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Marker-less online MR-guided stereotactic body radiotherapy of liver metastases at a 1.5 T MR-Linac – Feasibility, workflow data and patient acceptance

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ABSTRACT

Introduction: Stereotactic body radiotherapy (SBRT) is an established ablative treatment for liver tumors with excellent local control rates. Magnetic resonance imaging guided radiotherapy (MRgRT) provides superior soft tissue contrast and may therefore facilitate a marker-less liver SBRT workflow. The goal of the present study was to investigate feasibility, workflow parameters, toxicity and patient acceptance of MRgSBRT on a 1.5 T MR-Linac.

Methods: Ten consecutive patients with liver metastases treated on a 1.5 T MR-Linac were included in this prospective trial. Tumor delineation was performed on four-dimensional computed tomography scans and both exhale triggered and free-breathing T2 MRI scans from the MR-Linac. An internal target volume based approach was applied. Organ at risk constraints were based on the UKSABR guidelines (Version 6.1). Patient acceptance regarding device specific aspects was assessed and toxicity was scored according to the common toxicity criteria of adverse events, version 5.

Results: Nine of ten tumors were clearly visible on the 1.5 T MR-Linac. No patient had fiducial markers placed for treatment. All patients were treated with three or five fractions. Median dose to 98% of the gross tumor volume was 38.5 Gy. The median time from "patient identity check" until "beam-off" was 31 min. Median beam on time was 9.6 min. Online MRgRT was well accepted in general and no treatment had to be interrupted on patient request. No event of symptomatic radiation induced liver disease was observed after a median follow-up of ten month (range 3–17 months).

Conclusion: Our early experience suggests that online 1.5 T MRgSBRT of liver metastases represents a promising new non-invasive marker-free treatment modality based on high image quality, clinically reasonable in-room times and high patient acceptance. Further studies are necessary to assess clinical outcome, to validate advanced motion management and to explore the benefit of online response adaptive liver SBRT.

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1. Introduction

The liver is a frequent site of metastatic disease [1]. Various treatment options are available for the treatment of liver metastases in the context of oligometastatic or oligoprogressive disease, such as surgery, radiofrequency ablation or microwave ablation [2,3]. Over the last two to three decades radiotherapy of the liver has developed from a palliative treatment of the entire liver to a highly conformal and ablative procedure known as stereotactic body radiotherapy (SBRT). This was facilitated by increasingly conformal radiotherapy techniques and the introduction of image guided radiotherapy [4]. Nowadays radiotherapy is a well-established ablative treatment option for liver tumors with local control rates over 90% in contemporary series [5]. One of the most recent technical advances in radiotherapy is the introduction of

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online magnetic resonance tomography guided adaptive radiotherapy (MRgRT) [6–9]. Two major advantages of online MRgRT include a) the superior soft tissue contrast of MR imaging compared with cone-beam computed tomography (CBCT) based treatment guidance and b) the possibility of daily online plan adaptation [10]. Both features appear highly relevant for the upper abdomen where the poor soft tissue contrast of CBCT in general does not permit to directly visualize target lesions and organs at risk (OAR) such as small bowel, which show a great day-to-day and intrafractional variation [11]. Despite being a routine procedure, fiducial markers placement is an invasive procedure, can result in minor complications and may be a barrier to undergo SBRT instead of radiofrequency ablation [12]. In the present work we report our initial experience with online MRgRT of liver tumors with a focus on feasibility, patient acceptance and toxicity.

2. Methods

2.1. Patient selection

Patients who received online MR-guided SBRT at a 1.5 T MR-Linac (Unity ®, Elekta, Crawley, UK) with single doses of at least 6 Gy were included in this study which is a sub-study of a basket phase 2 feasibility trial (NCT04172753). All patients provided written informed consent. All patients and available therapeutic options for the treatment of liver metastasis were discussed in a multidisciplinary tumor board. Patients with Child B or Child C cirrhotic liver disease or previous radiotherapy of the liver were not considered for liver SBRT. The study was approved by the institutional review board of the medical faculty Tübingen (IRB 659/2017BO1).

2.2. Treatment planning and radiotherapy workflow

A four dimensional CT simulation scan in treatment position with arms above head using indexed patient positioning aids was acquired and four respiratory phases were reconstructed. Additionally three MR simulation scans on the 1.5 T MR-Linac were performed in the same position: A triggered T2 (voxel size 2 mm × 2 mm × 2.4 mm, TE 206 ms, TR 2100 ms) and T2 spair (voxel size 2 mm × 2 mm × 2.4 mm, TE 248 ms, TR 2100 ms) at near exhale and non– triggered T2 (voxel size 2 mm × 2 mm × 2.4 mm, TE 206 ms, TR 2100 ms). Patients were instructed not to eat for three hours prior to simulation scans and treatments. Delineation was performed in Monaco ®, V.5.4. An internal target volume was created under consideration of all available imaging studies. For this purpose the respiratory motion of the tumor was determined using the information from the 4D CT. A planning target volume (PTV) margin of three to six millimeters depending on factors such as patient constitution, treatment duration, residual liver volume etc., was added to account for intrafractional uncertainties. In general, for dose prescription and organs-at-risk constraints the UK SABR guidelines were followed [13]. If constraints for OARs could not be met PTV coverage was relaxed accordingly.

Treatment plans were generated in Monaco ®, V.5.4 using eight to eleven individual beam angles to avoid high-density edges of the couch structure. Plans were calculated based on the 4D CT in the reconstructed exhale phase. They were optimized to an average of 2323 monitor units (MU), varying between 1235 MU for 6 Gy and 4937 MU for 15 Gy and a mean segment number of 56, ranging between 32 and 70.

For SBRT application the workflow was as follows: After patient positioning a free breathing T2 scan (voxel size 2 mm × 2 mm × 2.4 mm, TE 206 ms, TR 2100 ms) is acquired. This scan is rigidly registered to the initial simulation CT scan with the upper edge of the tumor on T2 imaging aligned to the upper edge of the ITV contour. The automated fusion generated by Monaco ® is then manually adjusted to ensure adequate coverage of the tumor. In order to account for positional shifts, the "adapt to position" workflow was applied and a new plan was calculated online [7]. The adapted plan is then evaluated by the treating physician and after online quality assurance (QA)-checks and plan approval the beam is initiated. During dose delivery, cine MR imaging permits the visualization of the anatomy in relation to a pre-defined structure, in general the PTV. After completion of treatment a "post-treatment" T2 scan is acquired. For research purposes additional sequences such as diffusion weighted imaging can be taken [14,15]. The time (in minutes) required for each step was assessed by radiotherapy therapists and rounded to whole minutes. Toxicity during treatment and follow-up was scored according to the Common Toxicity Criteria, Version 5. Patients were either seen in person for follow-up or were contacted by phone. Statistics were calculated with Microsoft Excel. Patient reported acceptance of online MRgSBRT was assessed by a questionnaire based on previously published items, modified by H McNair [16,17]. Radiation induced liver disease (RILD) was defined according to Lawrence et al. [18].

3. Results

Ten patients were treated with online MR-guided radiotherapy for metastatic liver disease between March 2019 and July 2019. Patient characteristics are summarized in Table 1.

Median patient age was 68 years (range 48 – 81 years). Five patients were treated for oligometastatic and five for oligoprogressive disease. Seven patients had received systemic treatment prior to SBRT. In eight patients a single lesion was treated, one patient received treatment of three metastases with two separate treatment plans. A third patient was treated for four oligoprogressive metastasis. Since all four lesions were located in segment 8, radiotherapy was applied with a single plan. In nine out of ten patients, metastases were easily visible during the online workflow. The only metastasis that was challenging to identify on T2-weighted imaging on the MR-linac was a melanoma metastasis. However due to the location in liver segment 1, accurate MRI to CT fusion and beam alignment was feasible. Representative sections from planning CT, navigated T2 scans on the 1.5 T MR-Linac and free-

Table 1
Patient and treatment characteristics.

	n
Sex	
male	5
female	5
Age (range)	68 (48–86)
Primary site of cancer	
Colorectal	5
Esophageal SCC	1
Melanoma	1
Cystic duct	1
GIST	1
Head & Neck (ACC)	1
Extent of metastatic disease	
Oligometastatic	5
Oligoprogressive	5
Previous Chemotherapy	
yes	7
No	3
Previous hepatic surgery	
Yes	3
No	7

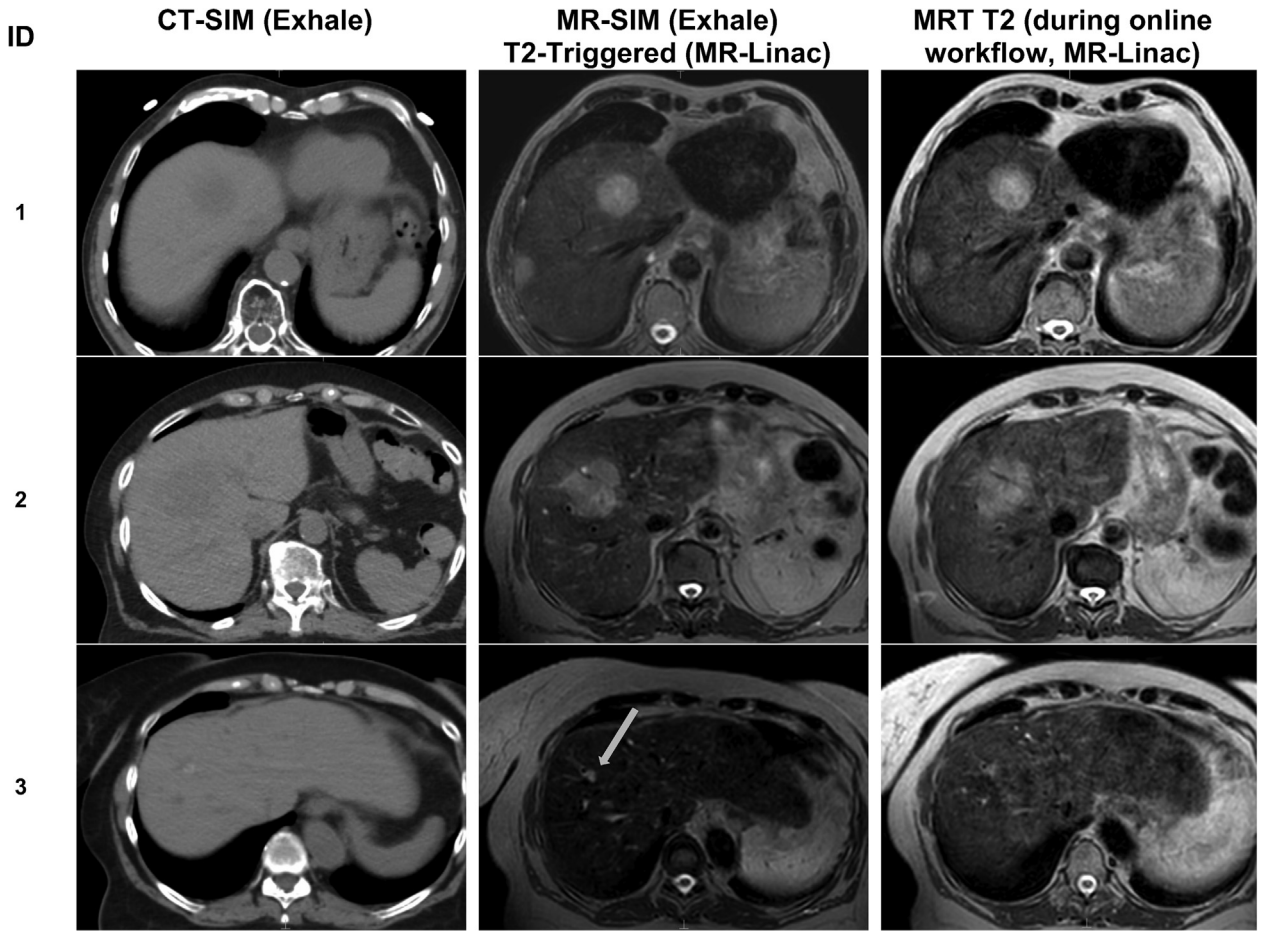

Fig. 1. Representative transversal scans of the first three patients. Shown are non-contrast enhanced simulations computed tomography scans, exhale triggered T2 scans on the 1.5 T MR-Linac and non-triggered T2 scans from the online workflow on the 1.5 T MR-Linac. SIM-simulation.

breathing T2 scans on the MR-Linac are shown in Fig. 1 and Supplemental Fig. 1. Dosimetric parameters are summarized in Table 2.

Beam-on time was 9.6 min on average. The median (range) time from "patient identity check" until "beam-off" was 31 min (26.4 min to 36 min). Table 3 provides a detailed summary of treatment times (in minutes).

Patient acceptance of online MRgSBRT was high as shown in Fig. 2. Eight patients completed the previously described patient acceptance questionnaires. The mode responses were either 'rather agree' and 'fully agree' to the questions establishing coping and were either 'rather disagree' and 'fully agree' to the questions regarding discomfort. Three patients reported 'rather disagree' with the statement "I found it easy to stay still and remain in the treatment position". Treatment interruptions occurred in 7 of 47 (14.9%) treatments. All interruptions were due to technical reasons; no treatment was terminated due to patient specific factors such as claustrophobia or discomfort. In all cases treatment could be continued in the same session without the need to take the patient off the table before completion of the treatment session. In one instance treatment was interrupted due to pronounced inspiration on motion monitoring. The patient was then remotely instructed via audio channel to breathe shallower. After shallow breathing was confirmed on motion monitoring treatment was continued. SBRT was well tolerated with no increase in transaminases beyond CTCAE grade I or gastrointestinal toxicity requiring medical intervention. After a median follow-up of ten months (range 3–17 months) no event of symptomatic RILD was scored.

4. Discussion

We herein present one of the first reports of online MR guided liver SBRT using a high-field MR-Linac. Treatment was well toler-

Table 2
Dosimetric parameters. GTV-Gross tumor volume, IQR-Inter quartile range.

	median	minimal	maximal	25% quartile	75% quartile	IQR
GTV volume (cc)	34,6	0,8	186,4	14,5	84,2	69,7
PTV volume (cc)	96,2	11,3	399,5	46,4	180,9	134,5
Liver volume (cc)	1132,7	786,6	1778,8	1112,4	1376,9	264,5
Liver minus GTV Volume (cc)	1156,6	752,9	1720,7	1067,9	1221,8	153,9
Mean dose liver minus GTV (Gy)	10,2	5,0	16,1	8,2	11,9	3,7
Mean dose GTV (Gy)	40,0	29,7	53,0	36,1	48,5	12,4
Maximum dose GTV (Gy)	46,0	31,5	58,6	40,1	51,1	11,0
GTV D98% (Gy)	38,6	24,5	51,4	34,0	43,0	9,0
Small bowel D0.5 cc (Gy)	15,5	0,8	29,9	4,7	22,1	17,5

Table 3
a) Mean treatment times per fraction in minutes. Time from "patient ID check" until "beam-off" is shown. During fraction 2 and 5 of patient 1 imaging and adaptation were repeated due to patient motion during the online workflow. Patient 1 was treated sequentially for two lesions, with three fractions for each lesion. Beam interruption occurred twice during the application of fraction 1 of patient 6. b) Mean time per patient in minutes for individual steps of the online adaptive workflow. Time was rounded to full minutes in all instances.

a)

		Fraction					
		1	2	3	4	5	6
Patient	1	38	45	32	28	39	36
	2	34	25	27	24	25	
	3	37	37	27			
	4	24	28	28	25	27	
	5	33	30	34	33	32	
	6	56	27	27	31	23	
	7	38	27	28	28	29	
	8	28	30	35	29	28	
	9	28	26	32	28	28	
	10	33	33	29			

b)

Patient	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Average**
Patient ID check	1	1	1	1	1	1	1	1	1	1	1
MR safety check	1	1	1	1	1	1	1	1	1	2	1
Setup immobilisation devices	3	1	1	2	2	2	2	2	1	3	2
Patient positioning	5	3	6	2	3	3	3	3	2	3	3
Pre-treatment MRI-scan	4	3	3	3	4	4	4	3	3	3	3
Image fusion and plan adaptation	5	5	5	5	6	6	5	4	5	4	5
Plan approval (Physician)	4	3	6	3	3	6	3	4	3	2	4
Plan transfer	1	1	1	1	1	1	1	1	1	1	1
Plausibility check (Physics)	1	1	1	1	1	1	1	1	1	1	1
Irradiation ("beam-on")	12	8	8	7	10	8	8	10	10	12	9
Post-treatment imaging	6	4	6	5	5	6	7	7	8	8	6
Total	42	31	40	32	37	38	37	37	36	40	37

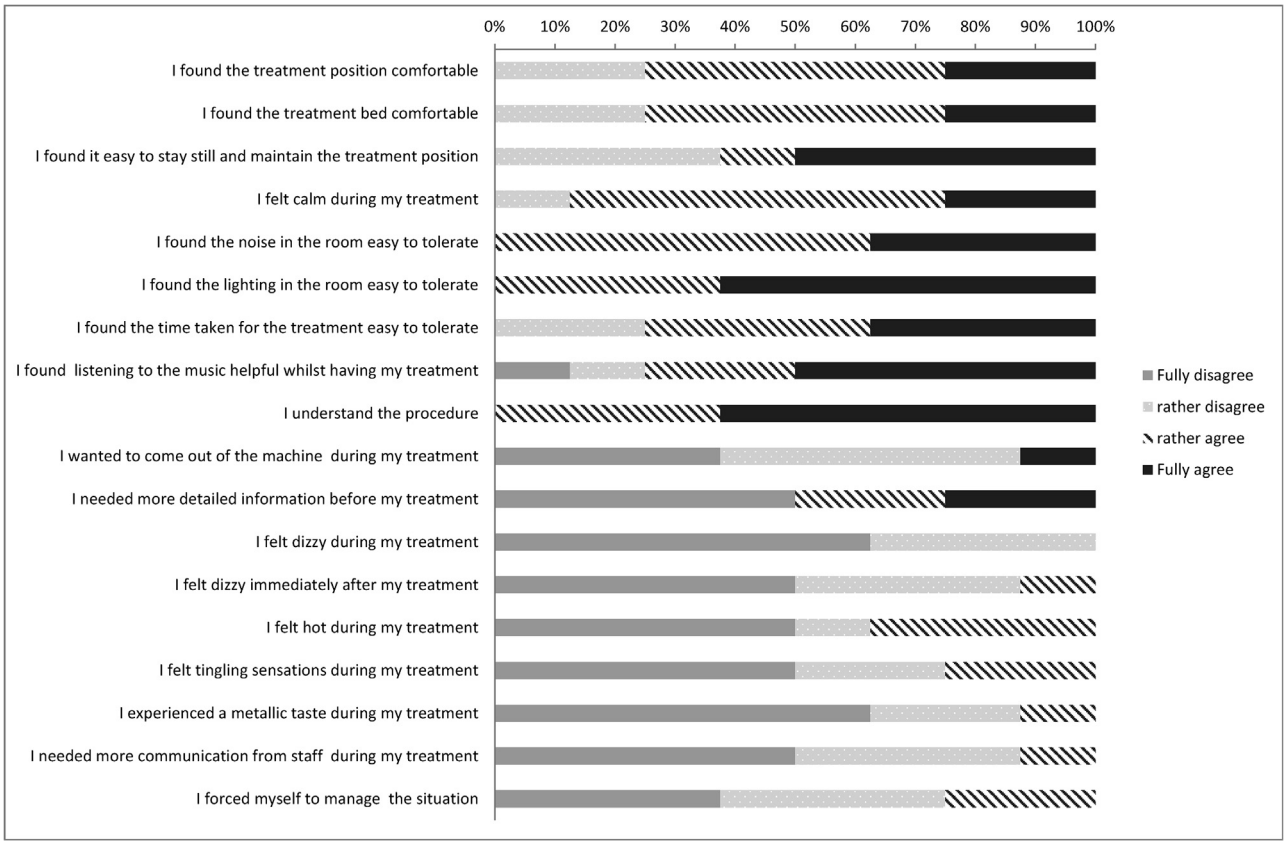

Fig. 2. Patient acceptance of various aspects of online MRgSBRT.

ated in all cases with no severe toxicity observed during follow-up. This is in line with studies by Rosenberg et al. and Hall et al., who reported their experience with online MR guided liver SBRT on 0.35 T and 1.5 T systems [19,20]. In the study by Rosenberg et al. only two of 26 patients developed CTCAE grade III gastrointestinal toxicity despite a preexisting Child-Pugh A or higher liver dysfunction in more than 50% of the patients [20]. Hall et al. report no grade III toxicities during follow-up in patients treated for liver tumors [19]. In general liver SBRT is established as a treatment with a very favorable toxicity profile as long as dose constrains for organs at risk are met [21]. Our median in-room time (from "room-in" to "beam off") of 31 min compares well to a recent report of online MR guided radiotherapy on the 0.35 T hybrid device and data for robotic guided SBRT. It should be considered though, that 21 of 26 patients in the report by Feldman et al. were treated in breath hold resulting in longer treatment times compared with a workflow with a permanent beam [22]. We used a patient centered questionnaire to assess various aspects of feasibility showing a broad acceptance as already reported for the 0.35 T device [23,24].

Data to support local treatments of oligometastatic is growing rapidly. Two recent randomized trials have shown a significant benefit in overall survival with the inclusion of local treatments in oligometastatic disease. Gomez et al. randomized 49 patients with metastatic lung cancer who had not progressed after first line chemotherapy to either standard of care or local treatment of all active tumor sites. The trial was closed prematurely following a recommendation of the data safety and monitoring board when a clear benefit in terms of progression free survival was seen which also translated in an overall survival benefit after a median follow-up 38.8 months [25]. Patients who had received local treatment had a median overall survival (OS) of 41.2 months compared with 18.9 months in patients who had received standard treatment. Similarly the SABR-COMET trial randomized 99 patients with various primary tumors and up to five metastatic lesions to either SBRT of all metastatic sites or standard of care. Again a longer median OS was seen with the inclusion of local treatments in the management (41 months vs 28 months) [26]. Among the most frequent metastatic sites, liver metastases can be considered the most challenging for ablative treatments [27].

While bony and pulmonary lesions can be visualized on cone-beam imaging in general, this is only rarely the case for liver metastases or intrahepatic hepatic vessels to guide beam alignment. This often requires the invasive placement of fiducial markers as a surrogate. In our study nine out of ten metastases were clearly visible on MR imaging acquired during the online adaptive workflow which facilitated online MR guided SBRT without the need for placement of fiducial markers. Another advantage of online adaptive MR-guided radiotherapy is the possibility to reoptimize the dose distribution based on the anatomy of the day. This may be particularly relevant in tumors located at the edges of the liver with proximity to very radiosensitive normal tissues such as the small bowel or stomach.

In the present study an ITV concept was applied for motion management. Alternative motion management strategies such as MLC-tracking, a "mid-position approach" or respiratory gating including audiovisual feedback are currently studied or already in routine use [19,28–30]. All these techniques come with specific advantages and disadvantages. The ITV approach is fast since the beam is permanently on. Compared to an ITV concept the other strategies will result in smaller volumes of irradiated healthy tissue, which could be particularly relevant in patients with limited liver volume or function. The smallest possible volume is realized by respiratory gating at the expense of a longer treatment time.

Our study has some limitations. Patients with claustrophobia were excluded a priori which has to be considered when interpreting the very high compliance rate with no treatment interruption due to patient request. Furthermore, our cohort was limited to patients with liver metastases and a sufficient liver function. Moreover, data on local control still has to mature and will be reported separately.

Beyond adaptation solely based on anatomical changes, the inclusion of functional imaging parameters into personalized adaptive radiotherapy protocols is a highly interesting strategy [31]. It is well known from the fractionated treatment of tumors of the rectum or the esophagus that early changes in diffusion restriction are highly predictive of the response to treatment [32,33]. One could envision to transfer this approach to liver tumors and adapt the prescribed dose to the tumor based on changes seen on functional imaging or define areas of residual diffusion restriction that require higher doses of radiotherapy. MR-Linac hybrid devices might facility the identification and treatment of such subvolumes in a single real time online adaptive workflow [31,34,35]. Hall et al. have recently reported quantitative imaging data acquired on the 1.5 T MR-linac during the treatment of a patient with a liver tumor. Indeed, a continuous increase of the apparent diffusion coefficient could be measured form fraction to fraction [19]. Clearly, novel interventional approaches based on quantitative imaging data need to be validated and tested within well designed clinical trials.

In summary, our early experience suggests that online 1.5 T MRgSBRT of liver metastases represents a promising new treatment modality based on high image quality, non-invasive marker-free procedure, clinically reasonable in-room times and high patient acceptance. Further studies are necessary to assess clinical outcome, to validate advanced motion management and to explore the benefit of online response adaptive SBRT of liver metastases.

Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2020.11.014.

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