Journal of Cancer Research and Clinical Oncology (2021) 147:2057–2068
https://doi.org/10.1007/s00432-020-03480-8

ORIGINAL ARTICLE – CLINICAL ONCOLOGY

MRI-guided stereotactic radiation therapy for hepatocellular carcinoma: a feasible and safe innovative treatment approach

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Received: 16 October 2020 / Accepted: 22 November 2020 / Published online: 4 January 2021

Abstract

Purpose Hepatocellular carcinoma (HCC) in early stages benefits from local ablative treatments such as radiofrequency ablation (RFA) or transarterial chemoembolization (TACE). In this context, radiotherapy (RT) has shown promising results but has not been thoroughly evaluated. Magnetic resonance-guided RT (MRgRT) may represent a paradigm shifting improvement in stereotactic body radiotherapy (SBRT) for liver tumors.

Methods We retrospectively evaluated HCC patients treated on a hybrid low-tesla MRgRT unit. A total biologically effective dose (BED) > 100 Gy was delivered in 5 consecutive fractions, respecting the appropriate organs-at-risk constraints. Hybrid MR scans were used for treatment planning and cine MR was used for delivery gating. Patients were followed up for toxicity and treatment–response assessment.

Results Ten patients were enrolled, with a total of 12 lesions. All the lesions were irradiated with no interruptions. Six patients had already performed previous local therapies. Median follow-up after SBRT was 6.5 months (1–25). Two cases of acute toxicity were reported (G ≤ 2 according to CTCAE v4.0). At the time of the analysis, 90% of the population presented local control. Child–Pugh before and after treatment remained unchanged in all but one patient.

Conclusion MRgRT is a feasible and safe option showing favorable toxicity profile for HCC treatment.

Keywords Hepatocellular carcinoma · Radiotherapy · Multimodality treatment · Stereotactic body radiotherapy · Magnetic resonance-guided radiotherapy

Introduction

Liver cancer is the sixth-most diagnosed cancer and the fourth-most common cause of cancer-related death worldwide. Death rates increased by 43% between 2000 and 2016 in the United States, while a growing trend in Southern Europe and East Asia has been recently reported (Bertuccio et al. 2017).

Hepatocellular carcinoma (HCC) accounts for the large majority of primary liver cancers and usually occurs in patients affected by underlying chronic liver diseases. Its incidence increases with advancing age and with significant differences in its peak in the different geographical areas (El-Serag 2012).

Nevertheless, promising progresses have been made in the diagnosis and treatment of HCC in the last years.

Several systems have been developed for the classification and staging of HCC, considering disease characteristics, liver function, and patient performance status. The Barcelona Clinic Liver Cancer (BCLC) stage provides a prognostic prediction and treatment indication for each of the five identified stages and supports physicians in clinical decision-making (Kinoshita et al. 2015).

Patients belonging to the "very early" or "early" stages, particularly when not eligible for surgery, can benefit from ablative therapies, such as radiofrequency ablation (RFA) but also microwave ablation (MWA), percutaneous ethanol injection (PEI), and transarterial chemoembolization (TACE) (Murray and Dawson 2017).

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The use of radiation therapy (RT) was historically limited due to the risk of radiation-induced liver disease (RILD) and the available evidence is scarce, so that the role of RT in HCC treatment is still far to be thoroughly explored and understood (European Association for the Study of the Liver 2018; Marrero et al. 2018).

In this context, RT treatment planning and delivery techniques have substantially improved in the last years; it is now possible to deliver high doses to well-visualized target volumes, monitoring their motion with confidence thanks to dedicated on-board imaging systems (i.e., stereotactic body radiation therapy—SBRT—with appropriate image guided radiotherapy—IGRT—solutions) and reducing the amount of unnecessarily irradiated normal liver tissue.

SBRT performances for HCC treatment have been prospectively and retrospectively evaluated, both in exclusive setting or coupled with other ablative procedures (e.g., TACE or RFA), showing good results in terms of local control and safety profile also in the cirrhotic liver (Culleton et al. 2014; Lasley et al. 2015; Wahl et al. 2016). Moreover, high-conformal high-dose rate (HDR) brachytherapy can also be considered an alternative in HCC patients with 0-A BCLC stage, having shown efficacy and favorable toxicity profile in several studies (Vogel et al. 2018; Hass et al. 2019).

The recent developments in the field of RT have opened new perspectives for the irradiation of liver volumes, significantly improving treatments' quality and safety (Murray and Dawson 2017).

One of the most significant technical advancements is represented by MR-Linacs, RT hybrid delivery units that couple low- or high-tesla (0.35 or 1.5) on-board MR scanners with standard linear accelerators.

Compared to the current patients' positioning imaging reference standard, represented by on-board cone beam computed tomography (CBCT), on-board MR imaging provides better anatomic target definition thanks to the higher soft tissue contrast and imaging characteristics.

Furthermore, the availability of continuous 2D cine MR images provides an accurate and reliable motion management solution, without the need for external markers or implanted fiducials, normally required in traditional irradiation techniques (Noel et al. 2015; Hunt et al. 2018).

Primary aim of this study is to assess the safety and feasibility of MR-guided Radiotherapy (MRgRT) for the treatment of HCC lesions.

Materials and methods

Patient selection

Patients affected by HCC and treated from February 2018 to July 2020 on a low-T MRgRT unit (MRIdian, ViewRay Inc, Mountain View, CA, USA) were retrospectively included in this study.

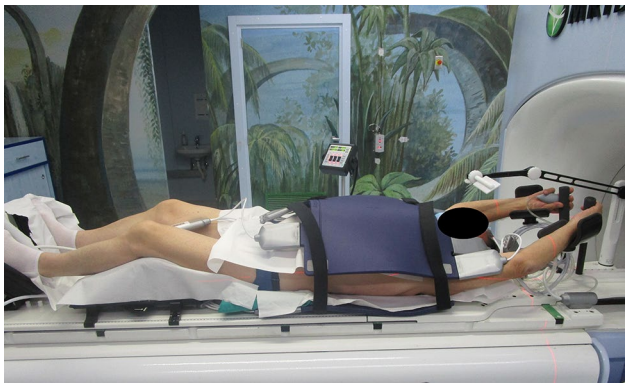

Fig. 1 Patient set-up

All patients underwent pathological diagnosis of the lesion and staging clinical imaging with dynamic multidetector computed tomography (MDCT) and/or MRI.

Disease was staged using BCLC and Child–Pugh classifications and all the patients were tested for viral hepatitis.

The therapeutic workflow was agreed after the discussion in the dedicated hepatobiliary malignancies multidisciplinary tumor board.

No restrictions about previous HCC ablative treatments (i.e., TACE, PEI, and RFA) have been applied for selecting the patients.

Poor performance status (ECOG ≥ 3) or clinical contraindication to MRI was instead considered absolute exclusion criteria (Boldrini et al. 2020).

All the patients were evaluated by the attending radiation oncologist to exclude the presence of absolute contraindications to RT and specific informed consent to MRgRT treatment was contextually obtained.

Acute and late toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 scale. Acute toxicity was evaluated during RT treatment and up to six months after the end of RT treatment. Late toxicity was evaluated six months after the end of RT treatment, during scheduled follow-up visits.

Treatment preparation

All the patients performed a 0.35 T MRI simulation on the MRIdian system.

Patients were immobilized in supine position with both arms above their head using dedicated immobilization device (Fluxboard™, MacroMedics, The Netherlands) in the most comfortable position. MRI coils were placed under and over the abdomen of the patient (see Fig. 1).

To increase the reproducibility of the treatment, patients were asked to fast for at least 4 h before simulation and treatment delivery.

Twenty-five seconds of true fast imaging (TRUFI) MR scans in free breathing (FB) and in breath-hold inspiration (BHI) conditions were acquired to verify inspiration breath-hold compliance and patient's correct positioning. In case of inadequate BHI, patients were evaluated for FB treatment.

A cine MRI was acquired on sagittal plane to monitor target and organs'-at-risk (OARs) motion and to quantitatively assess patients' compliance to BHI and its reproducibility.

No contrast agents have been administered to the patients for on-board MRI acquisition.

Following the evaluation of lesion's visibility on the positioning MRI and the recorded motion, the attending radiation oncologist selected the delivery gating protocols deemed as most appropriate, using either the lesion itself or its indirect surrogates (i.e., surrounding large vascular structures, cystic lesions or whole liver) as gating target volumes (Boldrini et al. 2018; Massaccesi et al. 2019).

In this phase, treatment delivery parameters are also defined in terms of the region of interest percentage (ROI%) and relative boundary values to personalize the target gating approach.

The boundary determines the maximum allowed intra-fraction motion value of the target volume, while the ROI% is the maximum percentage value of the considered target structure allowed to be outside the boundary during treatment delivery. If the target structure exceeds the boundary for a value larger than the foreseen ROI%, treatment delivery is automatically stopped by the system. Figure 2 shows the relation between target volumes and boundaries.

To complete the simulation steps, a standard planning CT was also acquired in BHI on a helical CT scanner (GE HiSpeed DX/i Spiral, Boston, MA, USA) within 30 min since the acquisition of the MRI simulation, to guarantee anatomical consistency.

CT slice thickness was 1.25 mm and no intravenous contrast agent was administered.

This CT scan was then co-registered with the simulation MR using deformable registration algorithms, to obtain the electron density data required for dose calculation.

Treatment planning

The MR simulation scan was chosen as primary image, while planning CT and other diagnostic imaging (i.e., staging MRI) were used for the definition of the Gross Tumor Volume (GTV).

The target volume and organs at risk (i.e., healthy liver, inferior vena cava, chest wall, ribs, duodenum, small bowel, colon, kidneys, stomach, and spinal cord) were contoured by a radiation oncologist with specific expertise in the treatment of hepato-biliary malignancies.

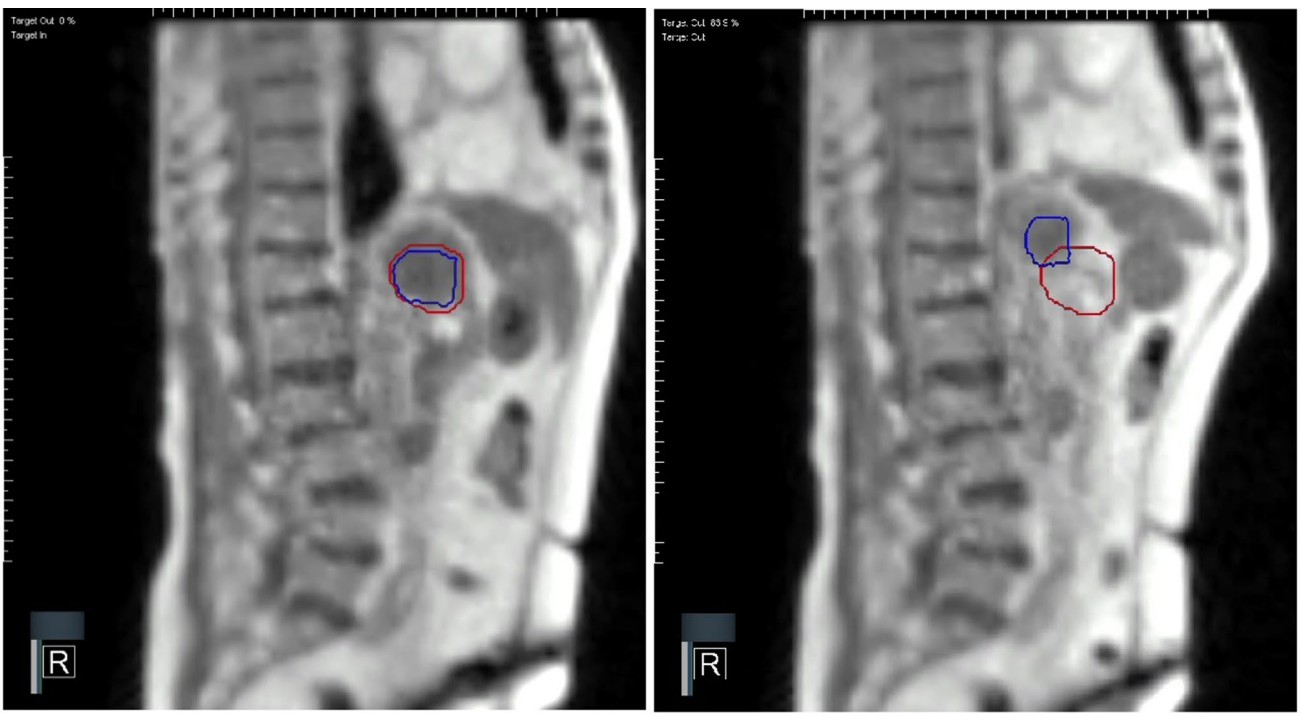

Fig. 2 Target (blue) is inside (left) and outside (right) the corresponding boundary. The beam is automatically triggered accordingly

The clinical target volume (CTV) was considered equal to GTV and the corresponding planning target volume (PTV) was obtained with an isotropic expansion of 3–5 mm from GTV, depending on the radiological characteristics of the lesions and on clinical judgment, to account for intra-fractional uncertainties (Cusumano et al. 2018).

A SBRT treatment was planned with a total prescribed dose resulting in biologically effective dose (BED) > 100 Gy in 5 fractions, considering a tumor alpha/beta of 10 (van Leeuwen et al. 2018).

The AAPM Task Group 101 dose constraints for SBRT treatments were applied to OARs (Benedict et al. 2010).

Furthermore, as suggested by some published experiences (Velec et al. 2017; Rosenberg et al. 2019), the mean dose to the liver was precautiously kept between 13 and 15 Gy and a volume inferior to 700 cc of healthy liver had to receive less than 15 Gy (Schefter et al. 2005; Baumann et al. 2018).

These planning objectives were preferable but not considered hard constraints, balancing between appropriate target coverage and OARs irradiation.

Treatment was prescribed to the PTV and planning was carried out using the stand-alone MRIdian treatment-planning system (ViewRay Inc., Mountain View, CA, USA).

Dose calculation was performed using a Monte Carlo computation algorithm considering the presence of the magnetic field since the elaboration of the fluence map and setting 2 mm as grid calculation size.

Step-and-shoot IMRT plans with 7–16 beams per plan were calculated, including the influence of the 0.35 T magnetic field on the dose calculation.

Treatment delivery

The delivery was carried out according to the parameters that were set during the simulation phase. First of all, a 25-s FB MR scan was acquired for patient alignment and then co-registered to the planning MR scan based on rigid co-registration on the target lesion.

After the set-up correction, a second scan was acquired in FB or BHI conditions, depending on the breathing characteristics of the simulation phase for a single patient.

After the last alignment adjustments of the patient, the most appropriate sagittal plane for gating was selected and the treatment parameters defined during simulation step (ROI% and boundary) were applied for online daily cine-MR monitoring.

Patients had the opportunity to actively participate in the treatment through the use of visual feedback system which displayed the online cine-MRI of their treatment. In this way, patients successfully contributed to the gating treatment by keeping the target within the boundary thanks to guided breaths.

In addition to the visual feedback, patients were also coached by the attending Radiation Therapy Technologist staff in the treatment room to optimize target positioning.

Follow-up

Patient follow-up was performed every 3–6 months. Clinical history, laboratory tests, and the required imaging (contrast enhanced CT or MRI) were collected during dedicated visits.

The follow-up diagnostic imaging was reviewed in comparison to the treatment plan images, to assess response or possible toxicity onset. Local response to treatment and impact of local therapy at systemic level were assessed according to mRECIST criteria (Llovet and Lencioni 2020).

Complete, partial response or stable disease were considered as tumor local control (LC).

Data describing acute toxicity, treatment tolerability, overall survival, progression-free survival, and local control were reported for all the enrolled patients.

Results

Ten (10) patients affected by HCC were retrospectively evaluated in this study.

Patients' median age was 81.5 (70–87) years, ECOG performance status was ≤ 2, BCLC stage was A in 2 and C in 8 patients presenting portal vein invasion; while Child–Pugh disease stage was A in 9 and B in 1.

In 70% of cases, an anamnestic correlation of HCC with HCV infection was observed, while in the remaining 30% of cases, the cause was non-alcoholic steatohepatitis (NASH).

Six patients (60%) had performed previous local therapies (i.e., PEI,TACE,RFA,MWA) with a median of 2.5 (2–3) prior received procedures.

Of these, one patient was previously treated with MWA, TACE, and SBRT on a previous HCC nodule, different from the target considered for this analysis.

One patient (10%) received Sorafenib sequentially to local therapy, four patients (40%) had received no previous treatment and no patient underwent surgery.

A total of 12 HCC nodules were evaluated. The median number of lesions per patient was one (1–3); two patients presented two nodules each and one presented two synchronous lesions. The median lesion size was 18.5 mm (9–50 mm) in maximum diameter and nodules were distributed all over the hepatic parenchyma, as shown in

Table 1 Patients clinical and RT planning characteristics

Clinical characteristics	*N*
Age (year) median (range)	81.5 (70–87)
Gender	
Male	6
Female	4
ECOG	
0–1	9
2	1
Nodules	12
Location of the nodules (liver segment)	
1	2
4	3
5	2
6	2
8	1
3–4	1
5–8	1
Pre-treatment	
Child–Pugh class	
A	9
B	1
BCLC class	
A	2
C	8
Previous therapy	
None	4
Surgery	0
Sorafenib	1
PEI-TACE-RFA-MWA	6
RT	1
MRIdian system	
Tri-cobalt	5 (50)
6 MV Linac	5 (50)
Post-treatment	
Child–Pugh class	8 (80%)
A	2 (20%)
B	
RT planning characteristics	**Median (Range)**
Tumor diameter (mm)	18.5 (9–50)
PTV (cc)	22.6 (3.2–116.9)
Liver (cc)	1395(797.9–1878.5)
Prescribed SBRT dose (Gy) to PTV	50 (50–55)
Liver mean dose (Gy)	8.05 (2.85–17.94)
Liver V21Gy (cc)	132.8 (28.54–468.16)

Table 1. The median PTV size was 22.6 cc (3.2–116.9 cc). Patients were treated with a median dose of 50 (50–55) Gy delivered in 5 consecutive fractions, reaching a calculated $BED_{10} > 100$ Gy in all the cases.

For 7 nodules, a Dmean prescription was chosen, while the remaining 5 were prescribed to 80% isodose.

Target volumes were residual disease or de novo recurrence after focal therapies in 50% of the cases and nodules of new diagnosis in the remaining cases.

Patients' compliance to gating was evaluated, on a case by case basis, during simulation phases; BHI-gated delivery was chosen in 80% of patients, while FB was preferred in the remaining 20%, due to poor compliance to breath hold.

All treatment plans have been approved in accordance with the planning objectives and dose limits recommended by AAPM Task Group 101 (Benedict et al. 2010).

Treatments were delivered in 5 patients using a MRIdian Tri-cobalt system 0.35 T from February 2018 to May 2019, while the remaining ones with a MRIdian 6 MV hybrid MR-Linac, due to local system upgrade.

The RT treatment was completed without interruptions and was overall well tolerated by all patients.

Acute toxicity onset was observed in two patients. One patient complained of mild gastrointestinal symptoms (nausea G1) and another patient reported fatigue G2 during treatment, subsequently developing ascites G2, three months after the end of RT.

The median follow-up was 6.5 months (1–25).

At the time of this analysis, 90% of patients reported local control of disease with 2 patients having complete response (CR), 3 stable disease (SD), and 4 partial response (PR), according to the aforementioned mRECIST criteria.

Only one patient underwent local failure with concomitant generalized progression of liver disease at a seven-month follow-up.

Patients' Child–Pugh score persisted unchanged in all the cases except for one patient, who progressed from score A to B and presented ascites of grade G2 after three months from the end of RT treatment, although with stable liver disease.

This patient presented 2 lesions (in liver segments I and IV), which were simultaneously irradiated with a dose prescription of 50 Gy in 5 fractions to the mean dose and a resulting total PTV volume of 116 cc.

The mean liver dose was 17.94 Gy and the D700 cc was 15.3 Gy, with a V21Gy of 468.16 cc, thus fully respecting the constraints of AAPM Task Group 101.

Two patients are deceased at the time of analysis. Not surprisingly, they were the patients with the longest history of underlying liver disease (death occurred 87 and 69 months after diagnosis, respectively).

Discussion

The role of RT in the treatment of HCC has significantly changed over the years and the current recommendations are oriented toward the use of focal therapies in patients who are not candidate for surgery or as part of more complex patient's therapeutic paths (Murray and Dawson 2017).

Early experiences have described RT as a resource in palliative setting alone, with low-survival rates, generally burdened also by the underlying poor general clinical conditions of the irradiated patients. The recent evolution of radiotherapy delivery technologies has led to the introduction of SBRT in clinical practice, allowing the delivery of high doses with ablative intent, reducing the unnecessary irradiation of the surrounding organs at risk and preventing toxicity.

RFA, TACE, and SBRT are to-date considered as valid therapeutic options in early BCLC class patients. More specifically, RFA is recognized as a curative option for patients with < 3 HCC lesions, while TACE is generally reserved for patients who are not candidates for RFA whose lesions do not invade major vessels.

Comparison data between RFA and SBRT have reported discordant 2- and 3-year OS and toxicity rates (Wahl et al. 2016; Hara et al. 2019), with significantly lower 3-year LC rate in the SBRT patient cohort (5.3% vs 12.9%) (Hara et al. 2019).

SBRT has also been successfully associated with TACE, showing an improvement in LC and DFS when compared to TACE alone, but at the price of increased gastrointestinal toxicity, thrombocytopenia, and fever, despite generally easily manageable and successfully treated (Huo and Eslick 2015).

Moon et al. (2018) showed that prior liver-directed therapies did not affect LC or survival, also with no impact on toxicity. SBRT appeared therefore to be safe and effective even in the setting of prior ablative therapies o as bridge to transplantation option.

Dose levels also play a significant role in treatment efficacy and a total dose of at least 45 Gy in 3 fractions is suggested, as lower dose levels have been correlated with local failures (Murray and Dawson 2017).

Bujold et al. (2013) and Jang et al. (2013) have demonstrated that increased RT doses are associated with improved LC and patient survival in primary HCC patients was irradiated with conventional SBRT techniques. Two-year LC rates of 90% and 95% for 48 Gy in 3 fractions and 45 Gy in 3 fractions have been reported, respectively (Louis et al. 2010; Andolino et al. 2011).

Based on the TCP model, a dose of 54.8 Gy in 3 fractions produces 2-year LC with a probability of 90% (Jang et al. 2013). The need for dose escalation studies, supported by innovative imaging solutions for appropriate target identification and adequate motion management strategies has also been suggested by Xi et al. (2013) and Kong and colleagues (Kong et al. 2017), who have demonstrated the feasibility of high-dose SBRT with encouraging results on survival outcomes.

Besides dose escalation, an interesting area of further development is the use of concomitant drugs together with SBRT treatments, aiming to additive effects, even if the association of RT with Sorafenib has historically shown discordant results in different trials, mainly due to liver toxicity (Chen et al. 2014, p. 2).

Table 2 summarizes the studies published in the last 10 years on the application of SBRT for the management of HCC, highlighting the used technological solutions and dose levels.

As clearly reported in the table, many of these studies show large heterogeneity in terms of clinical conditions (e.g., previous treatments, comorbidities) and sample dimensions. Furthermore, at the time of this study, no randomized trials extensively compared SBRT with other local therapies for the treatment of HCC.

Nevertheless, the local control, survival, and toxicity rates reported by SBRT are very promising.

In particular, different experiences reported that LC is associated with lesions size, number, and received dose (Kang et al. 2012; Scorsetti et al. 2015), while survival outcomes are affected by the patient's general clinical conditions and liver function, as defined by the Child–Pugh status and cirrhosis severity (Huertas et al. 2015; Gerum et al. 2018).

The OS and LC results of our experience overlap with those published in literature, with promising toxicity rates.

The use of MRgRT allows to maximize SBRT objectives, taking advantage of all the opportunities offered by MR guidance and this advantage may have been translated in a particularly favorable and safe delivery setting.

The improved soft tissue contrast resolution offered by on-board MRI allows better target definition and may lead to clinically significant reductions in treatment volume margins.

Furthermore, the use of on-board cine-MRI allows direct visualization of tumor motion, ensuring accurate delivery and effective OARs sparing which represents a significant dose limiting factor with standard RT technologies.

The observed LC and OS rates are therefore excellent and potentially equivalent to RFA rates, although a direct comparison is unfortunately still not feasible due to the large inhomogeneity of the cohorts in literature.

As for the first specific MRgRT evidences, Rosenberg et al. (2019) analyzed 26 patients with HCC and metastatic liver lesions, reporting 7.7% acute G3 toxicity, while in the cohort treated by Feldman et al. (2019), which included 29 patients of which 26 HCC patients, the maximum acute reported toxicity was G2.

MRgRT has been well tolerated also in our cohort of patients, with no significant acute toxicity or evidence of RILD and only 20% of patients reporting mild toxicity symptoms, which were easily managed (max G2).

Online MRgRT adaptation strategies, that proved to be particularly efficient in the upper abdomen, pave the way to near future paradigm shifting dose escalation strategies aiming to optimize target coverage and ensure normal tissues preservation, especially in those patients who have had previous local treatments and suffer from underlying liver comorbidities that may hamper its function (Bohoudi et al. 2017; Boldrini et al. 2019; Placidi et al. 2020).

Online adaptive applications may therefore further enhance MRgRT treatment quality, as suggested in a first phase I prospective study investigating the potential of MR-guided online adaptive radiotherapy for upper GI malignancies (Henke et al. 2018).

Conclusions

Our experience confirms the safety and feasibility of MRgRT for the treatment of HCC nodules with favorable toxicity profile and may be of help as background for new dose escalating studies, taking full advantage of the significant innovations introduced by this technology in the field of clinical radiation oncology.

Table 2 Studies of the last 10 years evaluating the role of SBRT in HCC

Authors	Year	Technique	Dose	Patients (*n*)	Outcomes	Max acute toxicity recorded
Rosenberg et al. (2019)	2019	MRgRT	Median 50 Gy (30–60)/5 fractions	6 HCC 20 MLL	FFLP (21.2 months median follow-up)100% PFS 33% 1-year OS 69% 2-year OS 60% Entire coort	G2
Liu et al. (2013)	2013	ABC/4DCT	Median BED 100 Gy (42.6–180)	37 HCC 6 ICC 69 MLSL	1-year FFLP rate 93% 2-year FFLP rate 93% 2-year OS 29% 1-year OS 81% 2-year OS 52% Entire coort	G3
Bujold et al. (2013)	2013	ABC or Abdominal compression	24–54 Gy/6 fractions	102 HCC	1-year LC 87% Median OS 17.0 months Median TTP 6.0 months	G5
Andolino et al. (2011)	2011	Abdominal compression	24–48 Gy/3–5 fractions	60 HCC	2-year LC 90% 2-year PFS 48% 2-year OS 67%, Median TTP 47.8 months	G3
Weiner et al. (2016)	2016	4DCT	Median total dose 55 (40–55) Gy/5 fx	12 HCC, 12 IHC, 2 biphenotypic tumor	1-year OS 38% median survival 9.8 months Median PFS 5.3 months 1-year PFS 48% 1-year LC 91% Entire coort	G3
Henke et al. (2018)	2018	MR-guided Adaptive SBRT	50 Gy in/5 fractions	10 non-liver abdomen lesions 6 MLL 4 HCC	3-month LPFS 95% Entire coort 6-month LPFS 89.1% 1-year OS 75%	G2
Feldman et al. (2019)	2019	MRgRT	45–50 Gy/5 fractions	26 HCC 2 ICC 1 MLL	1 year LC 96.5% 1 year OS 92.8%	G2
Gerum et al. (2018)	2018	4DCT/ Abdominal compression	Median BED 168.1 (60.3–190)	36 HCC 28 MLL	1- and 2-year FFHF 41% 1-year OS 68% 2-year OS 57%	G4
Kang et al. (2012)	2012	Cyberknife/ Abdominal compression	42–60 Gy/3 fractions	47 HCC	2-year LC 94.6% 2-year OS 68.7% 2-year PFS 33.8%	G4
Sanuki et al. (2014)	2013	Abdominal compression	35–40 Gy/5 fractions	185 HCC	1-year LC 99% 2-year LC 93% 3-year LC 91% 1-year OS 95% 2-year OS 83% 3-year OS 70%	G5
Culleton et al. (2014)	2014	4DCT/ABC/ Abdominal compression	Median 30 Gy/6 fractions	29 HCC	median OS 7.9 months 1-year OS 32.3%	G2
Lasley et al. (2015)	2015	4DCT	36–48 Gy/3–5 fractions	59 HCC	1 year LC CPA 91% 1-year LC CPB 82% 1-year OS 94% 1-year OS 57%	G4
Scorsetti et al. (2015)	2015	Abdominal compression 4CDT	48–75 Gy/3 fractions or 30–60 Gy/6 fractions	43 HCC	6-month LC 94.2% 1-year LC 86% 6-month OS 91.1% 1-year OS 78%	G3

Table 2 (continued)

Authors	Year	Technique	Dose	Patients (*n*)	Outcomes	Max acute toxicity recorded
Bibault et al. (2013)	2013	Cyberknife Synchrony system	24–45 Gy or 8–15 Gy /3 fractions	75 HCC	1-year LC 89,8% 2-year LC 89,8% 1-year OS 78,5% 2-year OS 50, 4%	G2
Jang et al. (2013)	2013	Abdominal compression	Median dose 51 Gy/3 fractions	108 HCC	2-year LC 87% 5-year LC 82% 2- year OS 63% 5-year OS 39%	G4
Yoon et al. (2013)	2013	4DCT	30–60 Gy/3 fractions	93 HCC	1-year OS 86% 3-year OS 53.8% 1-year LC 94,8% 3-year LC 92.1% 1-year DMFS 87,9% 3-year DMFS 72.2%	G4
Takeda et al. (2014)	2014	Abdominal compression	35–40 Gy/5 fractions	221 HCC	1-year LC 100% 2-year LC 95% 3-year LC 92% 1-year IRFR 76% 2-year IRFR 55% 3-year IRFR 36% 1-year OS 100% 2-year OS 87% 3-year OS 73%	G3
Huertas et al. (2015)	2015	Cyberknife Synchrony system	45 Gy/3 fractions	77 HCC	1- and 2- year LC 99% 1-year OS rate 81.8% 2-year OS rate 56.6% 1-year PFS 69.3% 2-year PFS 44.4% median TTP 9 months	G5
Kimura et al. (2015)	2015	ABC	48 Gy/4 fractions or 60 Gy/8 fractions	65 HCC	2-year OS 76% 2-year PFS 40% 2-year LC 100%	G4
Yamashita et al. (2015)	2015	Abdominal compression FB/BHI/gating	Median BED 96.3 (75–106)	79 HCC	2-year OS 53% 2-year PFS 40% 2-year DMFS 76%	G2
Su et al. (2016)	2016	Cyberknife Synchrony system	42–46 Gy/3–5 fractions and 28–30 Gy/1 fraction	132 HCC	1-year LC 90.9% 1-year OS 94,1% 2-year OS 73,5% 5-year OS 64.3% 1-year PFS 82,7% 2-year PFS 58,3% 5-year PFS 36.4%	G5
Wahl et al. (2016)	2016	ABC or 4DCT	Median Bed 100	83 HCC	1- year FFLP 97,4% 2-year FFLP 83,8% 1-year OS 74,1% 2-year OS 46.3%	G4
Cárdenes et al. (2010)	2010	Abdominal compression	36–48 Gy/3 fractions	17 HCC	1-year OS 75% 2-year OS 60% 2-year LC 100%	G4
Louis et al. (2010)	2010	Cyberknife Synchrony system	45 Gy/3 fractions	25 HCC	1- and 2-year LC 95% 1-year OS 79% 2-years OS 52%	G3

Table 2 (continued)

Authors	Year	Technique	Dose	Patients (*n*)	Outcomes	Max acute toxicity recorded
Kwon et al. (2010)	2010	Cyberknife BHI	30–39 Gy/3 fractions	42 HCC	1-year OS 92,9% 3-year OS 58,6% 1-year in field PFS 72% 3-year in field PFS 67,5%	G2
Seo et al. (2010)	2010	Cyberknife Abdominal compression	33–57 Gy/3–4 fractions	38 HCC	2-years OS 61,4% 2-year PFS 66.4% 3-month local response 63%	G3
Huang et al. (2012)	2012	Cyberknife Synchrony system	Median dose 37 Gy (range 25–48 Gy)/4–5 fraction	36 HCC	1- year IFFFR 87.6% 2-year IFFFR 75.1% 2-year OS 64.0% median TTP 8.0 months	G3
Bae et al. (2013)	2013	Cyberknife	median BED was 101 Gy (range 58–180 Gy)	35 HCC	1-year OS 52% 3-year OS 21%	G4
Xi et al. (2013)	2013	4DCT	36 Gy (30–48 Gy)/6 fractions	41 HCC	1-year OS 50.3%	G5
Dewas et al. (2012)	2012	Cyberknife Synchrony system	Median dose 45 (27–45)/3 fractions	72 MLL 42 HCC 6 ICC	1- and 2-years LC 90.5% Median TTR 3.71 months	
Goodman et al. (2010)	2010	Cyberknife Synchrony system or 4DCT	18–30 Gy/1 fraction	19 MLL 5 ICC 2 HCC	1-year OS 71.4% 2-year OS 53.6%	G2
Baumann et al. (2018)	2018	BHI or 4DCT with abdominal compression	50 Gy/5 fractions	37 HCC	1-year LC 95% 1-year FFLP 66% 1-year DMFS 95% 1-year OS 87%	G3
Moon et al. (2018)	2018	Cyberknife	Median dose 45 Gy in 3 fractions	11 HCC 19 MLL	1-year LC 82% 1-year OS 36%	G3

MRgRT Magnetic Resonance guided Radiation Therapy, *HCC* Hepatocellular Carcinoma, *MLl* metastatic liver lesions, *FFLP* freedom from local progression, *PFS* progression free survival, *OS* overall survival, *ABC* active breathing control, *ICC* Intrahepatic cholangiocarcinoma, *TTP* time to progression, *LC* local control, *LPFS* local progression-free survival, *FFHF* freedom from hepatic failure, *CPA* Child–Pugh Class A, *CPB* Child–Pugh Class B, *DMFS* distant metastasis-free survival, *IRFR* intrahepatic recurrence-free rate, *IFFFR* in-field failure-free rates, *TTR* time to recurrence

Author contributions Conceptualization, LB, and AR; methodology, GCM, VV; data analysis, FC, DC; data curation, SM, LP, and LI; writing—original draft preparation, AR and SM; writing—review and editing, LB, GCM, FC; visualization, SM, GC; supervision, MAG, GCM, and VV. All authors have read and agreed to the published version of the manuscript.

Funding Not applicable.

Data availability All data generated or analyzed during this study are included in this published article.

Compliance with ethical standards

Conflict of interest Dr. Luca Boldrini and Dr. Davide Cusumano have active research agreements with ViewRay Inc and received speaker honoraria for scientific presentations. Prof. Vincenzo Valentini has received departmental research grants from Varian Medical Systems, ViewRay Inc., Elekta, Merck-Serono, Roche.

Ethical approval This research study was conducted retrospectively in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication Patients signed informed consent regarding publishing their data.

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