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Hypofractionation in Hepatocellular Carcinoma – The Effect of Fractionation Size

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Abstract

The use of stereotactic body radiotherapy (SBRT) in hepatocellular carcinoma (HCC) has increased over the years. Several prospective studies have demonstrated its safety and efficacy, and randomised trials are underway. The advancement in technology has enabled the transition from three-dimensional conformal radiotherapy to highly focused SBRT. Liver damage is the primary limiting toxicity with radiation, with the incidence of grade 3 varying from 0 to 30%. The reported radiotherapy fractionation schedule for HCC, and in practice use, ranges from one to 10 fractions, based on clinician preference and technology available, tumour location and tumour size. This review summarises the safety and efficacy of various SBRT fractionation schedules for HCC.

Keywords: Dose fractionation; Hypofractionation; Hepatocellular carcinoma (HCC); Stereotactic body radiotherapy (SBRT); External beam radiotherapy (EBRT); Radiotherapy

Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignant tumour of the liver, accounting for 90% of cases [1]. Viral cirrhosis (hepatitis B or C), alcoholic cirrhosis and non-alcoholic fatty liver disease are significant contributory factors to the development of the disease. HCC is the second leading cause of mortality worldwide, and its incidence will increase by 35% by 2030 [2]. Most tumours are localised at diagnosis. However, various factors beyond the stage of the disease, such as age, the status of existing liver disease, liver function status and medical comorbidities, play a significant role in selecting appropriate treatment. A liver transplant is the only known curative treatment option. Less than 20% of patients are eligible at diagnosis, with a shortage of donors in Asian countries [3]. The available alternative options for local treatment include partial hepatectomies, local ablative therapies such as radiofrequency ablation (RFA) and microwave ablation, catheter-based therapies such as transarterial chemoembolisation (TACE), transarterial radioembolisation (TARE) and radiotherapy [4]. Although RFA and TACE are preferred in the setting of localised unresectable disease, a significant proportion of patients are unsuitable for these treatments because of liver function, the location of the tumour and medical comorbidities [5,6].

Radiotherapy has assumed a more significant role in the treatment of HCC over the years [7]. The possible indications for radiotherapy include definitive treatment in Barcelona Clinic Liver Cancer (BCLC) A or B, bridging to transplant, recurrent or large unresectable tumours, combination with TACE for large BCLC B, BCLC C with portal vein thrombosis and palliative treatment. The evidence supporting radiation has grown, and recent trials have shown results comparable with other modalities, like RFA [8]. It may serve as a good alternative in the definitive and salvage setting, and recommendations regarding the use of stereotactic body radiotherapy (SBRT) vary widely in the current clinical guidelines available [1,7,9]. Trials comparing SBRT with other liver-directed therapies (RFA/TACE/TARE) in a definitive setting and combination with systemic treatment, mainly immunotherapy, should be explored.

The advancement of radiation technology, higher precision and motion management strategies have paved the way for improved outcomes with lesser toxicity. The radiotherapy evolved from the whole liver, essentially a palliative role to a

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focal targeted curative treatment [10]. Acute classical radiation-induced liver disease (RILD) is now seldom seen (<1%), and the risk of deterioration in the liver function of more than 1 Child-Pugh score can be kept below 5% [11,12]. Hypofractionated radiotherapy, mainly SBRT, is increasingly used to reduce toxicity risk and maximise outcomes.

Rationale for Stereotactic Body Radiotherapy

Radiotherapy aims to deliver tumoricidal doses to the tumour while minimising dose to critical nearby normal tissues [13]. SBRT is an advanced radiation technique that provides a highly conformal ablative radiation dose (high dose per fraction) over a protracted period (one to five fractions) [14]. Superior image guidance, tumour localisation and motion management strategies enable accurate tumour targeting [15]. The steep dose gradient maximises organ sparing. The high precision of this technique provides an avenue to reduce margins and dose escalation. SBRT is a paradigm shift in radiotherapy practice and has shown impressive results of tumour control with minimal toxicity for various cancers, including HCC. The primary means of radiation cell kill is through double-stranded breaks in the deoxyribonucleic acid (DNA) [16]. SBRT has a higher antitumour efficacy compared with standard fractionation [17]. Due to the short schedule, the 5 Rs of radiobiology may not wholly apply to SBRT, like reoxygenation, repair and redistribution. SBRT has superior cell kill due to direct DNA damage from a high dose per fraction [17].

Radiotherapy dosing above 10 Gray (Gy) in a single fraction or 20–60 Gy in limited fractions results in severe vascular injury and subsequent tumour hypoperfusion, hypoxia and indirect cell death [18]. There is also damage to the vascular endothelium, causing apoptosis and vascular leakage [17]. A high dose per fraction can injure the radioresistant stem cell in the perivascular niche area. There are also reports of immunostimulatory effects of radiation resulting in immunogenic cell death. The massive release of tumour antigens causes the presentation to cytotoxic T cells through dendritic cells and results in activation of CD8 T cell-mediated antitumour response, potentiating cell death. These immune-stimulatory effects have also resulted in the abscopal effect, wherein localised radiation at one site induces an antitumour response at distant unirradiated sites [19]. Many trials are underway to enhance these effects by combining SBRT with immunotherapy in metastatic cancers.

The most commonly used fractionation schedules of SBRT for HCC range from three to 10 fractions of 8–15 Gy per fraction (Figures 1 and 2). Ultra-hypofractionation refers to the radiation schedule with dose per fraction of more than 5 Gy delivered in 10 or fewer fractions, whereas SBRT specifically is radiation delivered in five or fewer fractions. It is unclear whether a higher biological effective dose (BED) > 100 Gy is associated with a better outcome in HCC, with few supporting it and others refuting it, with tumour size and radiation dose not directly impacting the key outcomes [20]. There is no clear guideline for selecting dose fractionation based on the location and size of the tumour in practice. This review aims to assess evidence for various SBRT and hypofractionated schedules. We have limited the evidence to studies with more than 25 patients treated with SBRT (one to 10 fractions) over the last 10 years.

Stereotactic Body Radiotherapy with a Single-fraction Schedule

Single-fraction SBRT has been the preferred schedule for decades for treating brain metastases [21,22]. Advances in the delivery of SBRT (motion management, tumour localisation, immobilisation and image guidance) have enabled single-fraction schedules in extracranial targets, such as lung, pancreas, kidney, prostate and oligometastases-lung, liver, bone and lymph nodes [23–27]. Two randomised trials have proven its efficacy and safety in lung cancer; long-term follow-up is awaited [28,29].

During the COVID-19 pandemic, single-fraction SBRT was preferred for lung cancer and metastases to prevent transmission. The proximity of critical gastrointestinal structures and the inherent liver sensitivity (alpha/beta ratio of 2–2.5) makes applying single-fraction SBRT challenging for the liver lesions [30]. Blomgren *et al.* [31] reported single-fraction SBRT for liver and lung lesions in 1998 using a stereotactic frame and abdominal compression. Fatal radiation induced liver disease (RILD) was noted in an HCC patient treated with 30 Gy to a tumour volume of 229 cm^3, and this patient was excluded from the final analysis [31]. This highlights the importance of an appropriate selection of patients for this schedule. There is hesitancy in the acceptance of a single fraction for concern of poor control and toxicity.

Three phase I/II trials have reported using single-fraction SBRT in liver metastases [27,32,33]. The dose commonly used ranged from 26 to 30 Gy, with a recent trial escalating the dose to 35 and 40 Gy. Goodman *et al.* [32] noted duodenal ulceration in three patients with tumours close to porta hepatis (one patient received a dose maximum of 29 Gy and another had reirradiation following SBRT). Meyers *et al.* [33] excluded tumours within 2 cm of the portal vein until its bifurcation.

The literature on single-fraction SBRT in HCC is sparse. Goodman *et al.* [32] treated two HCC patients in a series of 26 patients with SBRT 18–30 Gy with local control at 1 year of 77% in the entire cohort. A maximum size of tumour up to 5 cm was allowed in the study, and there was no toxicity. Although no grade 3 liver toxicity was observed in liver metastases, the same may not be accurate for HCC, where most have cirrhosis and underlying liver dysfunction. The proper selection of patients with emphasis on adequate liver function and tumour location, preferably peripheral, together with rigid immobilisation and use of motion management is critical. Magnetic resonance-guided radiotherapy and protons may be advantageous in this setting.

Lack of literature makes it difficult to propose recommendations in this setting. However, small HCC ≤2 cm with Child-Pugh A5/A6 in a peripheral location may be an ideal

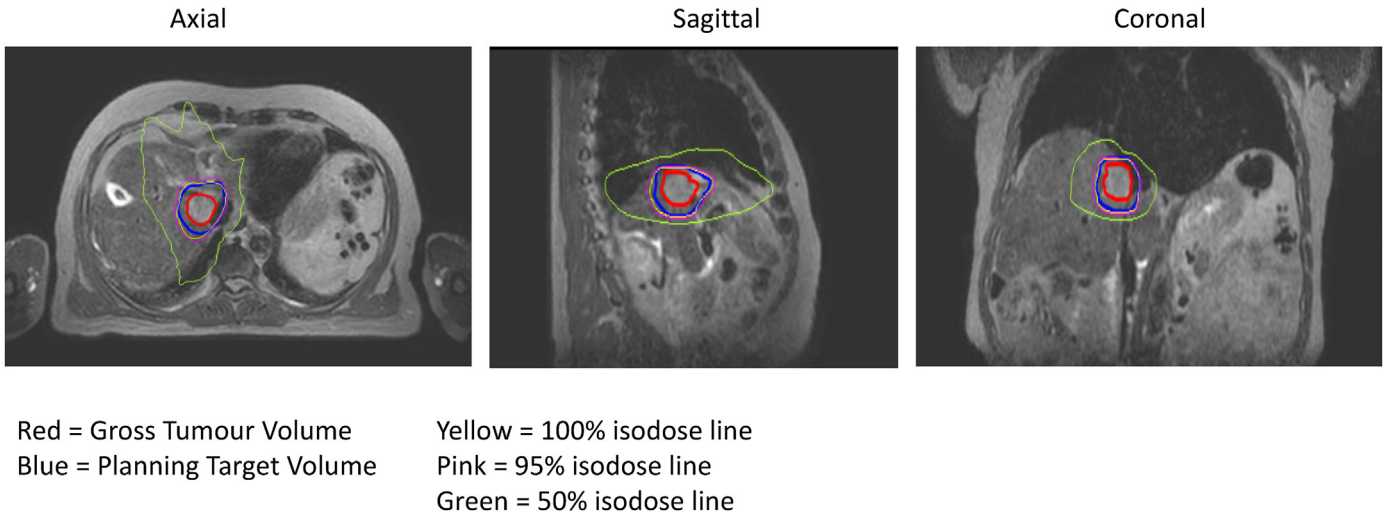

Fig 1. Axial, sagittal and coronal cuts through a T2 magnetic resonance linear accelerator plan of a hepatocellular carcinoma receiving 4000 cGy in five fractions.

target in a trial setting. Prospective trials exploring the use of single-fraction SBRT in this select group should be considered and the use of magnetic resonance-based adaptive online treatment would be best suited [34].

Stereotactic Body Radiotherapy with a Three-fraction Schedule

The safety and efficacy of three-fraction SBRT were first demonstrated in metastatic liver tumours [35]. In non-cirrhotic livers, the high dose per fraction from 18 to 20 Gy yielded high local control with low toxicity [35].

In HCC, several prospective and retrospective studies have used this schedule with good results, as outlined in Table 1 [12,36–48]. Most patients in these studies were early stage (BCLC 0 and A), with well-preserved liver function (Child-Pugh A 80–100%), with a median tumour size of around 3 cm. Small peripheral lesions not suitable for RFA due to proximity to vessels or dome were preferred in the study by Yoon *et al.* [36]. The dose per fraction in most studies ranged from 10 to 25 Gy (BED 10 60–262 Gy) with excellent local control rates (87–100%) and grade 3 liver (Child-Pugh >2 points) toxicity of 3–18.5%.

Jang *et al.* [44] and Kang *et al.* [47] reported that a total dose >54 Gy was associated with local control of 100% at 2 years. Andolino *et al.* [48] and Lasley *et al.* [42] used Child-Pugh status for fractionation (three versus five fractions), with three-fraction schedules in Child-Pugh A. Scorsetti *et al.* [43] chose three-fraction schedules in lesions less than 3 cm with local control of 100% at 1 year. Similarly, Park *et al.* [12] showed higher local control >90% in lesions <3 cm. Tumour size was a significant factor affecting survival, as Yoon *et al.* [36] and Park *et al.* [12] showed. A maximum dose of 75 Gy in three fractions (25 Gy per fraction) was used by Scorcetti *et al.* [43] with two patients developing

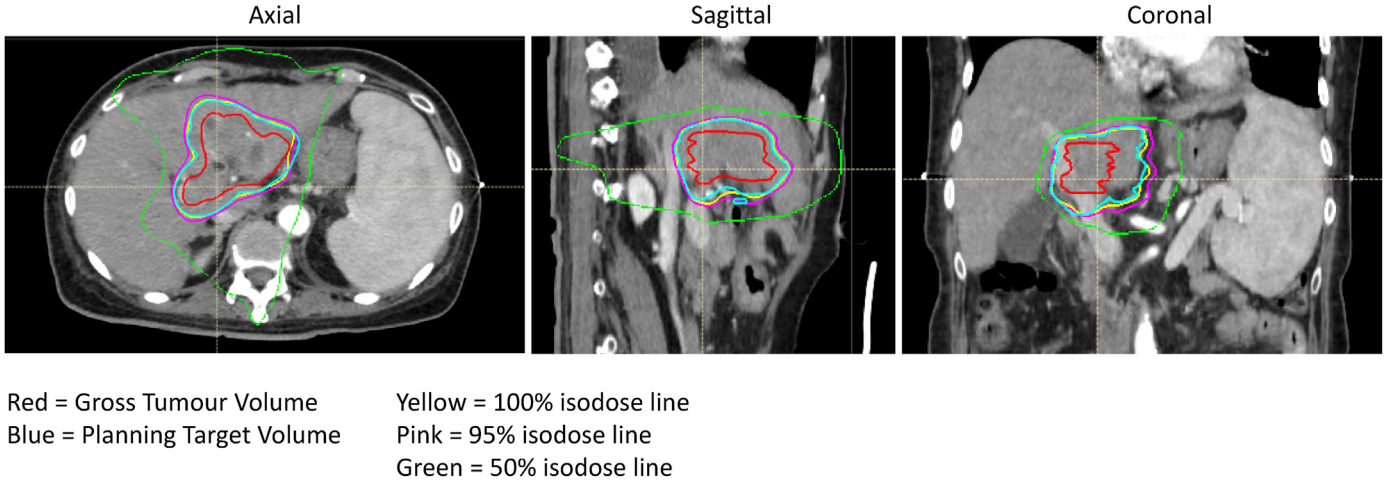

Fig 2. Axial, sagittal and coronal cuts through an arterial phase of a computed tomography linear accelerator plan receiving 3000 cGy in five fractions for hepatocellular carcinoma.

Table 1
Studies with three-fraction stereotactic body radiotherapy for hepatocellular carcinoma

Reference	Study type	Number of patients	Indication BCLC/AJCC stage	SBRT dose (Gy)	Child-Pugh status	Tumour location	Tumour size	Follow-up	Local control	Survival	Toxicity
[36]	Prospective, phase II	50	Small HCC, 0 and A	45 in 3 fractions	A 5/6: 100%	Subcapsular, perivascular, dome, RFA margin	1.3 cm (0.7 −3.1)	47.8 months	2-year: 100% 5-year: 97.1%	5-year: 77.6%	Grade 3: nil Child-Pugh +2: 4% Rib fracture:10% Biliary grade 1 −2: 8%
[37]	Prospective, phase II	43	A–C PVT: 12%	45 in 3 fractions	A: 88% B: 12%	NA	2.8 cm (1–6)	4 years	2-year: 94%	2-year OS: 69% 2-year PFS: 48%	Grade 3 GI: 5% Liver enzymes: 21% Child-Pugh score change (+2): 6 months: 12% 18 months: 23%
[38]	Prospective, phase II	65	0: 54% A: 49% B: 6% C: 6%	60 in 3 fractions	A: 98% B: 1.5%	NA	2.4 cm (1–9.9)	41 months	2-year: 97% 3-year: 95%	2-year OS: 84% 2-year PFS: 48%	RILD: 2% GI: grade 1/2: 32% grade 3: 2%
[12]	Retrospective	290	0–A	30–60 in 3 fractions	A: 86% B: 14%	NA	1.7 cm (0.7–6)	38.2 months	5-year: 91.3%% <3 cm: 93.3% >3 cm: 76.5%	5-year OS: 44.9%	Grade 3+ liver: 2.2% Child-Pugh 2+: 5.5% Grade 3+ Bil: 8.8%
[39]	Retrospective	65	0: 56.9% A: 43.1%	48 in 4 fractions	A: 86.2% B: 13.8%	NA	1.6 cm (0.5 −4.7)	41 months	3-year: 100% 5-year: 100%	3-year: 56.3% 5-year: 41.4%	Grade 3 Liver: 3.1% Ascites: 6% GI: nil
[40]	Retrospective	44	0: 70% A: 25% C: 5%	45–60 in 3 fractions	A: 100%	NA	1.4 cm (0.8 −2.8)	29 months	1-year: 97.7% 3-year: 95%	1-year: 97.7% 3-year: 80.7%	Child-Pugh +2: 4.5%
[41]	Retrospective	77	A: 45% B: 8% C: 47%	45 in 3 fractions	A: 86% B: 14%	NA	2.4 cm	24 months	1-year: 99% 2-year: 99%	1-year: 81.8% 2-year: 56.6%	Liver toxicity: 23% at 2 years Non-classic RILD: 4% Classic RILD: 1.3%
[42]	Prospective	59	A–B: 80% C: 20%	48 in 3 fractions in Child-Pugh A	A: 64%	NA	100.6 cm^3	33.3 months	3-year: 91%	Median PFS: 22.3 months 3-year PFS: 47.3% Median OS: 44.8 months 3-year OS: 61.3%	Grade 3/4 Liver: 10.5%

Table 1 (*continued*)

Reference	Study type	Number of patients	Indication BCLC/AJCC stage	SBRT dose (Gy)	Child-Pugh status	Tumour location	Tumour size	Follow-up	Local control	Survival	Toxicity
[43]	Prospective	43	A: 44% B: 36% C: 20%	48−75 in 3 fractions (51% lesion <3 cm)	A: 53% B: 47%	NA	NA	8 months	1-year: 100% (for 3 fractions)	1-year: 78% 2-year: 45%	Grade 3 hepatic: 16% No RILD
[44]	Retrospective	82	A: 53% B: 29% C: 18%	33−60 in 3 fractions	A: 90% B: 10%	NA	3 cm (1−7)	30 months	2-year: 87% 5-year: 82%	2-year: 63% 5-year: 39%	Grade 3+: 6% Classic RILD: 0% Non-classic RILD: 7%
[45]	Retrospective	92	Small HCC (<6 cm)	30−60 in 3 −4 fractions	A: 74% B: 26%	NA	8.6 cm^3 (0.6 −125.3)	25.7 months	3-year: 92%	Median OS: 53.6 months 1-year: 87% 3-year: 54%	RILD grade 2+: 18.5%
[46]	Retrospective	93	Small HCC (<6 cm)	30−60/3−4	A: 74% B: 26%	NA	2 cm (1−6)	25.6 months	1-year: 94.8% 3-year: 92.1%	1-year: 86% 3-year: 53.8%	Grade 3 liver: 6.5%
[47]	Prospective, phase II	47	A: 17% B: 66% C: 17%	42−60 in 3 fractions	A: 87% B: 13%	NA	2.9 cm (1.3 −7.8)	17 months	2-year: 94.6%	2-year: 68.7%	Grade 3 GI: 6.4% Grade 4 GI: 4.3% Child-Pugh +2: 13%
[48]	Prospective phase I/II	60	T1: 78.3% T2: 20% T3:1.4%	44 in 3 fractions in Child-Pugh A	A: 60% B: 40%	NA	3.1 cm (1−6.5)	27 months	2-year: 90%	2-year: 67% Median OS: 44.4 months	Child-Pugh +2: 19%

AJCC, American Joint Committee on Cancer; BCLC, Barcelona Clinic Liver Cancer; Bil, Biliary; GI, gastrointestinal; HCC, Hepatocellular carcinoma; NA, Not available; OS, overall survival; PFS, progression-free survival; PVT, Portal vein thrombosis; RFA, radiofrequency ablation; RILD, radiation-induced liver disease.

grade 3 liver toxicity (one had isolated enzyme elevation and another Child-Pugh worsening at 4 months after SBRT).

Stereotactic Body Radiotherapy with a Four-to Six-fraction Schedule

SBRT in four to six fractions is the most reported treatment regimen. The dose varies from 24 to 60 Gy in four to six fractions with a BED of 33–150 Gy, as shown in Table 2 [42,49–75]. The trials' study populations were heterogeneous, with large tumours, previously treated with TACE/RFA, varying liver dysfunction and stage. About 30–65% of patients had portal vein thrombosis.

The prospective phase I and II trials from 2004 to 2007 treated at Princess Margaret Hospital showed local control of 87% with grade 3 toxicity of 30% [75]. A phase III randomised trial using this fractionation is ongoing [76]. The 2-year local control ranged from 80 to 100% across the studies. The liver's baseline function and achievable dose constraints (mean dose or Veff) decide the fractionation, as the outcomes should be balanced with toxicity. Culleton *et al.* [77] reported higher toxicity with SBRT in patients with baseline Child-Pugh B8 and above, whereas small lesions with B7 tolerated modest SBRT doses. Proximity to the bile duct impacted dose selection by Sun *et al.* [57] and Teraoka *et al.* [64] preferred seven to eight fractions, whereas Lazarev *et al.* [60] showed adequate local control and toxicity with five fractions. Classic RILD was infrequent (<5%) across the cohorts, with grade 3 liver toxicity (Child-Pugh +2, enzyme elevation) 15–38%, gastrointestinal <5% and biliary 17.5%.

Hypofractionated in 10 Fractions Schedule

The literature using a hypofractionated schedule primarily included protons (summarised in Table 3) [8,78–85]. The dose ranged from 40 to 72.6 Gy in 10 fractions, with a resultant BED of 56–125 Gy. The proportion of patients with Child-Pugh B function were 12–25%, and the reported local control was over 85% in all studies. Three studies used the distance from gastrointestinal organs to choose the dose with 10 fractions, with a higher dose (66 Gy equivalent) for tumours ≥2 cm from gastrointestinal organs [79,82,85]. The prospective study from Japan by Fukuda *et al.* [82] showed an impressive 5-year local control of 95% at a median follow of 55 months with no grade II gastrointestinal or liver toxicity. A phase II study by Hong *et al.* [86] showed a 2-year local control of 94.8% with protons in 15 fractions. The meta-analysis by Qi *et al.* [87] showed that charged particle therapy demonstrated comparable efficacy with SBRT.

Dose-response with Fractionation

The choice of fractionation is at the treating physician's discretion, taking into account tumour size, location, baseline liver function and the ability to meet the dose constraints. Unlike SBRT for non-small cell lung cancer or liver metastases, the literature is divided on whether the total dose and BED impact outcomes in HCC, particularly local control and survival [88,89]. A clear dose-response relationship that could guide dose selection in HCC is lacking. Sheth *et al.* [90] studied the fractionation schedules for HCC in the United States of America. The most commonly used schedules were 8–10 Gy in five fractions (63%), followed by 15 Gy × three fractions (32.3%). The patients treated with BED >100Gy were associated with improved survival (30.8 months versus 20.8 months); however, this was not significant on multivariate analysis.

Ohri *et al.* [91] tested the influence of BED on local control in HCC treated with SBRT in five studies from 2010 to 2013. There was no dose-response relationship for the range of BEDs from 60 to 180 Gy, and local control was similar irrespective of BED ≤100 Gy or >100 Gy. A multicentric retrospective study by Su *et al.* [92] reported the outcomes for 602 HCC patients treated with SBRT 28–55 Gy in one to six fractions from 2011 to 2017. The SBRT dose was classified based on BED and equivalent dose in 2 Gy fractions (EQD2) into high (BED >100 Gy), moderate (BED <100 Gy, EQD2 > 74 Gy) and low (BED <100 Gy, EQD2 < 74 Gy). Patients with smaller tumours, BCLC A and low albumin bilirubin, received a higher dose. The high radiation dose was associated with improved overall survival, progression-free survival and intrahepatic control. SBRT dose >42 Gy in fewer fractions (≤3) was indicative of better overall survival and progression-free survival. The authors propose a high dose schedule with BED >100 Gy to be the preferred dose, followed by SBRT with EQD2 > 74 Gy. Further prospective studies are required to test higher (BED >100 Gy) versus lower dose (BED ≤100 Gy) schedules while controlling for lesion size, stage and baseline liver function.

Recommendation

The preferred total dose and fractionation for ablative treatments of HCC are still uncertain. Data show that local control is excellent regardless of the fractionation used. Normal tissue toxicity and liver function might drive the selection of preferred dose and fractionation. We propose a risk-adapted approach where lesions close to critical structures receive multiple-fraction SBRT (three to five) and lesions away from critical structures receive fewer fractions (one to three) (Figure 3). The use of image guidance will have implications on the number of fractions considered – magnetic resonance-guided radiotherapy might permit the lower fractions spectrum to be considered. If maintaining synthetic liver function is critical, protons might be considered (if available).

Advances in Stereotactic Body Radiotherapy

Dose Escalation

Magnetic resonance radiotherapy is a novel revolutionising technology and offers promising outcomes for HCC [93]. Magnetic resonance-guided delivery of SBRT has the

Table 2
Studies with four-to six-fraction stereotactic body radiotherapy (SBRT) for hepatocellular carcinoma

Reference	Study type	Number of patients	Indication BCLC/AJCC stage	SBRT dose (Gy)	Child-Pugh status	Tumour location	Tumour size	Follow-up	Local control	Survival	Toxicity
[49]	Retrospective	297	0/A: 27% B: 18% C/D: 53%	27–60/3–6 fractions	A: 76% B: 17%	NA	2.7 cm (0.5–18.1)	19.9 months	3-year: 87%	3-year: 39%	Child-Pugh +2: 16%
[50]	Retrospective	389	Salvage SBRT 0: 27.5% A: 41% B: 2.2% C: 28.5% D: 0.7%	35–40/5 fractions	A: 90% B: 10%	NA	2.3 cm (1–6.2)	34.8 months	3-year: 89 –97.2%	3-year OS: 66.1–71.5%	RILD: none Grade 3: none
[51]	Retrospective	46	A/B: 58.8% C/D: 41.2%	28–60/4–5 fractions	A: 82.3% B: 17.7%	NA	Mean 4.9 cm (±1.3 SD)	17.1 months	1-year: 91.3% 2-year: 78.2% 3-year: 73.3%	1-year: 73.4% 2-year: 70.3% 3-year: 47.4%	Non-classic RILD: 19.6% Child-Pugh +2: 15%
[52]	Retrospective	133	A–C C: 31.5%	30/5–6 Protons versus photons	A: 62% B/C: 38%	NA	36–269 ml	14 months	2-year: 93% versus 90%	Median OS 31 months versus 14 months 2-year OS: 59% versus 28%	Non-classic RILD 15.7%
[53]	Retrospective	54	C: 100%	45/4–5	A: 64.8% B: 32.5%	NA	<8 cm: 52% >8 cm: 48%	6.2 months	NA	Median OS: 10.2 months	RILD classic: 3.7% RILD non-classic: 13%
[54]	Retrospective	33	After incomplete RFA BCLC 0/A	42/6	A: 100%	Central/ peripheral Close to vessels Close to capsule	4.1 cm (3.4–5.2)	27.2 months	2-year: 82%	3-year: 83.7%	NA
[55]	Retrospective	143	0: 39% A: 39% B: 0% C: 22%	35–40/5	A: 96% B: 4%	NA	1.7 cm (1–3)	30.2 months	3-year: 95.6%	3-year: 63.6%	Non-classic RILD: 8.2% RILD death: 2.7% Other grade 3+:0
[56]	Retrospective	178	A–C C: 17.2%	3–5 fractions with break	A: 67.4% B: 27.2% C: 2.8%	NA	2.6 cm (1.8–4.1)	23 months	1-year: 95.4% 2-year: 89.5%	NA	Child-Pugh +2: 27%

(*continued on next page*)

Table 2 (*continued*)

Reference	Study type	Number of patients	Indication BCLC/AJCC stage	SBRT dose (Gy)	Child-Pugh status	Tumour location	Tumour size	Follow-up	Local control	Survival	Toxicity
[57]	Retrospective	108	A or B	48/8, 49/7, 50/5, 54/6	A: 100%	Distance from bile duct – for choice of fractionation	2.3 cm (0.7-4.9)	42 months	1-year: 98.1% 2-year: 96.2% 3-year: 95.1%	1-year: 96.3% 2-year: 89.8% 3-year: 80.6%	Liver failure: 6 patients GI bleeding: 6 patients
[58]	Retrospective	91	0: 11% A: 64% B: 35%	45/5 (30–50/5)	A: 63% B: 37%	NA	3 cm (1.1–11)	18 months	1-year: 98% 2-year: 93%	DFS 1-year: 84% 2-year: 44%	Fatigue: grade 2:14%
[59]	Prospective	32	A: 96.7% B: 3.1%	36–60/4 fractions	A: 100%	NA	2.1 cm (1–4.5)	27 months	2-year: 36 Gy: 25 44 Gy: 66.7 52 Gy: 87.5 60 Gy: 94.1	1-year: 96.9% 2-year: 81.3%	Grade 2 liver: 15.6%
[60]	Retrospective	53	A: 24.5% B: 43.4% C: 32.1%	40/5 fractions	A: 62.3%	Segment 4, 5, or 8 adjacent to the hepatic hilum, or <1.5 cm from main portal branches (central)	3.4 cm (1.1–14)	12.2 months	2-year: 87.9%	2-year DSS: 53.2% 2-year OS: 39.1 %	Grade 3 (any): 17%
[61]	Retrospective	125	A–B	3–5 fractions	Median Child-Pugh 6	NA	2.3 cm (1–20)	12.3 months	1-year: 96.5% 2-year: 91.3%	1-year OS: 75.3% 2-year OS: 54.9%	Grade 3 (any): 8%
[62]	Retrospective	103	A: 30.1% B: 60.2% C: 8.7%	24–50/3–5	A: 59.2% B: 37.9% C: 1.9%	NA	3 cm (1.2–9.4)	15.1 months	1-year: 91% 2-year: 89%	Median OS: 23.9	NA
[63]	Retrospective	146	A: 4.9% C: 79.4% D: 15.7%	50/5 (72%) 45/18 (28%)	A: 46% B: 41% C: 13%	NA	NA	23 months	1-year: 97%	Median 22.3 months	Child-Pugh 2+: 31%
[64]	Retrospective	117	0–B	40-48/4 60/8	A: 88% B: 12%	Central versus peripheral for dose	1.6 cm (1–3)	30 months	1-year: 100% 2-year: 100% 3-year: 98%	1-year: 96% 3-year: 67%	NA
[65]	Retrospective	40	NA	40/5	A: 67.5% B: 32.5%	NA	5.3 cm (1.9–12)	13 months	NA	NA	Grade 3 HB: 17.5%
[66]	Prospective	114	A–C	27–54/6 fractions	A: 89% B: 11%	NA	121 (1–1913 cm^3)	NA	NA	NA	Child-Pugh +2: 26%
[67]	Retrospective	82	A: 91.4% B: 8.6%	42–48/3–5 fractions	A: 100%	NA	3.1 cm	33 months	98.8%	1-year: 96% 3-year: 82% 5-year: 70%	Child-Pugh 2+: 2.4% RILD: none
[68]	Retrospective	36	Bridge for transplant 0–B	30–40/6 fractions	A: 61.1% B: 38.9%	NA	4.5 cm (2.9–5.8)	28.1 months	1-year: 93% 3-year: 84% 5-year: 84%	1-year: 83% 3-year: 61% 5-year: 61%	Acute liver: 38.9%

Table 2 (*continued*)

Reference	Study type	Number of patients	Indication BCLC/AJCC stage	SBRT dose (Gy)	Child-Pugh status	Tumour location	Tumour size	Follow-up	Local control	Survival	Toxicity
[69]	Retrospective	77	A: 68.5% B: 31%	30–50/3–5	A: 87% B: 13%	NA	8.5 cm (5.1–21)	20.5 months	NA	Median OS: 21–42 months 5-year OS: 32.9–46.9%	Grade 3 or 4: 11 patients Grade 5: 1 patient
[70]	Prospective, phase II	90	0: 34% A: 50% C: 16%	35–40/5	A: 91% B: 9%	Treated location map	2.3 cm (1–4)	41.7 months	3-year: 96.3%	3-year CSS: 72.5% 3-year OS: 66.7%	Child-Pugh +2: 8 patients Grade 3 enzyme: 6 patients
[71]	Retrospective	132	A: 55.3% B: 44.7%	42–46/3–5 28–30/1 fraction	A: 86.3% B: 13.6%	NA	3 cm (1.1–5)	21 months	1-year: 90.9% 2-year: 84.1%	1-year: 94.1% 2-year: 81.9% 3-year: 73.5% 5-year: 64.3%	Grade 3+ liver: 8.3%
[72]	Retrospective	79	I: 37% II: 27% III: 9% Recurrence: 14%	40/4–60/10	A: 84.4% B: 11.4% C: 1.3%	NA	2.7 cm (0.6–7)	21 months	2-year: 80%	2-year: 53%	Grade 3+ GI: 4.6% Grade 3 liver: nil
[73]	Prospective	222	NA	36/6	A: 95% B: 5%	NA	133 cm^3	NA	NA	Median 16.9 months 2-year: 33.6%	QOL: no change
[42]	Prospective	59	0-B C: 20%	Child-Pugh B: 40/5	A: 64%	NA	106.6 cm^3	33.3 months	3-year: 82%	Median PFS: 10 months 3-year PFS: 22.9% Median OS: 17 months 3-year OS: 26.1%	Grade 3/4 liver: 38%
[74]	Retrospective	185	0,A: 95% C: 4%	35–40/5	A: 86% B: 14%	NA	2.4–2.7 cm	31 months	3-year: 91%	3-year: 70%	Grade 5: 2 patients
[75]	Prospective	102	A/B: 34.3% C: 65.7%	24–54/6 fractions	A: 100%	NA	117 cm^3 (1.3–1913.4)	31.4 months	1-year: 87%	Median OS: 17 months	Grade 3: 30% RILD: none Death: 7%

AJCC,American Joint Committee on Cancer; BCLC, Barcelona Clinic Liver Cancer; CSS, Cause specific survival; DFS, disease-free survival; DSS, Disease specific survival; GI, gastro-intestinal; OS, overall survival; QOL, quality of life; PFS, progression-free survival; RFA, radiofrequency ablation; RILD, radiation-induced liver disease.

Table 3
Studies with 10-fraction hypofractionated schedule for hepatocellular carcinoma

Reference	Study type	Number of patients	Indication BCLC/AJCC	SBRT dose (Gy)	Child-Pugh status	Tumour location	Tumour size	Follow-up	Local control	Survival	Toxicity
[8]	Prospective	72	0: 5.6% A: 54.2% B: 33.3% C: 6.9%	66/10	A: 97.2% B: 2.8%	NA	1.2 cm (1–2.5)	51.6 months	2-year: 92.8%	2-year: 91.7%	Pneumonitis: grade 1: 32.5% Grade 3 liver: none
[78]	Retrospective	146	A–C	45/10 fractions Proton	A: 75.3% B/C: 24.7%	NA	220–553 cm^3	10.8 months	NA	NA	Grade 2 liver enzymes: 55% RILD: 19.7%
[79]	Retrospective	243	A-C	50–66/10 fractions Proton	A: 93.8% B7: 6.2%	Based on distance from GI organs	2.2 cm (1–17)	31.5 months	87.4%	3-year: 61.8% 5-year: 48.1%	Child-Pugh +2: 4.1% GI grade 3: 2.5%
[80]	Retrospective	136	0-C	66–72.6/10	A: 90% B7: 10%	NA	366 ± 549 cm^3	10 months	NA	NA	RILD: 14%
[81]	Retrospective	83	NA	60/10 fractions Proton	A: 88% B: 12%	NA	3 cm (1–11)	45 months	NA	2-year OS: 87.5% 5-year OS: 49.4%	No grade 3 toxicity
[82]	Prospective	129	0/A: 23% B: 26% C: 50%	66/10 fractions Proton	A: 78.3% B: 21.7%	Different dosing for central and near GI	3.9 cm (1–13.5)	55 months	5-year: 94%	5-year OS: 69% 5-year PFS: 28%	No grade 2 hepatic or GI
[83]	Retrospective	50	C: 36%	50–60/10 Photons	A: 94% B: 6%	NA	<3 cm	24.7 months	3-year: 89.7%	3-year OS: 57.4% 3-year PFS: 11.2%	LFT elevation: 4 patients Biliary: 12 patients
[84]	Retrospective	72	II: 17% III: 74% IVA: 10%	40–50/10	A: 75% B: 25%	NA	NA	NA	NA	NA	Child-Pugh score 2+: 44%
[85]	Retrospective	266	NA	66/10 Proton	A: 76% B: 23% C: 1%	Different dosing for central and near GI	1–9.9 cm	NA	1-year: 98% 3-year: 87% 5-year: 81%	Median: 50.6 months 1-year: 87% 3-year: 61% 5-year: 48%	Late toxicity: 4.5% GI: 2.3%

AJCC, American Joint Committee on Cancer; BCLC, Barcelona Clinic Liver Cancer; GI, gastrointestinal; LFT, Liver function test; NA, Not available; OS, overall survival; PFS, progression-free survival; RILD, radiation-induced liver disease; SBRT, stereotactic body radiotherapy.

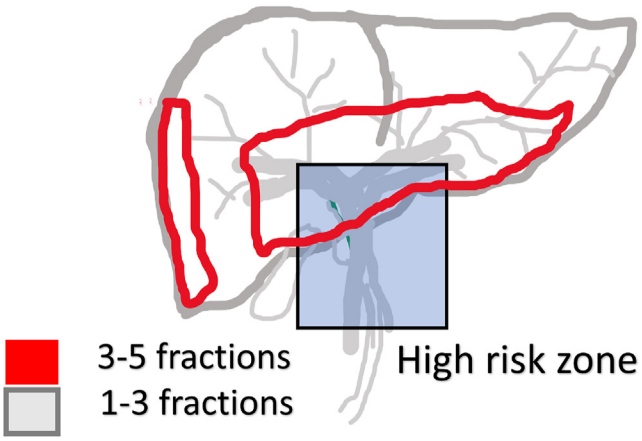

Fig 3. Diagrammatic representation of the high risk of toxicity – liver zones and proposed fractionation use. High risk zone refers to central liver zone – 2 cm expansion around portal vein until its bifurcation in liver and includes porta hepatis with the common bile duct and its bifurcation.

potential to safely allow dose escalation with high precision with maximal organ sparing. It provides the advantage of high soft-tissue contrast, adaptive online treatment leading to improved accuracy, organ sparing and a reduction in margins (Figure 1). Feldman *et al.* [94] demonstrated the feasibility of gated SBRT delivery with three to five fractions on magnetic resonance linear accelerator in patients with HCC with the advantage of lower mean liver dose. Rosenberg *et al.* [95] reported early experience of magnetic resonance-guided SBRT in 26 patients with liver tumours (HCC, $n = 6$) with a median dose of 50 Gy in five fractions. The local control was 80% (100% with HCC) with a median follow-up of 21 months; grade 3 gastrointestinal toxicity was reported in 7.7%. The recent series showed local control ranging from 88 to 100% [96–98]. The online adaptive magnetic resonance-guided SBRT with one to three fractions is best matched for dose escalation, and future trials will inform its efficacy. The long-term results of prospectively treated patients with this promising technology will advise whether it is superior to conventional delivery methods and enable decision making for patient selection and safety.

Functional Imaging

The functionality of the liver shows regional variation. SBRT planning based on total liver volume does not consider these regional variations and assumes liver function to be homogenous. Various functional imaging techniques have been tried, such as functional magnetic resonance imaging, [18F]-fluorodeoxyglucose positron emission tomography and single-photon emission computed tomography (SPECT) using 99mTc-labelled iminodiacetic acid [99]. However, these techniques are poorly validated. Shen *et al.* [100] used 99mTc-mebrofenin SPECT co-registered to the planning computed tomography, and regions of high uptake in the liver were taken as functional volume for avoidance during radiotherapy planning with resultant excellent dose coverage to the target and sparing of the healthy remnant liver volume was achieved. Furukawa *et al.* [101] showed that functional SBRT plans reduced mean liver dose by a median of 3 Gy and volume receiving 15 Gy by 40% while maintaining excellent tumour coverage. The translation of functional SBRT to a reduction in post-treatment toxicity should be explored prospectively.

Imaging Biomarker

Radiomics is being explored as a potential prognostic factor in oncology to develop personalised treatments. Wu *et al.* [102] used a combination of radiomic features and clinical characteristics to stratify HCC patients with portal vein tumour thrombosis treated with SBRT into low- and high-risk groups. The high-risk group had poorer survival. The use of radiomics should be explored during SBRT planning to individualise and escalate treatment dose potentially. Further research in the combination of genomic and radiomics to personalise SBRT treatment and dose/fractionation is warranted.

Conclusion

The role of SBRT for HCC is now embedded in clinical practice. The dose, fractionation and technological radiotherapy platform for delivery is still evolving. If tumours are located close to critical gastrointestinal structures, a risk-adapted approach with a higher number of fractions should be considered. Novel technologies such as magnetic resonance-guided radiotherapy and protons can offer further opportunities to deliver safer treatments. Biological knowledge and systemic therapies with evolving prospective trials are required to establish the safe delivery of total dose and number of fractions in biomarker-rich populations.

Conflict of interest

M.A. Hawkins reports financial support by University College London.

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