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4D-MRI assisted stereotactic body radiation therapy for unresectable colorectal cancer liver metastases

Hongzhi Wang [1], Xuan Zheng [1], Jiawen Sun [1], Xianggao Zhu, Dezuo Dong, Yi Du, Zhongsu Feng, Jian Gong, Hao Wu, Jianhao Geng, Shuai Li, Maxiaowei Song, Yangzi Zhang, Zhiyan Liu, Yong Cai, Yongheng Li, Weihu Wang *

Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Radiation Oncology, Peking University Cancer Hospital and Institute, Beijing 100142, China

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ABSTRACT

This study evaluated the feasibilities and outcomes following four-dimensional magnetic resonance imaging (4D-MRI) assisted stereotactic body radiation therapy (SBRT) for unresectable colorectal liver metastases (CRLMs). From March 2018 to January 2022, we identified 76 unresectable CRLMs patients with 123 lesions who received 4D-MRI guided SBRT in our institution. 4D-MRI simulation with or without abdominal compression was conducted for all patients. The prescription dose was 50–65 Gy in 5–12 fractions. The image quality of computed tomography (CT) and MRI were compared using the Clarity Score. Clinical outcomes and toxicity profiles were evaluated. 4D-MRI improved the image quality compared with CT images (mean Clarity Score: 1.67 vs 2.88, $P < 0.001$). The abdominal compression reduced motions in cranial–caudal direction ($P = 0.03$) with two phase T2 weighted images assessing tumor motion. The median follow-up time was 12.5 months. For 98 lesions assessed for best response, the complete response, partial response and stable disease rate were 57.1 %, 30.6 % and 12.2 %, respectively. The local control (LC) rate at 1 year was 97.3 %. 46.1 % of patients experienced grade 1–2 toxicities and only 2.6 % patients experienced grade 3 hematologic toxicities. The 4D-MRI technique allowed accurate target delineation and motion tracking in unresectable CRLMs patients. Favorable LC rate and mild toxicities were achieved. This study provided evidence for using 4D-MRI assisted SBRT as an alternative treatment in unresectable CRLMs.

1. Introduction

Liver metastases develop in more than 50 % of patients with colorectal cancer (CRC) and are the primary cause of death [1]. Systemic treatment along with local treatment have become the basis of therapeutic strategy in colorectal cancer liver metastases (CRLMs) [2]. Liver resection is the standard local treatment approach for resectable CRLMs. It provided opportunities for patients to be long-term survivors, with a 10-year overall survival (OS) of approximately 25 % [3]. However, patients with CRLMs were often deemed as unresectable as for the location and distribution of metastatic lesions, poor medical conditions or impaired liver function. Even with modern systemic treatment and advanced surgical techniques, only 10–40 % of CRLMs were resectable [4]. Radiofrequency ablation (RFA) is an alternative procedure for

Abbreviations: CRC, colorectal cancer; CRLMs, colorectal cancer liver metastases; OS, overall survival; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy; CT, computed tomography; LC, local control; ITV, internal target volume; 4D-CT, four-dimensional computed tomography; 4D-MRI, four-dimensional magnetic resonance imaging; ECOG, Eastern Cooperative Oncology Group; DWI, diffusion weighted imaging; ICRU, International Commission on Radiation Units and Measurements; GTV, gross target volume; PTV, planning target volume; CC, cranial–caudal; AP, anterior–posterior; LR, left–right; UK, United Kingdom; ASTRO, American Society for Radiation Oncology; IMRT, intensity modulated radiotherapy; VMAT, volumetric modulated arc therapy; CBCT, cone beam computed tomography; RECIST, Response Evaluation and Criteria in Solid Tumors; CTCAE, Common Toxicity Criteria Adverse Events version; PFS, progression-free survival; BED, biological equivalent dose; IQR, inter quartile range; CR, complete response; PR, partial response; SD, stable disease; MWA, microwave ablation.

* Corresponding Author: Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Radiation Oncology, Peking University Cancer Hospital and Institute, No. 52 Fu-cheng Road, Haidian District, Beijing 100142, China (Wei-Hu Wang).

E-mail address: wangweihu88@163.com (W. Wang).

[1] Hongzhi Wang, Xuan Zheng and Jiawen Sun contributed equally as first authors.

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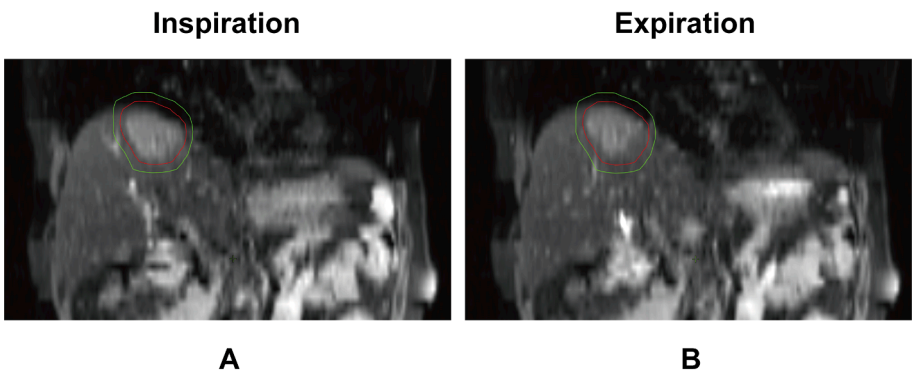

Fig. 1. Exemplary coronal slices of target volume delineation on T2 weighted sequences at the end of inspiration (A) and expiration (B). Red lines represent internal target volume, green lines represent planning target volume. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

unresectable disease. It leads to better survival outcomes compared to systemic treatment alone [5]. However, RFA is not widely applicable, especially for those with lesions larger than 3 cm, adjacent to major blood vessel, biliary tract or diaphragm [6,7].

Stereotactic body radiation therapy (SBRT) delivers high dose in few fractions to target lesions while mostly sparing the uninvolved normal tissues, which is increasingly used in the management of metastatic liver tumors [8]. In unresectable CRLMs, SBRT had demonstrated comparable results to other ablation therapies, especially in large lesions [9,10]. However, owing to the low contrast in computed tomography (CT) image and the large tumor motions during respiratory cycles for CRLMs, the delivery of SBRT was challenging. It was reported that the 2-year local control (LC) rate ranged from 40 % to 90 % following SBRT for CRLMs [11–20]. The observed variability in LC rates across these studies may be partly attributed to the heterogeneity in patient selection and SBRT schemes. More importantly, the techniques used for target delineation and motion management also emerged as crucial factors influencing LC outcomes [12,21].

The internal target volume (ITV) strategy is a widely adopted motion management approach for liver SBRT [22]. Four-dimensional CT (4D-CT) is a commonly used technique for monitoring tumor motions during respiratory cycles to generate ITV. However, due to the poor soft tissue contrast and quick elimination of intravenous contrast in liver tumors, CRLMs are hardly distinguishable in 4D-CT. Compared to 4D-CT, 4D magnetic resonance imaging (4D-MRI) has demonstrated superior ability in generating anatomical contrast and visualizing liver tumors [23]. Besides, a previous study has demonstrated the feasibility of acquiring T2 weighted 4D-MRI images based on respiratory amplitude, which was able to track tumor motion throughout respiratory cycles [24]. With these advantages, the utilization of 4D-MRI may optimize SBRT planning and potentially improve outcomes in CRLMs.

In this study, we explored the application of 4D-MRI with or without abdominal compression in patients with CRLMs as well as reporting the effectiveness and tolerance of 4D-MRI assisted SBRT in this setting.

2. Materials and methods

2.1. Patients

The criteria for CRLMs patients treated with SBRT in our institution included: (1) patients with unresectable liver metastases from colon or rectum adenocarcinoma; (2) no evidence of progressive extrahepatic disease; (3) Eastern Cooperative Oncology Group (ECOG) performance status 0–1; (4) less than 5 metastases; (5) adequate uninvolved liver volume; (6) no prior radiation therapy to the targeted area; (7) adequate liver, renal and hematological functions. A multidisciplinary discussion for each candidate patient was mandatory. All the patients were required to have had clinical, laboratory and imaging evaluation. From March 2018 to January 2022, 94 consecutives CRLMs patients treated with SBRT in our institution were reviewed. Among them, 76 patients had 4D-MRI with (n = 62) or without (n = 14) abdominal compression were included. This study was approved by the institutional review board of the Peking University Cancer Hospital and Institute (2022YJZ90). Written informed consent was obtained from all patients.

2.2. SBRT techniques

All patients underwent respiratory training before simulation. Patients were immobilized in a supine position with a customized vacuum cushion. Abdominal compression was used to reduce respiration-induced liver motion for selected patients who were able to tolerate the procedure. The abdominal compression device was positioned 2–5 cm below the costal arch. Following respiratory guidance, pressure was gradually applied at the end of expiration. Adjustment of compression intensity relied on the patient's tolerance, with avoidance of excessive pressure causing discomfort. Intravenous contrast enhancement CT and MRI images were acquired, with a slice thickness of 3–5 mm. MRI images included contrast-enhanced T1-weighted, two phase T2-weighted, diffusion weighted imaging (DWI) sequences. A pressure sensor was placed on the body surface to track the respiratory movements during MRI simulation. Two phase T2-weighted images were acquired at the end of inspiration and expiration with a prospective, amplitude-based triggering technique [24] using a 3 T Siemens Skyra MRI scanner (Magnetom Skyra, Siemens, Germany). Image registration was performed between simulating CT and 4D-MRI images to optimize the target and normal structure delineation using the Eclipse treatment planning system (Varian, Palo Alto, CA, USA).

The delineation of the target volume is guided by the International Commission on Radiation Units and Measurements reports (ICRU) 50, 62, and 83. The gross target volume (GTV) was contoured in planning CT-MRI fused images. Diagnostic CT and diagnostic MRI were also used as references to better identify the target lesion, especially for lesions that were not definable in neither simulation CT nor MRI images. ITV was determined as the sum of the GTVs from planning CT-MRI fused images. The planning target volume (PTV) was generated from ITV by adding 5 mm margin to ITV in the cranial–caudal (CC), anterior–posterior (AP) and left–right (LR) axes. Exemplary images of target volume definitions on two phase T2 weighted sequences are presented in Fig. 1. SBRT was delivered as multiple fractions of greater than or equal to 5 Gy per fraction. The 2022 United Kingdom (UK) consensus was employed to establish constraints for organs at risk in this study, with the American Society for Radiation Oncology (ASTRO) guideline used as a supplementary reference [25,26]. Prescriptions were individualized with consideration of dose constraint for normal tissues. The planning

Table 1
Patient demographic and treatment characteristics.

Characteristic	No. (%)
No. of patients	76
No. of lesions	123
Age, median (range), y	58 (27–87)
Sex	
Male	47 (61.8)
Female	29 (38.2)
ECOG performance status	
0	67 (88.2)
1	9 (11.8)
T stage	
2	3 (3.9)
3	50 (65.8)
4	21 (27.6)
NA	2 (2.6)
N stage	
0	11 (14.5)
1	41 (53.9)
2	24 (31.6)
Synchronous liver metastases	
Yes	61 (80.3)
No	15 (19.7)
Extrahepatic metastases	
Absent	64 (84.2)
Lung	6 (7.9)
Lymph nodes	3 (3.9)
Lung and lymph nodes	1 (1.3)
Abdomen or pelvis	2 (2.6)
Previous liver-directed therapy	
None	11 (14.5)
Surgery	21 (27.6)
RFA	1 (1.3)
Intra-arterial therapy	1 (1.3)
Surgery and RFA	27 (35.5)
Surgery and intra-arterial therapy	4 (5.3)
Intra-arterial therapy and RFA	1 (1.3)
Surgery, RFA and intra-arterial therapy	10 (13.2)
Systemic therapy within 3 months before SBRT	
Yes	51 (67.1)
No	25 (32.9)
Concurrent systemic therapy	
Yes	7 (9.2)
No	69 (90.8)
Time from diagnosis of CRLMs to SBRT, median (range), months	11.4 (0.5–56.6)
Tumor size, median (range), cm	1.7 (0.5–7.9)
Gross target volume, median (range), cm^3	8.1 (1.2–146.2)
Internal target volume, median (range), cm^3	10.3 (1.6–195.3)
Planning target volume, median (range), cm^3	36.9 (8.9–309.5)
Prescribed dose, fractionation (BED Gy_{10})	
50 Gy, 5 fractions (100.0 Gy_{10})	6 (7.9)
60 Gy, 5 fractions (132.0 Gy_{10})	20 (26.3)
60 Gy, 8 fractions (105.0 Gy_{10})	23 (30.3)
65 Gy, 10 fractions (107.3 Gy_{10})	2 (2.6)
60 Gy, 10 fractions (96.0 Gy_{10})	11 (14.5)
60 Gy, 12 fractions (90.0 Gy_{10})	14 (18.4)
Isocenter of treatment plan	
1	70 (92.1 %)
2	6 (7.9 %)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NA, not available; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy; CRLMs, colorectal cancer liver metastases.

goals were to deliver the prescribed dose to at least 95 % of the PTV. Intensity modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) planning with 6-MV X-rays was performed. Treatment was delivered using the Varian Edge linear accelerator (Varian, Palo Alto, CA, USA). Daily cone beam CT (CBCT) scans verify the target position in our institution. Image registration utilizes titanium clips from prior surgery and the liver contour to ensure precise localization between planning CT and CBCT images. The target volumes and corresponding CBCT images of exemplary cases were displayed in Supplemental Figs. 1 and 2.

2.3. Assessment and follow up

The image clarity of simulation CT and MRI images were evaluated using the Clarity Score proposed by Thomas et al [23], in which images quality were divided into 4 levels.

Patients were evaluated 1 month after SBRT, every 3 months for the first 2 years, every 6 months for the following 3 years and annually thereafter. Follow-up included symptoms, clinical examination, complete blood count, biochemical examinations and diagnostic imaging.

Tumor response was assessed with MRI images by the Response Evaluation and Criteria in Solid Tumors (RECIST) version 1.1. The treatment-related toxicities were evaluated using the Common Toxicity Criteria Adverse Events version (CTCAE) 4.0. Acute toxicities were defined as adverse events occurring within 3 months after SBRT, and late toxicities were those occurring after 3 months.

2.4. Statistical analysis

The endpoints in this study included tumor response, LC rate, OS and progression-free survival (PFS). OS was defined as the period from the first day of SBRT to the date of any death. PFS was defined as the period from the first day of SBRT to the date of progression any death. Local failure was defined as radiologically proven relapse within the PTV and LC was defined as being free of local failure. Survival analysis was performed with the Kaplan–Meier method. The local failure, intrahepatic recurrence and extrahepatic recurrence rate were calculated using a cumulative incidence analysis considering death as a competing event. Categorical data were compared with the chi-square test. Paired data were evaluated using the Wilcoxon rank sum test. Statistical analyses were performed using SPSS 26.0 (IBM, New York, NY) and the survival and cmprsk packages in R, version 4.2.1 (https://www.r-project.org/).

3. Results

3.1. Patients and treatments

A total of 76 patients and 123 lesions were treated. Patients' characteristics are listed in Table 1. The median age for this cohort is 58 years old, ranging between 27 and 87 years old. The male-to-female ratio was 1.62:1. The majority of patients were presented with synchronous liver metastases (80.3 %) and absent of extrahepatic metastases (84.2 %).

Patients were heavily pretreated before SBRT. Most patients (85.5 %) had undergone prior liver-directed therapy to lesions other than the ones that we intended to treat with SBRT, including surgical resection (81.6 %), RFA (51.3 %) and intra-arterial therapy (21.1 %). There were 51 patients (67.1 %) who had received systemic therapy within 3 months

Table 2
Qualitative evaluation of image quality for 123 lesions in simulation CT and 4D-MRI images using the Clarity Score.

Clarity Score*	CT images† N (%)	4D-MRI images‡ N (%)	*P* value
1	17 (13.8)	78 (63.4)	$P < 0.001$
2	24 (19.5)	20 (16.3)	
3	39 (31.7)	13 (10.6)	
4	43 (35.0)	12 (9.8)	
Mean	2.88	1.67	

*1. Diagnostic quality; 2. Non-diagnostic, but clearly demarcated lesion; 3. Less clear borders but definable for treatment planning; 4. Lesion undefinable for treatment planning.
†Include plain and contrast-enhanced CT images.
‡Include contrast-enhanced T1-weighted, two phase T2-weighted, diffusion weighted imaging (DWI) sequences.
Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging.

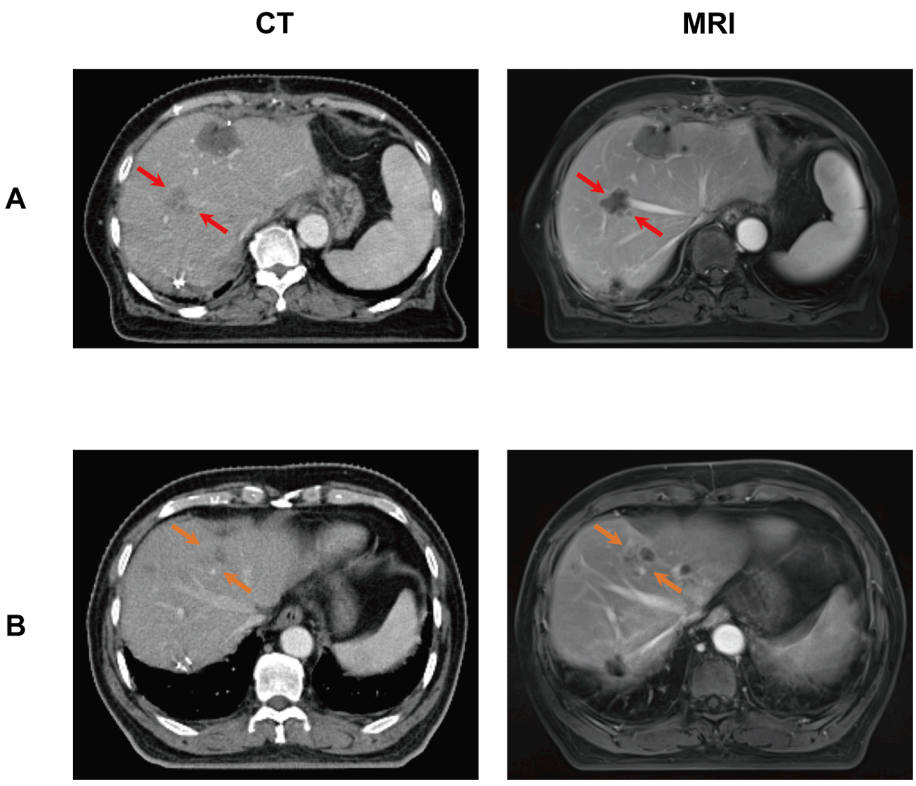

Fig. 2. Comparison of the Clarity Score of two lesions in CT and MRI images. (A) Lesion 1 (red arrow) with Clarity Score of 3 in CT images and 1 in MRI images. (B) Lesion 2 (orange arrow) with Clarity Score of 4 in CT images and 2 in MRI images. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

before SBRT.

The median number of treated lesions was 1 (range, 1–5) and the median lesion size was 1.7 cm (range, 0.5–7.9 cm). The prescription dose was 50–65 Gy in 5 to 12 fractions, the corresponding median value of BED was 105 Gy (range, 90–132 Gy). Most patients received 60 Gy in 8 fractions (30.3 %), followed by 60 Gy in 5 fractions (26.3 %). Among 25 patients (32.9 %) with 49 lesions (39.8 %) receiving a BED less than 100 Gy, the majority had either multiple lesions (64.0 %) or lesions exceeding 4 cm (20.0 %). Dose escalation was constrained by adjacent organs at risk.

3.2. Quality of simulation CT and 4D-MRI image

The Clarity Scores were assessed for all 123 lesions in simulation CT and 4D-MRI images (Table 2). 43 lesions (35.0 %) were not definable in CT images while only 12 lesions (9.8 %) were not identified in 4D-MRI images. The mean Clarity Scores were 2.88 for simulation CT images and 1.67 for simulation 4D-MRI images, 4D-MRI significantly improved image quality ($P < 0.001$). Exemplary images demonstrating the image quality of CT and 4D-MRI images are shown in Fig. 2.

3.3. Tumor motions reduced by abdominal compression in 4D-MRI images

62 patients (81.6 %) with 98 lesions (79.7 %) were able to use abdominal compression devices in simulation. Using the centroid of the tumor as reference point, the tumor motion in two phase T2 weighted images were assessed for all lesions. In the CC, AP and LR directions, the median tumor motions among those with abdominal compression were 5.0 mm [inter quartile range (IQR), 5.0–8.5 mm], 1.6 mm (IQR, 1.5–3.4 mm) and 1.5 mm (IQR, 1.4–1.5 mm), respectively. While they were 10.0 mm (IQR, 5.0–10.0 mm), 1.5 mm (IQR, 0–3.0 mm) and 1.5 mm (IQR, 0–2.3 mm), respectively for those without abdominal compression. Abdominal compression significantly reduced tumor motions in CC direction ($P = 0.03$).

3.4. Response and long-term outcomes

The median follow-up time was 12.5 months (range, 0.4–26.5 months) for the entire cohort and 11.8 months (range, 0.4–26.5 months) among living patients.

Overall, 68 patients and 98 lesions were evaluated for best response. 7 patients with 10 lesions were not available for response evaluation owing to the lack of radiographic data. According to RECIST version 1.1, 15 lesions were not evaluated as the maximum diameter were less than 10 mm. The complete response (CR), partial response (PR) and stable disease (SD) rate for the remaining 98 lesions were 57.1 %, 30.6 % and 12.2 %, respectively.

At the end of follow-up, 2 patients had experienced local failure. One case received 60 Gy in 5 fractions and experienced local failure at 3.8 months, the other one received 60 Gy in 8 fractions and failed at 2.7 months. Local failure was not observed in patients receiving BED less than 100 Gy. The cumulative rate of local failure at 1 year was 2.7 % (Fig. 3A). The corresponding LC rates for the entire cohort at 1 year was 97.3 %.

Overall, disease progressions were observed in 55 patients. Among them, 40 patients (52.6 %) experienced intrahepatic recurrence. The 1-year cumulative rate of intrahepatic recurrence was 53.9 % (Fig. 3B). Extrahepatic recurrence was observed in 39 patients. The most common failure site was lung (38.2 %), followed by lymph node (17.1 %) and bone (4.0 %). The 1-year cumulative rate of extrahepatic recurrence was 53.2 % (Fig. 3C). The median PFS for the whole cohort was 5.3 months. The 1- and 2-years PFS rates were 24.7 % and 16.4 %, respectively (Fig. 4A). At the time of analysis, 12 of 76 patients have died (15.8 %), the median OS was not reached. OS rate at 1 and 2 years were 90.8 % and 63.0 %, respectively (Fig. 4B).

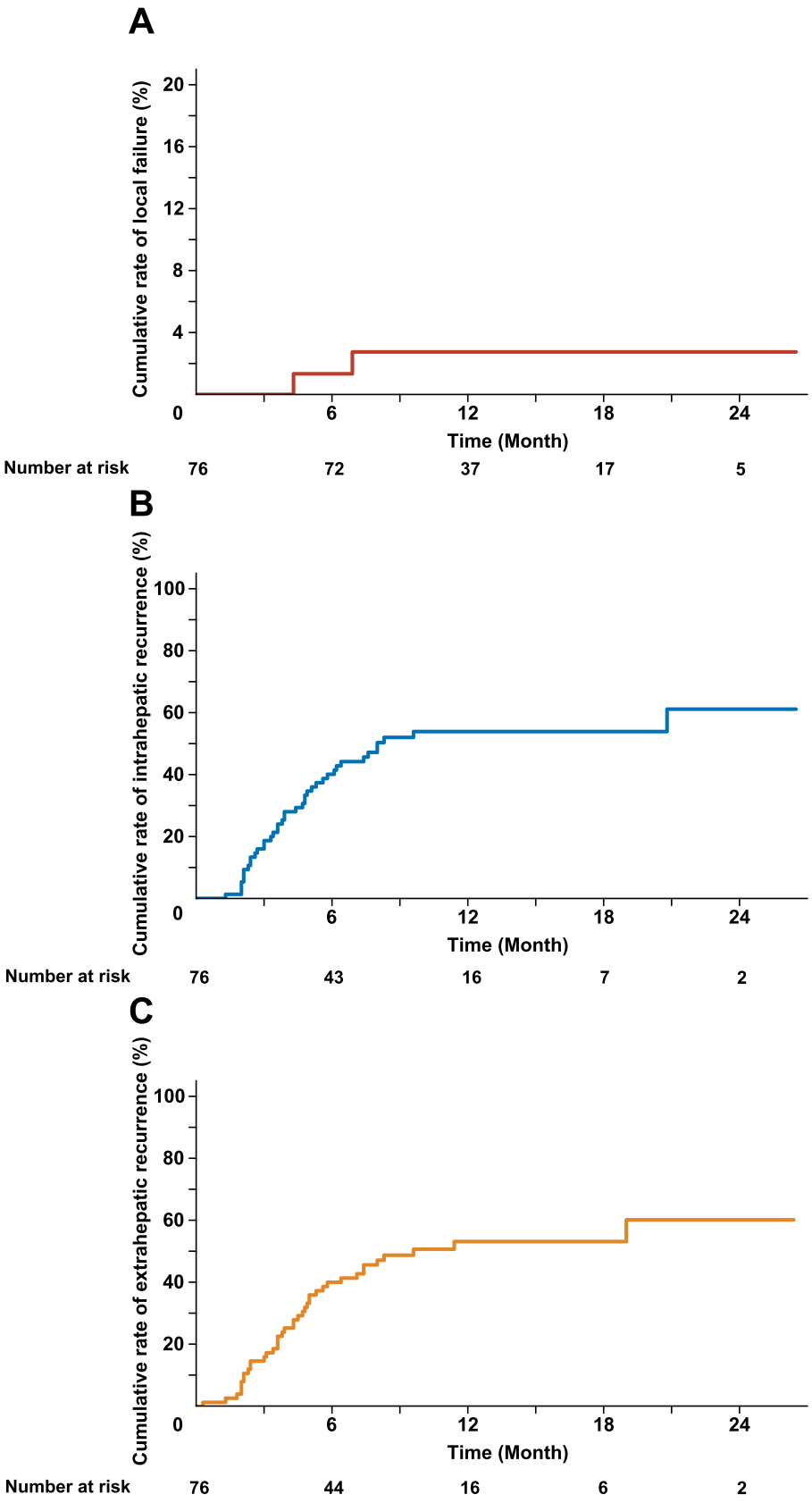

Fig. 3. Cumulative rate of local failure (A), intrahepatic recurrence (B) and extrahepatic recurrence (C) for all patients.

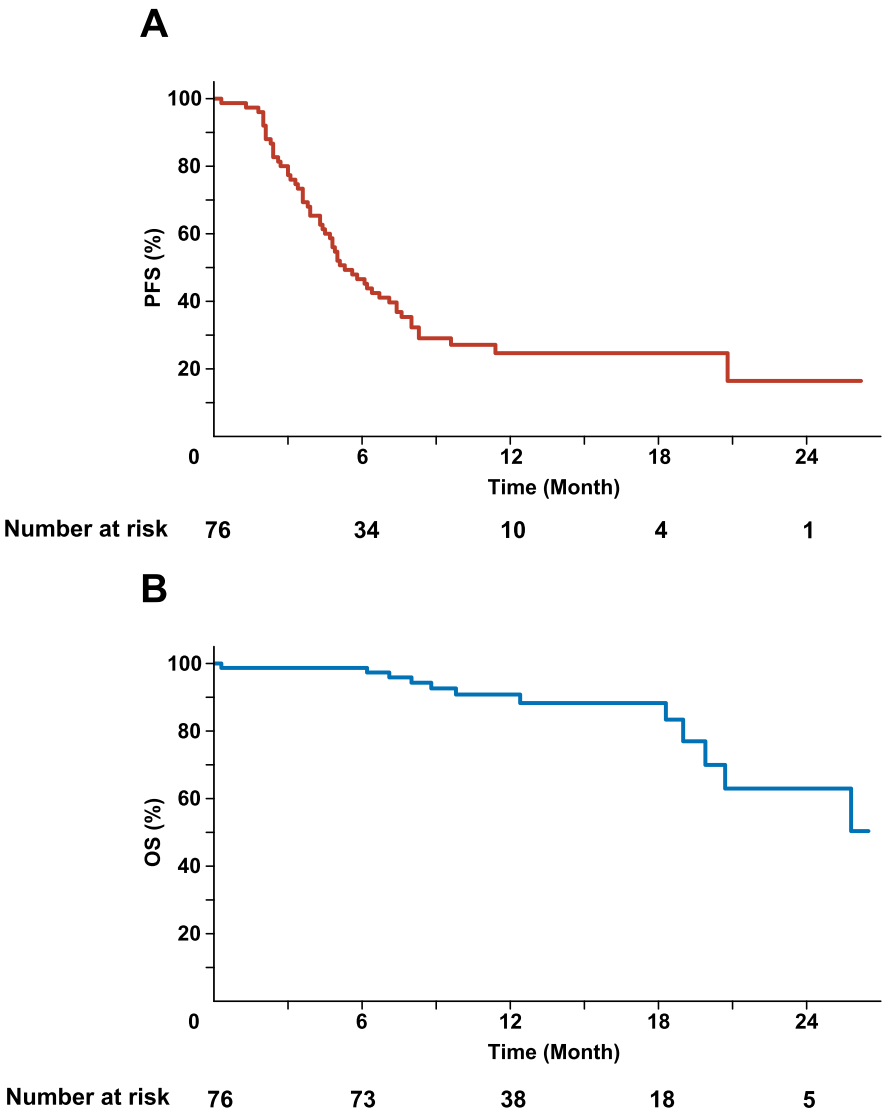

Fig. 4. Progression-free survival (A) and overall survival (B) for all patients.

Table 3
Treatment-related acute toxicities.

Toxicity	Grade 1 No. (%)	Grade 2 No. (%)	Grade 3 No. (%)
Leukopenia	18 (23.7)	11 (14.5)	1 (1.3)
Neutropenia	13 (17.1)	6 (7.9)	1 (1.3)
Thrombocytopenia	7 (9.2)	2 (2.6)	0 (0.0)
Anaemia	8 (10.5)	0 (0.0)	0 (0.0)
Elevated AST	3 (3.9)	0 (0.0)	0 (0.0)
Elevated ALT	4 (5.3)	0 (0.0)	0 (0.0)
Hyperbilirubinemia	5 (6.6)	0 (0.0)	0 (0.0)
Abdominal pain	0 (0.0)	1 (1.3)	0 (0.0)
Fatigue	3 (3.9)	0 (0.0)	0 (0.0)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhoea	1 (1.3)	0 (0.0)	0 (0.0)

Abbreviations: ALT, alanine aminotransferase, AST, aspartate aminotransferase.

3.5. Toxicity

SBRT was well tolerated in this study, with no radiation-induced liver disease. The acute toxicities were summarized in Table 3 and there was no late toxicity observed at the end of follow-up. 35 patients (46.1 %) experienced grade 1–2 toxicities and only 2 patients (2.6 %) experienced grade 3 hematologic toxicities. Overall, hematologic toxicities were most commonly seen in this cohort, with 39.5 % of patients experienced leukopenia, followed by neutropenia (26.3 %), thrombocytopenia (11.8 %) and anemia (10.5 %). Hepatic toxicities included grade 1 elevation of aminotransferase (5.3 %) and hyperbilirubinemia (6.6 %).

4. Discussion

In this study, we explored the feasibility and outcomes of 4D-MRI assisted SBRT in 76 patients with unresectable CRLMs. Compared with contrast-CT simulation, 4D-MRI images better visualized the target lesions, which is more reliable in determining tumor boundaries. The tumor motions were reduced by abdominal compression and tracked with two phase T2 weighted images, representing a viable combination for motion management. Besides, with 4D-MRI images assisting target delineation as well as accounting for respiratory-induced liver motions, we achieved favorable LC rate and mild toxicities for patients with CRLMs. These results provided support for the clinical application of 4D-MRI assisted SBRT for patients with unresectable CRLMs.

Treatments for unresectable CRLMs have evolved with the introduction of novel systemic therapies and advanced local therapies [27]. Ablative therapies, such as RFA and microwave ablation (MWA), represent the most commonly employed minimally invasive local

Table 4
Treatment outcomes of SBRT in patients with colorectal liver metastasis.

Author/year	Study type	No. of patients/ lesions	Size, median (Range), cm	Volume,median (Range) , cm^3	Motion management	Dose/ fraction	BED,median (Range) , Gy	Response, %	LC, % (y)	PFS, % (y)	OS, % (y)	G3 + toxicity, %
Kim/2009[19]	Retrospective	10/14	–	48.8 (3.4–271)	Abdominal compression	36–51 Gy /3f	- (79.2–137.7)	CR 20 PR 40 SD 40	40 (2)	30 (2)	60 (2)	0
Chang/2011[18]	Multicenter	65/102	–	30.1 (0.6–3088)	Respiratory tracking or abdominal compression or active breathing control	22–60 Gy /1–6f	75 (40.5–180)	–	45 (2)	–	38 (2)	3
Vautravers-Dewas/ 2011 [17]	Retrospective	30/62 (total)	3.4 (0.7–10.0) (total)	13 (0.6–245) (total)	Respiratory tracking	40 Gy /4f 45 Gy /3f	80 (80–112.5)	–	86 (2)	–	58 (2)	–
Kress/2012[35]	Retrospective	11/14	–	99.7 (21–225)	Respiratory tracking	16–42 Gy /2–5f	49.7 (28–100.8)	SD 80 PD 20	72 (1)	–	25.7 (2)	9
Berber/2013[36]	Multicenter	53/85	–	182 (mean) (60–581)	Respiratory tracking + respiratory gating	41 Gy /3f	96.76	CR 23 PR 38 SD 28 PD 11	56 (1)	–	60 (total)	0
Stintzing/2013 [16]	Retrospective	30/35	3.4 (mean) (0.7–5.3)	–	Respiratory tracking	24–26 Gy /1f	- (81.6–93.6)	–	80 (2)	–	–	0
Ahmed/2016[15]	Retrospective	22/27	2.0 (0.6–6.7)	–	Abdominal compression + 4D-CT or respiratory gating + 4D-CT	50–60 Gy /5f	132 (100–132)	–	59 (2)	–	73 (2)	–
Joo/2017[12]	Retrospective	70/103	2.9	–	Respiratory gating	45–60 Gy /3–4f	- (58–180)	–	73 (2)	35 (2)	75 (2)	0
Méndez Romero/ 2017 [11]	Retrospective	40/55	2.5 (0.7–6.2)	–	Abdominal compression ± respiratory tracking ± 4D-CT	37.5 Gy /3f or 50.25 Gy /3f	84.38 or 134.42	–	Low dose 74 High dose 90 (2)	–	Low dose 69 High dose 81 (2)	7.5
Vernaleone/2019 [37]	Retrospective	38/66	< 6	28 (2.86–221.84)	Respiratory tracking	25–45 Gy /3–5f	84.38 (37.5–112.5)	CR 7.9 PR 38.1 SD 25.4 PD 28.6	60.4 (1)	12.2 (2)	44.1 (2)	0
Clerici/2020[38]	Retrospective	104/-	≤6	–	Abdominal compression ± 4D-CT	52.5–75 Gy/ 3f	262.50 (144.38–262.50)	–	79 (3)	–	32 (3)	–
Flamarique/2020 [14]	Retrospective	22/31	≤7	–	4D-CT	24–60 Gy/ 3–10f	112.5 (39–180)	–	61.8 (2)	–	53.8 (2)	4.5
Py/2021[13]	Retrospective	67/99	2.3 (IQR: 1.6–3.3)	6.9 (IQR: 2.6–17.0)	Respiratory tracking	37.5–54.0 Gy/3–5f	112.5 (59.5–151.2)	–	72.4 (2)	54.0 (2)	81.4 (2)	3
McDermott/2023 [20]	Retrospective	48/58	3.85 (1.4–10.1)	20.7 (3.4–245.6)	4D-CT or respiratory gating or respiratory tracking	35–54 Gy/3-5f	112.5 (59.5–151.2)	–	61.2 (3)	10.8 (3)	44.9 (3)	2.1
Current study	Retrospective	76/123	1.7 (0.5–7.9)	10.3 (1.2–189.5)	4D-MRI ± abdominal compression	50–65 Gy/ 5–12f	105 (90–132)	CR 57.1 PR 30.6 SD 12.2	97.3 (1)	24.7 (1)	90.8 (1)	2.6

Abbreviations: BED, biological equivalent dose; LC, local control; PFS, progression-free survival; OS, overall survival; CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; 4D-CT, four-dimensional computed tomography; IQR, inter quartile range; 4D-MRI, four-dimensional magnetic resonance imaging.

treatments for CRLMs. These techniques leverage high-frequency electrical currents or electromagnetic microwaves to generate heat directly within the tumor, demonstrating a LC rate ranging from 60 % to 90 %. [28]. However, the outcomes of ablation were compromised in large tumors and those located close to major vessels [27]. SBRT can deliver ablative doses to target lesions in a few sessions through non-invasive approach. These features have broadened its applicability in the treatment of unresectable CRLMs when compared to other ablative therapies [9]. Previous studies have reported favorable outcomes and mild toxicities following SBRT for patients with CRLMs [11,12]. Though various motion management techniques were applied in these studies, the role of 4D-MRI has never been explored. To the best of our knowledge, this is the first study that investigated the clinical outcomes of integrating 4D-MRI technique into SBRT for CRLMs. The objective response rate and 1-year LC for this setting was 87.8 % and 97.3 %, respectively. Most toxic effects were of grade 1 or 2 and only 2.6 % of patients experienced grade 3 toxicities. These results were superior than most of the historical cohorts (2-year LC, 40 %-90 %, Table 4) and the results from other ablative therapies [28]. Despite the absence of high-level evidence, the promising result of this study as well as the past evidences indicating that SBRT could serve as an effective and safe alternative treatment for unresectable CRLMs.

Although the role of SBRT in the management of CRLMs is well established, the implementation of SBRT in clinical practice is challenging. The first difficulty occurs in target delineation. The accuracy of delineation were usually compromised by the low-contrast of CRLMs in CT images [12], while the superior soft tissue contrast of MRI images enables clearer visualization of the lesions [29]. In our cohort, only 65.0 % of lesions were definable in CT images and MRI images improved the image quality in a significant measure. Joo et al analyzed the prognostic factors for LC in 70 patients with CRLMs after SBRT, the multivariate analysis demonstrated that the utilization of diagnostic MRI to assist target delineation was an independent prognostic factor for LC(P = 0.03) [12]. Thus, MRI images are essential in SBRT for CRLMs. The second challenge lies in the wide range of respiratory-induced liver motions. Various motion management strategies were available for liver SBRT, including gating strategy, tracking strategy and ITV strategy [22]. The gating strategy administers treatment exclusively when the patient reaches a predetermined respiratory phase. While it allows for a reduction in the PTV volume, it does come at the cost of considerably prolonging the delivery time. Tumor tracking stands as another advanced technique, allowing for the real-time tracking of a moving tumor and real-time beam adaptation. However, when it came to liver SBRT, fiducial markers were usually required to be implanted via invasive procedures. The ITV strategy aims to encompass all GTV positions over time. 4D-CT is a commonly used non-invasive technique for assessing the respiratory motion and defining the ITV [30]. Nonetheless, due to its limited soft tissue contrast, it is difficult for 4D-CT to picture liver tumors. 4D-MRI can similarly provide fundamental motion information for treatment planning along with superior soft-tissue contrast [23]. While this strategy is easy to implement and time saving, it does result in an expansion of the irradiation volume. In this study, we used abdominal compression for those who can tolerate the procedure, which significantly reduced tumor motion in CC direction and consequently reduced the irradiation volume. The combination of 4D-MRI and abdominal compression brought about accurate treatment to the target lesions while adequately sparing the normal tissues, could serve as a viable approach for assisting SBRT planning in patients with CRLMs. In addition to these strategies, the utilization of MR-Linac in liver SBRT is on the rise. Combined with advanced motion management technique such as gating and 4D-MRI [31,32], it not only generates real-time MR images but also delivers precise treatment, making it an optimal approach for liver SBRT. However, it's important to note that utilizing SBRT with the MR-Linac demands considerable resources in terms of personnel, time, and financial investment, as well as requiring strict patient compliance. In clinical practice, selecting a motion management strategy is a complex matter, requiring consideration of factors such as the patient's performance status and tolerance, equipment availability, and economic considerations.

The main strength of this study is the utilization of 4D-MRI with abdominal compression in SBRT for patients with CRLMs in a relatively large cohort. The combination of 4D-MRI and abdominal compression turned out to be easy-to-use and effective. Besides, we have achieved favorable outcomes with 4D-MRI technique assisting SBRT planning, even in patients with large or multiple lesions. There were also limitations in this study. Firstly, we only acquired MRI images of two phases at the end of inspiration and expiration, the movement was not fully tracked in the respiratory cycle and the ITV might be underestimated in AP and LR directions [33]. However, as the most significant movement for liver tumors were in CC direction, a 5 mm margin added to PTV would be enough to compensate for the lateral movements, especially for patients with abdominal compression [34]. Secondly, selection bias may exist in this single center retrospective study. More evidences are needed before extending the conclusions. Lastly, the follow-up period is relatively short, long-term results are warranted in future studies.

In summary, the 4D-MRI technique enabled accurate target delineation and motion tracking in SBRT for unresectable CRLMs. The combination of 4D-MRI and abdominal compression represented a viable approach for assisting SBRT planning in CRLM patients. With 4D-MRI assisted SBRT, favorable LC rate and mild toxicities were achieved in unresectable CRLM patients. This study provided evidence for using 4D-MRI assisted SBRT as an alternative option for unresectable CRLMs.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2023.100714.

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