the first 3 patients were followed up for 3 months, and if none of the 3 patients experienced a DLT, the next dose level would be started. If 1 of 3 patients developed a DLT, an extra 3 patients would be enrolled

at the same dose level. If only one out of 6 patients experienced DLT, the dose escalation continued. When >1 of 3 patients, or ≥2 of 6 patients, experienced DLT, the dose escalation would be terminated. When the follow-up time was not due after 3 required patients enrolled, new eligible patients were enrolled at one dose level below the current testing level.

2.3 | CIRT details

The patients were immobilized in either a supine or prone position with arms up by customized vacuum lock and thermoplastic mask. Before planning, if without lipiodol deposited in the tumors by TACE, one or two metal markers were implanted percutaneously near the tumor avoiding the beam path, to aid in daily pre-treatment position verification. One of the following active motion management techniques was chosen, depending on the compliance of patients, to address the intrafractional geometrical changes: (1) Breath hold: Active breath coordinator (ABC) was the first choice if the patient could cooperate with ABC and hold their breath for 20–30 sec at the end of inspiration (BH patients); (2) Gating: Anzai respiratory gating system was the second choice when the patient breathed smoothly and regularly (gating patients); and (3) Abdominal compression: It was used for patients who failed with both ABC and the Anzai respiratory gating system. After abdominal compression, the tumor moving should be ≤5 mm (AC patients). For BH patients, two sets of CT scans were acquired. One was a plain CT for treatment planning, and the other had intravenous and oral contrast. For gating and AC patients, four-dimensional CT (4D-CT) was acquired without contrast for motion assessment and treatment planning.

Gross tumor volume (GTV), including primary tumor and any hilar nodes of ≥1 cm in diameter, was contoured based on contrast CT, MRI, and PET/CT. Internal gross tumor volume (IGTV) was a fused GTV from all GTVs contoured on each breath phase within the gating window for gating patients, or formed by combining the GTVs in all phases for AC patients, or by adding the reproducibility deviation among each breath holding to GTV for BH patients. The clinical target volume (CTV) was formed by adding a margin of 5 mm around the IGTV. The planning target volume (PTV) was produced by adding margins of 5–10 mm for the set-up error and beam range uncertainty with more margins along the beam direction. The deposited lipiodol inside the tumor was overridden with normal liver tissue density before dose calculation. For BH patients, plans were generated on the breath-hold plain CT. For gating patients, the gating window should be decided before planning. The criterion to select the gating window was that the residual target motion at any direction in the gating window be ≤5 mm. In general, the gating window was from 20% of the expiratory phase to 20% of inspiratory phase. The dose was calculated on the average CT of all phases in the gating window. For AC patients, the residual tumor motion must be ≤5 mm, and a plain CT was used for planning. Typically, 2–3 horizontal or 45-degree oblique beams with different couch positions were arranged. Requirements of target coverage and dose constraints for organs at risk (OAR) are detailed in Table 1 and Table 2, respectively. The normal tissue dose should be minimized as much as possible. If these constraints cannot be met, even when the mandatory requirements for target coverage are used, the patient should be removed from the trial. All treatment plans were generated by the Syngo treatment planning software system, and CIRT was delivered by Siemens synchrotron with energy from 88–430 MeV/u by raster scanning.

Prior to irradiation delivery, the plan was verified by a three-dimensional water phantom with 24 pinpoint chamber array. The 90% gamma index passing rate was used under 3%/3 mm criterion. For daily position verification, a pair of orthogonal kilovoltage X-ray films at anterior–posterior and right–left directions were taken immediately before each treatment fraction to measure and correct the set-up errors online. Furthermore, all patients were moved to a PET/CT room to undergo scanning within 20 min after completion of the first fraction of CIRT, as the gamma pair emitted by the annihilation of positrons produced by unstable isotopes created by inelastic interaction of incident carbon ions with patient tissue could be measured by PET/CT scanner, which had been effectively used for in vivo beam range verification by comparing the PET/CT image with a Monte Carlo simulation predicted dose deposition. Figure 1 shows the PET/CT image after CIRT and the planned dose distribution for a typical case. As an adaptive treatment strategy, offline 4D-CT review images were routinely acquired right before and weekly during the course of CIRT. Dose recalculations were carried out to determine whether adaptive replanning was needed to address the impact of interfractional anatomic changes.

TABLE 1 The dosimetric requirements for target volume coverage

Target	Optimal	Mandatory
IGTV	95% of prescribed dose covers 100% of IGTV	95% of prescribed dose covers <100% of IGTV, but remains ≥99%
PTV	95% of prescribed dose covers 100% of PTV	95% of prescribed dose covers <100% of PTV, but remains ≥95%
	D_{max} ≤ 110% of prescribed dose	D_{max} ≤ 115% of prescribed dose
	D_{min} ≥ 90% of prescribed dose	D_{min} ≥ 85% of prescribed dose

Abbreviations: D_{max}, maximum dose to a point that is 0.03 cc; D_{min}, minimum dose to a point that is 0.03 cc; IGTV, internal gross tumor volume; PTV, planning target volume.

TABLE 2 The dose constraints for organs at risk

Structure	Constraints
Liver minus GTV	$D_{mean} < 20$ Gy
Kidney (left and right)	$D_{mean} < 12$ Gy, $V_{14} < 30\%$
Spinal cord	$D_{max} < 30$ Gy
Stomach	$D_{max} < 40$ Gy
Duodenum	$D_{max} < 40$ Gy
Small bowel	$D_{max} < 40$ Gy
Large bowel	$D_{max} < 45$ Gy

Abbreviations: D_{max}, maximum RBE-weighted dose; D_{mean}, mean RBE-weighted dose; GTV, gross tumor volume; Gy, gray; V_{14}, percentage of volume receiving more than 14 Gy.

2.4 | Follow up and statistics

During CIRT, patients were examined weekly. After the completion of CIRT, patients were followed up every 3 months for the first 2 years and every 6 months afterwards. Physical examination, complete blood count, renal and hepatic function, and serum alpha-fetoprotein were obtained on each follow-up visit. The abdominal dynamic MRI was performed every 3 months for the first year and then every 6 months thereafter.

The primary endpoint of this study was to determine the MTD. The overall survival (OS), local progression-free survival (LPFS), and progression-free survival (PFS) were the secondary endpoints. Local progression was defined as ≥20% of the increase of the longest tumor diameter. The distant metastasis was diagnosed on the basis of image findings. The OS, LPFS, and PFS rates were estimated from the initiation of CIRT using the Kaplan–Meier method.

3 | RESULTS

3.1 | Patient characteristics

From January 2016 to July 2018, 23 patients were enrolled in this study, 5 at dose level 1, 6 at level 2, 8 at level 3, and 4 at level 4. The last follow up was performed in March 2022 with a median follow-up time of 56.1 months (range, 5.7–74.4 months) and by individual dose levels as follows: 34.7 months for level 1, 42.1 months for level 2, 58.0 months for level 3, and 50.2 months for level 4. The patient and treatment characteristics are summarized in Table 3. All patients had CP class A liver disease, and 8 (34.8%) presented with portal vein hypertension. The maximum tumor diameters ranged from 1.7 to 8.5 cm, with a median of 4.3 cm. Eight patients (34.8%) had multiple tumors, and 6 (26.1%) had vascular tumor thrombosis. There were 17 patients (73.9%) with initial lesions and 6 (26.1%) with recurrent lesions after surgery or radiofrequency ablation. The pre-established dose constraints for each OAR and dosimetric requirements for target coverage were achieved for all 23 patients. Eleven (47.8%) patients fulfilled the optimal target coverage criteria,

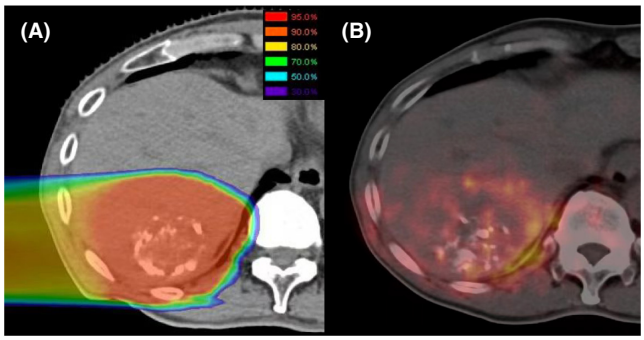

FIGURE 1 In vivo beam range verification by PET/CT scans from a typical case. A hepatocellular carcinoma (HCC) in the right lobe after two sessions of transcatheter arterial chemoembolization received carbon ion radiotherapy with D_{RBE} of 55 Gy in 10 fractions over 2 weeks. (A) Dose distribution by two lateral beams, which shows 55 Gy in brown color wash. (B) PET/CT image after 5.5 Gy, which shows acquired PET activity distribution roughly corresponding to the area of 55 Gy. No measured activity in the spinal cord demonstrates that the beam stopped in front of it.

and for the remaining 12 (52.2%), target coverage was moderately compromised to comply with OAR constraints, but still met the mandatory criteria.

3.2 | Toxicity and tolerance

All patients completed the planned CIRT without interruption. No DLT was observed until 70 Gy, and MTD had not been reached. No patients experienced radiation-induced liver disease as defined by CP score progression of two points during CIRT and 6 months thereafter. Acute and late toxicities during the long-term follow-up period are listed in Table 4. Two patients (at the 65 Gy and 70 Gy dose levels, one each) experienced stomach bleeding 4 and 17 months after the CIRT, respectively, attributing to their cirrhotic portal hypertension. Both of them were treated with the medication of somatostatin or its analogues and eventually recovered.

3.3 | Tumor control and survival

At the last follow-up visit, 10 patients survived with no evidence of disease, and 6 survived with lung ($n = 3$), bone ($n = 1$) or intrahepatic metastases ($n = 3$) but no local progressions. Seven patients died of intrahepatic metastases without local progression ($n = 3$), lung metastasis ($n = 1$), bone metastasis ($n = 1$), local progression with intrahepatic and lung metastasis ($n = 1$), or portal vein hypertension ($n = 1$). Overall, 1 patient failed locally and was allocated to the dose level of 55 Gy. Among 5 patients with lung metastases, 3 patients survived after nivolumab and X-ray irradiation, 1 patient died with local progression and intrahepatic metastasis, and 1 died with no treatment. The OS rates at 1, 3, and 5 years were 91.3% (95% CI, 69.5%–97.8%), 81.9% (95% CI, 58.6%–92.8%), and 67.1% (95% CI, 42.9%–82.9%), respectively. The LPFS and PFS rates at 1, 3, and

TABLE 3 Patient and treatment characteristics

Characteristics		Number of patients
Median age (range), years	57 (28–76)	
Gender	Male/Female	20/3
ECOG PS	0/1	12/11
BCLC stage	0/A/B/C	1/0/12/10
AJCC stage	I–II/III	14/9
Median tumor size (range), cm	4.3 (1.7–8.5)	
Diagnosis	Cytology or histology/Clinical	9/14
Surgery	Unresectable or inoperable/Refusal	20/3
AFP	Positive/Negative	15/8
Hepatitis B	Yes/No	18/5
Child-Pugh score	A5/A6	20/3
TACE	No/Yes	4/19
CIRT dose, D_{RBE}	55 Gy in 10 fraction 60 Gy in 10 fraction 65 Gy in 10 fraction 70 Gy in 10 fraction	5 6 8 4
Motion management techniques	BH gating AC	13 8 2

Abbreviations: AC, abdominal compression; AFP, alpha-fetoprotein; AJCC, American Joint Committee on Cancer; BCLC, Barcelona Clinic Liver Cancer; BH, breath hold; CIRT, carbon ion radiotherapy; D_{RBE}, RBE-weighted dose; ECOG PS, Eastern Cooperative Oncology Group performance status; TACE, transcatheter arterial chemoembolization.

TABLE 4 Acute and late toxicities after carbon ion radiotherapy in 23 patients with hepatocellular carcinoma

Toxicities	Grade 1 *n* (%)	Grade 2 *n* (%)	Grade 3 *n* (%)	Grade 4 *n* (%)
Acute				
Skin injury	10 (43.5)	-	-	-
Abdominal pain	4 (17.4)	-	-	-
Leukocytopenia	4 (17.4)	2 (8.7)	2 (8.7)	-
Neutrocytopenia	3 (13.0)	6 (26.1)	-	-
Thrombocytopenia	3 (13.0)	2 (8.7)	-	-
ALP increase	2 (8.7)	-	-	-
Bilirubin increase	-	1 (4.3)	-	-
Albumin decrease	2 (8.7)	1 (4.3)	-	-
Late				
Stomach bleeding	-	-	2 (8.7)	-

Abbreviation: ALP, alkaline phosphatase.

5 years were 100%, 94.4% (95% CI, 66.6%–99.2%), and 94.4% (95% CI, 66.6%–99.2%) and 73.6% (95% CI, 50.5%–87.2%), 59.2% (95% CI, 36.0%–76.4%), and 37.0% (95% CI, 16.6%–57.7%), respectively (Figure 2). The median PFS was 41.1 months, and median OS and LPFS were not reached.

4 | DISCUSSION

As a state-of-the-art technique, PRT and CIRT yielded more promising outcomes for HCC than photon radiotherapy.[20] We previously performed a dosimetric study to compare IMRT, PRT, and CIRT showing that both PRT and CIRT delivered a much lower mean dose to normal liver (MDTNL) than IMRT, and CIRT delivered the least MDTNL, which enabled CIRT to safely treat HCC of a larger size.[21] Furthermore, CIRT exhibits an increased LET in the spread-out Bragg-peak region, leading to more direct and severe cellular damage and bringing a biological advantage over photon and proton therapy.

We were facing two great challenges. The first one was the dose delivery technique. In most published HCC studies, the dose was delivered by passive broad beam technique relying on 3DCRT treatment planning. In contrast, the pencil beam scanning technique allows intensity modulation with highly conformal dose distribution, sparing more normal tissue in the entrance path. In addition, it eliminates time and resources needed for the use of a collimator and compensator and reduces neutron production in the air due to the absence of beam modifying hardware in the beam line. With these distinct advantages, it is becoming the new standard technique in particle therapy and being adopted by more and more new centers, often as the only treatment modality. However, the interplay effect, describing the dosimetric impact that derives from the interaction

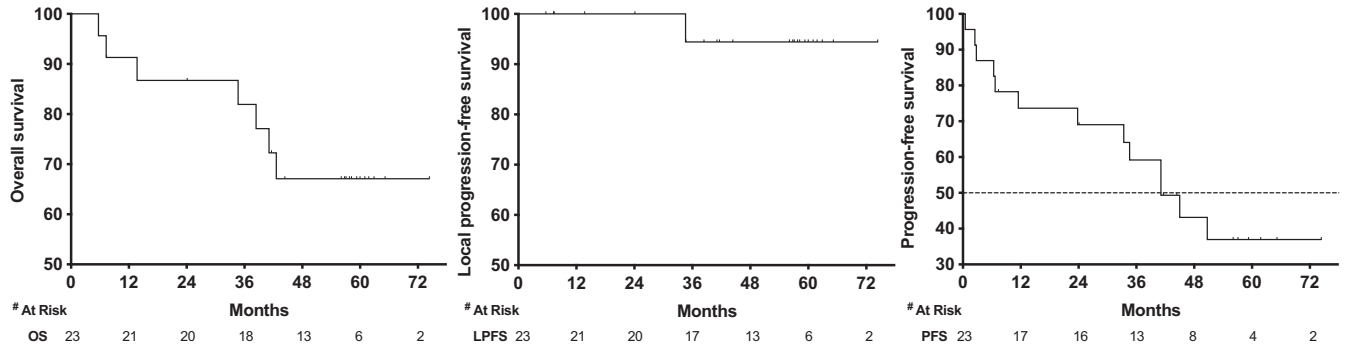

FIGURE 2 Kaplan–Meier estimates of overall survival (OS), local progression-free survival (LPFS), and progression-free survival (PFS) for all 23 patients

of the dynamic beam delivery with the target's motion, becomes a particular challenge.[22] Several measures were used to reduce the interplay effect during our planning process: (1) the target motion amplitude in the gating window, or residual target motion after abdominal compression should be ≤5 mm, by which the dose inhomogeneity was acceptable based on our moving phantom study[23]; (2) beam angles were arranged with the shortest distance to the target, and beams went through the homogeneity tissues; (3) appropriate beam spot size of 10 mm with spot spacing of 2 mm were used, which was demonstrated to improve dose homogeneity by German study;[24] (4) Multiple beams with single beam optimization (SBO) were preferred, which had an inherent rescanning effect and could provide additional robustness against the motion effect; and (5) because of the limited beam angles and no rescanning technique in our facilities, moderate hypofractionation of 10 fractions, but not ultra-hypofractionation, was used to mimic effective rescanning and further smear the local dose heterogeneities within the target.

The second challenge we were facing was the difference in clinically applied RBE models between different facilities. Compared to the identical absorbed photon dose, a higher RBE resulting from increased LET of carbon ions is considered and calculated using RBE models in the treatment planning system. The comparison study showed that the same amount of absorbed dose had a different result for D_{RBE} for the MKM or LEM model due to their different RBE predictions.[25–27] In other words, the identical D_{RBE} distributions by different models will be related to different absorbed dose distribution, leading to different biological effectiveness. As such, prescription D_{RBE} using different RBE models at different treatment centers cannot be regarded as equivalent, which is in contrast to photon therapy. In the literature, all CIRT clinical studies reported by Japanese centers use the MKM model, but the LEM-I model is used in our center. Although we knew what the optimal fractionation and total dose for HCC were at Japanese centers, we could not use them in our patients directly. HIT published their CIRT protocol for HCC in 2011,[28] and in 2013, they reported the first data of 6 patients enrolled in that trial to demonstrate the feasibility of the technique and the acute response.[16] However, no reports have been released since then. Therefore, it was necessary for us to carry out a dose escalation study again to know what the MTD was with the LEM-I model. As a consequence, the observed toxicities of LEM-I-based dose fractionations in our study appeared to be tolerable and acceptable. With the median tumor diameter of 4.3 cm and 87.0% of the tumors unresectable or inoperable in 23 patients, CIRT yielded encouraging outcomes, which were as good as those reported by Japanese centers. However, the majority of failure patterns were intrahepatic and/or distant metastases. Therefore, CIRT might need to be combined with regional and systemic therapies, including TACE, molecular targeted therapy, and immunotherapy, to reduce the out-of-radiation field recurrences.

Regarding what the optimal dose fractionation schedule for HCC was, we were not able to conclude as only 23 patients were enrolled. However, 1 local failure patient received 55 Gy in 10 fractions over 2 weeks; thus, it seemed like 55 Gy was not high enough. As reported in the literature, the biological equivalent dose for α/β ratio of 10 Gy (BED_{10}) >100 Gy was proposed to be the ablative dose for HCC in SBRT.[29,30] We would like to recommend 65–70 Gy in 10 fractions over 2 weeks (BED_{10} of 107 or 119) as the optimal dose. However, given that the MDTNL would probably be over the dose constraint for many patients with a small volume of normal liver when 70 Gy is prescribed, 65 Gy in 10 fractions over 2 weeks could be optimal.

In this study, besides the water phantom dose verification before the treatment, we used a more direct method to image the dose deposition from CIRT in the patient. Several positron-emitting isotopes were produced as induced radioactivity during nuclear fragmentation in CIRT, including the projectile or target fragment of ^{11}C, ^{15}O, and ^{13}N. As the half decay time of ^{11}C is 20 min, the radioactivity detected by a commercial PET/CT scanner was predominantly from ^{11}C.[31,32] Therefore, the images were acquired as soon as possible after CIRT, and the tissues containing more carbon atoms would show higher radioactivity than others. Although the PET images represented the geometric distribution of positron emitters but not really quantitative measurement of dose distribution, they were still meaningful, as shown in Figure 1, revealing that no radioactivity was detected in the spinal cord, which helped us verify the beam range and confirm the accuracy of CIRT delivery.

In summary, our study demonstrated that the pencil beam scanning (raster scanning) technique was feasible for HCC. However, caution should be exercised to mitigate the interplay effect. Patients could tolerate CIRT up to 70 Gy in 10 fractions over 2 weeks. The preliminary outcomes were encouraging.

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None.

DISCLOSURE

The authors declare no conflicts of interest.

ETHICS STATEMENT

This study was reviewed and approved by the ethical committee of the Shanghai Proton and Heavy Ion Center and registered at ClinicalTrials.gov (Trial registration number: NCT02802124). All patients signed an informed consent form before the initiation of CIRT. Animal Studies: N/A.

ORCID

Wenna Zhang https://orcid.org/0000-0002-6370-8482

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