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Original Article

Stereotactic Body Radiotherapy for Small Unresectable Hepatocellular Carcinomas

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Abstract

Aims: Stereotactic body radiotherapy (SBRT) is an option for the treatment of hepatocellular carcinoma (HCC) in patients ineligible for standard local therapies. This study reports on the safety and efficacy of SBRT in small HCC tumours (≤5 cm) in the province of British Columbia.
Materials and methods: Between March 2011 and July 2015, 31 patients with Child–Pugh Class A or B, with small HCCs measuring ≤5 cm were treated with SBRT at our institution. Primary end points were local control, progression-free survival, overall survival and toxicity.
Results: Thirty-four hepatomas (median size 3.3 cm, range 1.3–5.0 cm) were treated. The median follow-up was 18.3 months. Twenty-six patients (84%) had received previous liver-directed treatments. Most patients (88%) were treated with 45 Gy in three or five fractions. Six patients (19%) had worsened Child–Pugh score by two or more points during follow-up; overall 32% of patients experienced ≥ grade 3 + toxicities. One-year local control and overall survival were 94 and 84%, respectively. One-year progression-free survival was 49%; 81% of patients with disease progression received further HCC therapy. On univariate analysis, small tumour size predicted for improved overall survival ($P = 0.01$) whereas prescription biological equivalent dose (BED_{10}) ≥$100Gy_{10}$ approached significance ($P = 0.06$).
Conclusion: SBRT provides high local control to small inoperable HCC. SBRT can be delivered safely even after previous liver-directed therapies and further liver therapies can follow treatment with SBRT. Although overall 32% of patients experienced ≥ grade 3 + toxicities, and 19% had a deterioration in Child–Pugh score of two or more points, these changes were mainly transient with minimal clinical impact. Despite excellent local control, disease progression outside of the irradiated site remains prominent. Further studies are warranted to examine combined therapy approaches to maximise disease control.

Key words: Hepatocellular carcinoma; Stereotactic body radiotherapy

Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and is the second leading cause of cancer-related death worldwide [1]. Although the incidence of HCC is highest in South East Asia, rates have increased significantly in Western Europe and North America, due to an increase in the prevalence of obesity and alcoholic liver disease [2].

Treatment of HCC is dependent on many factors, including stage, location, size of tumour(s) as well as underlying liver function and comorbidities [3,4]. Standard curative treatment options for operable HCC include surgical resection and liver transplant, with the latter providing a long-term survival of up to 70–85% at 4 years [5]. For small inoperable tumours, typically <3 cm, radiofrequency ablation (RFA) and percutaneous ethanol injection have been used as curative options [3]. Transarterial

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chemoembolisation (TACE) has been shown to improve survival compared with best supportive care in large inoperable tumours, and in multifocal disease, although is not considered curative [6,7].

Historically, radiotherapy for HCC was not regarded as a safe or effective treatment option due to high rates of radiation-induced liver disease (RILD) [8]. Advances in technology and in the biological understanding of liver radiation tolerances have led to the development of more conformal radiotherapy techniques allowing for partial liver irradiation while significantly reducing the risk of RILD. Stereotactic body radiotherapy (SBRT) has therefore emerged as a feasible and safe treatment option for patients with HCC ineligible for other local treatments, with local control rates comparable with those of RFA [9–19]. For tumours ≥2 cm, SBRT may even offer superior local control when compared with RFA [19]. In this study, we contribute to the published literature by reporting on the clinical outcomes of patients with small (≤5 cm) HCCs treated with SBRT at our institution.

Materials and Methods

Patient Population

This retrospective, single institution study included the first 31 HCC patients with small tumours (≤5 cm) treated with SBRT at the British Columbia Cancer Agency between March 2011 and July 2015. Eligibility criteria included patients with fewer than five synchronous lesions with none greater than 5 cm, Child–Pugh score A or B, no evidence of extrahepatic disease and an Eastern Cooperative Oncology Group (ECOG) score ≤2. Patients who had received prior liver-directed treatments were included. Treatment decisions were made at the discretion of the institutional multidisciplinary liver tumour board, following National Comprehensive Cancer Network (NCCN) guidelines. RFA was typically used as first choice for small tumours (<3 cm) whereas SBRT was reserved for patients ineligible or unsuitable for other local treatments, due to liver function, tumour position or progression after TACE or RFA. A diagnosis of HCC was established by biopsy or by meeting radiological criteria according to the American Association for the Study of Liver Disease [4]. Pretreatment evaluation of all patients included a clinical examination, multiphasic computed tomography scan and/or magnetic resonance imaging (MRI), baseline complete blood count, liver function tests, liver enzymes and alpha fetoprotein. Approval for this study was obtained from the British Columbia Cancer Agency Research Ethics Board.

Stereotactic Body Radiotherapy Treatment

At least three gold fiducial markers were implanted in proximity to the tumour(s) under ultrasound guidance prior to radiotherapy planning, unless previous implanted markers such as surgical clips, bile duct stents or lipiodol were deemed adequate for tumour targeting. At the time of simulation, liver motion during respiration was evaluated on fluoroscopy to determine if the patient would be best suited for gated treatments. Patients with a ≥2 cm cranial-caudal movement of fiducials and adequate correlation between the external respiratory marker block and fiducials were gated to reduce treatment volume. For patients unsuitable for gated treatments, a standard contrast-enhanced helical computed tomography simulation scan and free-breathing four-dimensional computed tomography scan were obtained. For gated patients, a contrast-enhanced computed tomography scan during expiratory breath hold was obtained in place of a helical computed tomography scan. In addition, a four-dimensional computed tomography scan was obtained to evaluate motion within the gating window. All patients were simulated supine in a customised Vac-Lok for immobilisation. Abdominal compression was not used.

Postfiducial placement, pretreatment diagnostic multiphasic computed tomography and MRI scans were fused with the radiation planning computed tomography scans to aid in tumour delineation in gated and non-gated patients. Scans were fused using rigid deformation, matched to fiducials, with priority given to the fiducial closest to the tumour. Gross tumour volume (GTV) was defined as the arterial enhancing lesion(s) with washout on delayed phase of the coregistered diagnostic scan. The clinical target volume (CTV) was an isotropic 5 mm margin around the GTV, but not extending outside of liver parenchyma. For non-gated patients, an anisotropic margin of 2–10 mm was added to the CTV in all directions to generate an internal target volume (ITV), based on fiducial movement on the four-dimensional computed tomography scan. No ITV was created for gated patients. The planning target volume (PTV) corresponded to the CTV (or ITV) with a 3–5 mm isotropic margin. PTV margins were determined based on the accuracy of the fusion between diagnostic and planning computed tomography scans, as well as the size and visibility of the target lesion on the planning computed tomography scan.

Organs at risk (OAR) were contoured on the helical radiation planning computed tomography for non-gated patients and the exhale breath hold computed tomography for gated patients. These included: spinal cord, liver, stomach, duodenum, small bowel, large bowel, skin, kidneys, great vessels and chest/abdominal wall. American Association of Physicists in Medicine Task Group (AAPM TG) 101 dose constraint guidelines were followed [20] (see Table 1). Liver dose constraints were based on liver minus GTV volume.

Treatment was delivered using volumetric arc radiotherapy with 6 or 10 MV photon energy on a Varian TrueBeam™ linear accelerator. Treatment doses were individualised based on the location of the tumour in relation to the tolerance of nearby OAR. The planning aim was to cover 95% of the PTV by the prescription dose and 99% of the PTV by at least 90% of the prescription dose. The dose prescribed to the PTV ranged from 40 to 55 Gy in three to five fractions. Dose constraints to OAR were placed as a higher priority than PTV coverage and, as such, PTV under-coverage was allowed. Daily image guidance with cone-beam computed

Table 1
Summary of organ at risk tissue dose constraints [20]

Organ	Maximum critical volume above threshold (cm^3)	Three fractions		Five fractions	
		Threshold dose (Gy)	Maximum point dose* (Gy)	Threshold dose (Gy)	Maximum point dose* (Gy)
Spinal cord	<0.35	18	21.9	23	30
Liver†	700	15	NA	18	NA
Oesophagus	<5	17.7	25.2	19.5	35
Heart/pericardium	<15	24	30	32	38
Great vessels	<10	39	45	47	53
Stomach	<10	16.5	22.2	18	32
Duodenum	<5	16.5	22.2	18	32
Large bowel	<20	24	28.2	25	38

NA, not applicable as parallel tissue.
* 'Point' defined as 0.035 cm^3 or less.
† Minimum critical volume estimate: ≥700 cm^3 of normal liver (liver − gross tumour volume) to receive ≤15 Gy in three fractions and ≤18 Gy in five fractions.

tomography was carried out to localise the target before treatment delivery for non-gated patients, whereas orthogonal fluoroscopy before and during treatment delivery was used for gated patients.

Follow-Up

Patients were evaluated every 3 months for the first year after treatment and every 6 months thereafter. A clinical examination, blood work and either multiphasic computed tomography or contrast-enhanced MRI were carried out at each follow-up visit. Toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v.4.0 and measured from the end date of radiotherapy and censored at the time of disease progression, upon delivery of other liver-directed treatments or at the last follow-up. Classic RILD was defined as: anicteric hepatomegaly and ascites, typically occurring between 2 weeks and 3 months after therapy, with an elevated alkaline phosphatase (more than twice the upper limit of normal or baseline value) [21]. Response Evaluation Criteria in Solid Tumours (RECIST) were used to assess the local tumour response [22]. Progression was defined either as local failure (occurring within the PTV), regional failure (occurring within the liver but outside the PTV) or metastatic progression.

Statistical Analysis

Quantitative variables were reported by median and range, and qualitative variables by frequency and percentage. Local control, progression-free survival (PFS) and overall survival were calculated from the end of radiotherapy and analysed using Kaplan–Meier survival analyses with Log-rank testing. A univariate analysis was carried out to explore the impact of patient-, tumour- and treatment-related factors on outcomes. *P* values less than 0.05 were considered statistically significant. Results were analysed with SAS Version 9.3 for Microsoft Windows (SAS Institute Inc., Cary, NC, USA).

Results

Patient and Treatment Characteristics

Thirty-four separate hepatomas in 31 patients were treated, with a median size of 3.3 cm (range 1.3–5.0 cm). Baseline patient and treatment demographics are presented in Table 2. The most common cirrhosis aetiologies were hepatitis B and C (52 and 29%, respectively). Thirty patients (97%) had a pretreatment Child–Pugh score of ≤B7; one patient had a baseline Child–Pugh score of B8. Twenty-six patients (84%) had received liver-directed therapy prior to SBRT. In total, there were 50 previous liver-directed therapies in these 26 patients (median 2, range 0–4).

Treatment factors are shown in Table 3. Radiotherapy prescription doses ranged from 40 to 55 Gy in three to five fractions, with 88% of lesions receiving 45 Gy in three or five fractions. Four patients (13%) were treated with a gated plan. Biological equivalent dose, assuming an α/β of 10 (BED_{10}), was calculated and reported in light of the heterogeneous prescription doses. Twenty-four (71%) lesions were treated with a BED_{10} prescription dose ≥100 Gy_{10}. The median BED_{10} to 95% of the PTV (D95) was 104.8 Gy_{10} (range 45.0–116.5 Gy_{10}). BED_{10} D95 for the PTV was ≥100 Gy_{10} in 20 patients (59%) and ≥80 Gy_{10} in 27 patients (79%).

Treatment Outcomes

The median follow-up was 18.3 months (range 2.1–50.1 months); at the time of last follow-up, 20 patients (65%) were alive. Local control was 94% at both 1 and 2 years (Figure 1A). PFS at 1 and 2 years was 49 and 37%, respectively, whereas overall survival was 84% at 1 year and 74% at 2 years (Figure 1B, C). Twenty-one patients (68%) had developed progression of disease at the time of analysis: 16 patients developed regional failure (occurring within the liver but outside the PTV), there were three local failures at the same time as regional failure and two patients developed distance relapse as first presentation of disease

Table 2
Baseline patient and prior treatment characteristics

Characteristics	All patients ($n = 31$) n (%)
Age, years	
Median	64
Range	48–88
Gender	
Male	24 (77.4%)
Female	7 (22.6%)
ECOG status	
≤1	28 (90.3%)
2	3 (9.7%)
Cirrhosis aetiology	
Unknown	2 (6.5%)
Hepatitis C	9 (29.0%)
Hepatitis B	16 (51.6%)
Alcohol	0 (0%)
Combination	4 (12.9%)
Pretreatment Child–Pugh score	
A5	19 (61.3%)
A6	9 (29.0%)
B7	2 (6.5%)
B8	1 (3.3%)
Portal venous thrombosis	3 (9.7%)
Baseline AFP	
Median	18
Range	1.3–6100
Baseline ALBI score	
Grade 1	16 (51.6%)
Grade 2	13 (41.9%)
Grade 3	2 (6.5%)
Previous treatment	
None	5 (16.1%)
Any*	26 (83.9%)
Previous TACE	15 (48.4 %)
Previous RFA	17 (55%)
Previous PEI	3 (9.7%)
Previous surgery	14 (45.2%)
Previous Y-90	1 (3.2%)

AFP, alpha fetoprotein; ALBI, albumin–bilirubin score; ECOG, Eastern Cooperative Oncology Group; TACE, transarterial embolisation; RFA, radiofrequency ablation: PEI, percutaneous ethanol injection: Y-90, yttrium-90.
* Includes TACE, RFA, PEI, surgery and Y-90.

Table 3
Tumour and dosimetric parameters of treated hepatomas

Characteristics	All tumours ($n = 34$) n (%)
Tumour size (cm)	
Median	3.3
Range	1.3–5.0
Prescription dose (n, %)	
55 Gy/3 fractions	1 (2.9%)
45 Gy/3 fractions	22 (64.7%)
50 Gy/5 fractions	1 (2.9%)
48 Gy/5 fractions	1 (2.9%)
45 Gy/5 fractions	8 (23.5%)
40 Gy/5 fractions	1 (2.9%)
Prescription $BED_{10} \geq 100$ Gy_{10}	24 (70.6%)
Gated plan	4 (11.8%)
PTV volume (cm^3)	
Median	82.0
Range	22.4–252
PTV V100%	
Median	93
Range	64–99
PTV V95	
Median	98
Range	70–100
D95 BED_{10}, Gy_{10}	
Median	104.8
Range	45.0–116.5
D95 BED_{10} (Gy) ≥ 80 Gy_{10}	27 (79.4%)
D95 BED_{10} (Gy) ≥ 100 Gy_{10}	20 (58.8%)
Liver − GTV mean dose, Gy	
Median	10.1
Range	3.7–20.1

BED, biological equivalent dose assuming $\alpha/\beta = 10$; D95, minimum dose delivered to 95% of the PTV; GTV, gross tumour volume: PTV, planning target volume; PTV Vx, PTV receiving x% of prescribed dose.

progression (Table 4). Two patients died prior to radiological evidence of relapse while eight patients had no evidence of disease progression at the time of the analysis. Of the three patients who developed local failure, two had tumour progression within the 95% isodose line, whereas one patient had progression within the 50% isodose line.

Seventeen (81%) patients with disease progression went on to receive further HCC therapy. Three patients received sorafenib, whereas 14 patients had further liver-directed treatments for disease progressing within the liver outside the SBRT site, including three patients who underwent liver transplantation. Four patients did not receive further treatment after progression due to advanced disease, a decline in performance status or markedly worsening liver function.

Two of the three patients who underwent liver transplantation had radiographic documentation of disease progression outside the SBRT site. Pathology showed mostly necrosis within the treated volume with viable tumour elsewhere. The third patient who underwent a transplant had worsening liver function without evidence of residual disease or disease progression on imaging. Pathology at the time of the transplant, however, revealed residual disease at the site of SBRT.

No patient, tumour or treatment factors, including age, presence of portal vein thrombosis, baseline Child–Pugh score or change in Child–Pugh score, tumour size pretreatment alpha fetoprotein, prescription dose or PTV coverage, were predictive of improved local control on univariate analysis. For PFS, only a higher baseline albumin–bilirubin (ALBI) score [23], analysed as a continuous variable, predicted for a worse outcome ($P = 0.02$). For overall survival, larger tumour size, analysed as a continuous variable, was associated with a worse outcome ($P = 0.01$), whereas prescription BED_{10} dose ≥ 100 Gy_{10} approached significance for improved survival ($P = 0.06$) (Table 5). Baseline Child–Pugh score $\geq$ B7, an increase in Child–Pugh score at 3 months by two or more points and a

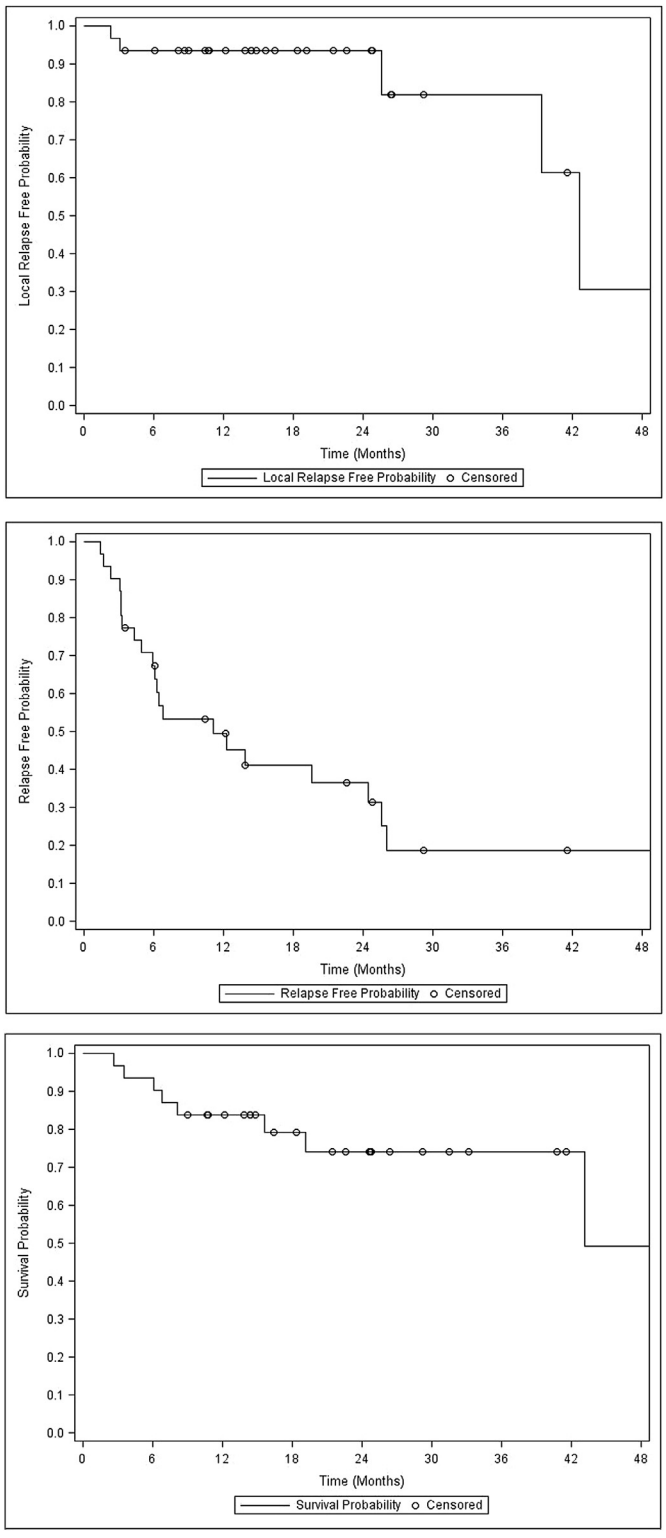

Fig 1. Kaplan–Meier curve of (A) local control, (B) progression-free survival, (C) overall survival.

higher baseline ALBI score were not predictive of worse overall survival ($P = 0.18$, $P = 0.30$ and $P = 0.27$, respectively). Due to low cohort numbers, a multivariate analysis was not carried out.

Toxicity

There were no reported cases of classic RILD during follow-up. Six patients (19%) had a worsened Child–Pugh score by two or more points, which occurred at a median follow-up of 3 months after SBRT. This was associated with disease progression in two patients. Of the four patients who did not progress, two A6 patients worsened to B8, one to a B9 and one to C12 (secondary to hepatitis reactivation). Child–Pugh score worsening was transient for two patients but persistent in the remaining two.

Overall, 10 patients (32%) had documented grade 3 or higher toxicity during follow-up after SBRT. In seven of these 10 patients, the grade 3 + toxicity occurred within 3 months after treatment. Three of these patients had elevation in gamma-glutamyltransferase (GGT), one had elevation in bilirubin and one had aspartate aminotransferase elevation. Three patients with grade 3 elevated liver function tests (one with hyperbilirubinaemia and two with elevated GGT) had progressive regional liver disease at first follow-up and this may have contributed to their laboratory values. Toxicity was transient in the one patient with raised aspartate aminotransferase, whereas one patient had a grade 3 elevation of GGT at baseline that did not change after SBRT.

There was one acute grade 3 gastrointestinal bleed; this patient did require hospital admission due to melaena but did not require a transfusion. Endoscopy revealed a 1.5 cm non-metastatic duodenal ulcer, but no deterioration of oesophageal varices. This patient received 40 Gy in five fractions and the maximum dose to the duodenum was 31.0 Gy, lower than the accepted dose tolerance of 32 Gy published in the literature [20]. One patient developed acute G4 toxicity due to liver failure and elevation of bilirubin. This occurred 3 months after SBRT, but was felt secondary to decompensation of underlying liver cirrhosis from hepatitis C. The patient had a baseline Child–Pugh score of A6, which increased to a score of C12 at 3 months. The patient had received previous TACE and RFA procedures and was treated with a dose of 45 Gy in three fractions to a 3.6 cm diameter hepatoma. The mean liver dose was 7.9 Gy and 1116 cm^3 of liver received <15 Gy, meeting acceptable liver dose tolerances [21]. The patient passed away 3.5 months after SBRT.

Three patients developed late toxicity, occurring more than 3 months after treatment. In one patient this was a transient thrombocytopenia and in another a transient elevation in GGT. Overall, only one patient had irreversible grade 3 toxicity (hyperbilirubinaemia) without evidence of disease progression that occurred 8 months after treatment.

Discussion

There is a growing body of literature supporting the use of SBRT in the treatment of HCC, with recent studies showing local control rates comparable with RFA and improved local control rates when compared with TACE [19,24]. As a result, the 2018 NCCN guidelines suggest that

Table 4
Sites of first recurrence

Site of initial recurrence	Number of patients	Time to first recurrence (months) Median (10th, 90th percentile)
Regional*	16	6.4 (1.6, 24.4)
Local† and regional	3	3.1 (2.3, 25.6)
Distant relapse	2	4.7 (4.4, 5.0)

* Within the liver but outside the planning target volume (PTV).
† Within the PTV.

SBRT can be used as an alternative to RFA/TACE in inoperable HCC [25]. In contrast, the 2018 European Association for the Study of Liver Cancer (EASL) guidelines state that at present there is no robust evidence to support this therapeutic approach. Our study therefore contributes to the literature, by showing that SBRT is well tolerated and offers excellent local control rates for patients not suitable, or refractory, to other liver-directed therapies.

Our 1- and 2-year local control rates of 94% compare favourably with the 70–100% local control rates reported in most studies on SBRT, including one of the largest reported series by Sanuki *et al.* [9,11,13,15,16]. In our study, treatment dose and fractionation were individualised based on the location of the tumour in relation to the tolerance of nearby OAR. Despite this, PTV coverage was good, with a median D95 BED_{10} dose coverage of 104.8 Gy_{10} (range 45.0–116.5 Gy_{10}). In the study by Sanuki *et al.* [16], the outcomes of 185 patients with tumours <5 cm treated with 35 or 40 Gy in five fractions were analysed. The 2-year local control was 93% and was not different between the two dose fractionations, suggesting that a lower dose than prescribed in our current institution may be equally effective in providing adequate local control [16]. By contrast, Bujold *et al.* [15] analysed the outcomes of 102 patients treated with doses ranging from 24 to 54 Gy (in six fractions) and showed that increased dose was associated with increased local control on univariate analysis.

Overall survival in our study was 84% at 1 year and 74% at 2 years, which is also in line with published literature [9–11,13,16,17,19,26]. On univariate analysis, smaller tumour size was predictive of improved overall survival, whereas prescription BED_{10} dose $\geq$100 Gy_{10} approached significance. In our series, tumour size and prescription dose may be interrelated, as larger tumours were more likely to have been prescribed a lower prescription dose to meet liver constraints. As with local control, there are conflicting reports on whether prescription BED_{10} and tumour size are prognostic for overall survival. This may be due to the use of variable size and dose criteria for analyses in published studies, as clinically relevant values are not known. In our study, tumour size was analysed as a continuous variable due to small cohort numbers. In a retrospective study by Scorsetti *et al.* [17], $BED_{10} > 100$ Gy_{10} and GTV < 5 cm predicted for improved overall survival in tumours <6 cm treated in three or six fractions. Similarly, Huang *et al.* [27] showed that tumours <4 cm were predictive of improved overall survival in recurrent HCC patients treated with 37 Gy in four to five fractions. Interestingly, $BED_{10} > 100$ Gy_{10} and tumour size <3 cm were not predictive of overall survival in a large Japanese retrospective study of 79 HCC patients [10]. Clearly, to definitively answer what dose is desired for best local control and overall survival, larger sample sizes with more congruent BED dose and tumour size datasets are needed.

Table 5
Univariate analysis of factors associated with overall survival

Variable	Hazard ratio	95% confidence interval	*P* value
Age at SBRT*	1.0	1.0–1.1	0.23
ECOG (2 versus 0–1)	1.7	0.2–14.3	0.62
Previous treatment	1.1	0.2–5.3	0.92
Tumour size*	3.3	1.3–8.3	0.01
Pretreatment AFP*	1.3	0.7–2.4	0.42
Pretreatment Child–Pugh score $\geq$ B7	2.4	0.7–9.1	0.18
Pretreatment ALBI score*	1.82	0.6–5.2	0.27
Prescription $BED_{10} \geq 100$ Gy_{10}	0.3	0.1–1.1	0.06
D95 $BED_{10} \geq 80Gy_{10}$	0.3	0.1–1.2	0.08
D95 $BED_{10} \geq 100Gy_{10}$	0.5	0.1–1.8	0.28
Child–Pugh score change after SBRT ($\geq$2 versus < 2)	2.1	0.5–8.9	0.30
Post SBRT treatment	0.8	0.5–1.3	0.41

AFP, alpha fetoprotein; ALBI, albumin–bilirubin score; BED, biological equivalent dose assuming $\alpha/\beta = 10$; D95, minimum dose delivered to 95% of the planning target volume; ECOG, Eastern Cooperative Oncology Group; SBRT, stereotactic body radiotherapy.
* Analysed as continuous variables.

Our 1- and 2-year PFS rates were 49 and 38%, respectively. Our reported PFS rates are low, but are in line with other published literature, indicating a high probability of progressive disease elsewhere in liver by 2 years despite excellent local control [11,17]. The lower PFS rates probably reflect the population being studied, as most (84%) patients in our cohort received prior treatment with other modalities and therefore have already shown a propensity for disease recurrence within the liver. Furthermore, as SBRT is often used later in a patient's disease course, PFS and overall survival after SBRT may appear shorter than other local modalities that are commonly used at first disease presentation. The low PFS rate provides a rationale for investigating combination therapy with SBRT, including systemic therapies and TACE. The RTOG 1112 clinical trial (NCT01730937) is currently accruing patients to investigate the role of adding SBRT to sorafenib therapy [28]. Retrospective studies and meta-analyses on combining TACE with SBRT have also shown favourable results, although larger prospective studies are required to confirm these findings [14,29–33].

In our cohort, 84% of patients received liver-directed therapy before SBRT, which is higher than most recent studies [12,13,15,18,34]. Liver-directed therapies can decrease the functional capacity of the liver, particularly in those with underlying liver disease, and increase the risk of adverse events from irradiation. Despite this, SBRT was well tolerated in our study, with no patients experiencing classic RILD and only six patients (19%) having a worsened Child–Pugh score by 2 or more points. This decline in Child–Pugh score is consistent with previous studies. For example, Andolino *et al.* [13] reported a 20% deterioration after SBRT, whereas Bujold *et al.* [15] reported a 29% decline (in those without disease progression). Although we report that overall 10 patients (32%) experienced grade 3 + toxicity during follow-up, seven patients (23%) developed toxicity within 3 months after treatment. The remaining three patients experienced late toxicity. Furthermore, most toxicities were haematological and transient in nature. Our acute toxicity rates are in keeping with comparable studies; Weiner *et al.* [40] recently reported on a cohort of patients with Child–Pugh score < 8 treated with SBRT and reported 23% acute grade 3 + toxicities, whereas Andolino *et al.* [13] reported that 36.7% of patients developed grade 3 + haematological toxicities after SBRT. Sanuki *et al.* [16] reported 24% grade 3 + toxicities (primarily thrombocytopenia) and Bujold *et al.* [15] reported 30% grade 3 + toxicities overall (predominately elevated in transaminases), which takes into account non-haematological toxicities beyond 3 months.

Our relatively low toxicity rates are therefore reassuring, particularly in our cohort of heavily pretreated patients. This may help to explain the large number of patients who went on to receive further liver-directed treatments after SBRT, despite their initial ineligibility for other treatments. SBRT provided excellent local control to tumours that could not be readily targeted by other therapies due to a variety of factors, including location, prior recurrence or tumour size. As patients frequently progressed outside the SBRT treated areas, the low toxicities and well-maintained Child–Pugh score after radiotherapy allowed patients to remain candidates for other local therapies. This does provide strong evidence that SBRT can be added safely into the HCC treatment algorithm in conjunction with other therapies and leads us to ask whether SBRT should now be considered earlier in the treatment pathway.

Although SBRT was not specifically used to downstage before transplant, it is interesting that three patients in our cohort underwent liver transplantation after receiving radiotherapy. Several studies have suggested a role for SBRT as a bridge to transplant, as it is well tolerated and can result in a complete pathological response [35–38]. Although beyond the scope of this study, the role of SBRT in bridging to transplant is intriguing and certainly warrants future investigation.

This study had the inherent limitations of a retrospective study from a single institution. Our patient population may therefore be individual to British Columbia; for example, none of our HCC cases were due to alcohol, whereas in North America and Europe alcohol accounts for 30–40% of cases [39]. Furthermore, as with most liver SBRT studies, the radiation dose was not homogenous. This common scenario reflects real-life practice where prescription dose is individualised to not exceed OAR dose tolerances. In general, our patient cohort received prescription doses in line with comparative studies. BED_{10} doses have also been reported to allow for comparison of outcomes to past and future studies.

In conclusion, SBRT to small inoperable HCC provides high local control rates with acceptable toxicities, even in patients who have received prior liver-directed treatment. Although overall 32% of patients experienced $\geq$ grade 3 + toxicities (23% acute) and 19% had a deterioration in Child–Pugh score of two or more points, these changes were mainly transient with minimal clinical impact. Despite excellent local control, disease progression outside of the irradiated site remains prominent. This study shows that SBRT can be delivered safely even after previous liver-directed therapies and that further liver therapies can follow treatment with SBRT. However, the exact positioning of SBRT within the HCC treatment algorithm remains uncertain and further studies are warranted to examine the role for SBRT in combination with other modalities to maximise disease control in the liver.

Conflict of interest

This trial was not funded by industry. However, Drs. Loewen, Ma and Schellenberg have received grant support from Varian Medical Systems for work related to SBRT delivery to large liver tumors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2019.01.012.

References

[1] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, *et al.* Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;136:E359–E386.

[2] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015;65:87–108.

[3] Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology* 2011;53:1020–1022.

[4] EASL. Clinical Practice Guidelines: management of hepatocellular carcinoma. *J Hepatol* 2018;69:182–236.

[5] Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, *et al.* Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *New Engl J Med* 1996;334:693–699.

[6] Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, *et al.* Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology* 2002;35:1164–1171.

[7] Llovet JM, Real MI, Montana X, Planas R, Coll S, Aponte J, *et al.* Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002; 359:1734–1739.

[8] Lawrence TS, Robertson JM, Anscher MS, Jirtle RL, Ensminger WD, Fajardo LF. Hepatic toxicity resulting from cancer treatment. *Int J Radiat Oncol Biol Phys* 1995;31: 1237–1248.

[9] Cardenes HR, Price TR, Perkins SM, Maluccio M, Kwo P, Breen TE, *et al.* Phase I feasibility trial of stereotactic body radiation therapy for primary hepatocellular carcinoma. *Clin Transl Oncol* 2010;12:218–225.

[10] Yamashita H, Onishi H, Murakami N, Matsumoto Y, Matsuo Y, Nomiya T, *et al.* Survival outcomes after stereotactic body radiotherapy for 79 Japanese patients with hepatocellular carcinoma. *J Radiat Res* 2015;56:561–567.

[11] Huertas A, Baumann AS, Saunier-Kubs F, Salleron J, Oldrini G, Croise-Laurent V, *et al.* Stereotactic body radiation therapy as an ablative treatment for inoperable hepatocellular carcinoma. *Radiother Oncol* 2015;115:211–216.

[12] Tse RV, Hawkins M, Lockwood G, Kim JJ, Cummings B, Knox J, *et al.* Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *J Clin Oncol* 2008;26:657–664.

[13] Andolino DL, Johnson CS, Maluccio M, Kwo P, Tector AJ, Zook J, *et al.* Stereotactic body radiotherapy for primary hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2011;81: e447–e453.

[14] Kang JK, Kim MS, Cho CK, Yang KM, Yoo HJ, Kim JH, *et al.* Stereotactic body radiation therapy for inoperable hepatocellular carcinoma as a local salvage treatment after incomplete transarterial chemoembolization. *Cancer* 2012;118: 5424–5431.

[15] Bujold A, Massey CA, Kim JJ, Brierley J, Cho C, Wong RK, *et al.* Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. *J Clin Oncol* 2013;31:1631–1639.

[16] Sanuki N, Takeda A, Oku Y, Mizuno T, Aoki Y, Eriguchi T, *et al.* Stereotactic body radiotherapy for small hepatocellular carcinoma: a retrospective outcome analysis in 185 patients. *Acta Oncol* 2014;53:399–404.

[17] Scorsetti M, Comito T, Cozzi L, Clerici E, Tozzi A, Franzese C, *et al.* The challenge of inoperable hepatocellular carcinoma (HCC): results of a single-institutional experience on stereotactic body radiation therapy (SBRT). *J Cancer Res Clin Oncol* 2015;141:1301–1309.

[18] Lasley FD, Mannina EM, Johnson CS, Perkins SM, Althouse S, Maluccio M, *et al.* Treatment variables related to liver toxicity in patients with hepatocellular carcinoma, Child-Pugh class A and B enrolled in a phase 1–2 trial of stereotactic body radiation therapy. *Pract Radiat Oncol* 2015;5: e443–e449.

[19] Wahl DR, Stenmark MH, Tao Y, Pollom EL, Caoili EM, Lawrence TS, *et al.* Outcomes after stereotactic body radiotherapy or radiofrequency ablation for hepatocellular carcinoma. *J Clin Oncol* 2016;34:452–459.

[20] Benedict SH, Yenice KM, Followill D, Galvin JM, Hinson W, Kavanagh B, *et al.* Stereotactic body radiation therapy: the report of AAPM Task Group 101. *Med Phys* 2010;37: 4078–4101.

[21] Pan CC, Kavanagh BD, Dawson LA, Li XA, Das SK, Miften M, *et al.* Radiation-associated liver injury. *Int J Radiat Oncol Biol Phys* 2010;76:S94–S100.

[22] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–247.

[23] Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, *et al.* Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach – the ALBI grade. *J Clin Oncol* 2015;33:550–558.

[24] Sapir E, Tao Y, Schipper MJ, Bazzi L, Novelli PM, Devlin P, *et al.* Stereotactic body radiation therapy as an alternative to transarterial chemoembolization for hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2018;100:122–130.

[25] National Comprehensive Cancer Network. *Hepatobiliary cancers (version 2.2018* 2018.

[26] Seo YS, Kim MS, Yoo SY, Cho CK, Choi CW, Kim JH, *et al.* Preliminary result of stereotactic body radiotherapy as a local salvage treatment for inoperable hepatocellular carcinoma. *J Surg Oncol* 2010;102:209–214.

[27] Huang WY, Jen YM, Lee MS, Chang LP, Chen CM, Ko KH, *et al.* Stereotactic body radiation therapy in recurrent hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2012;84: 355–361.

[28] Sorafenib tosylate with or without stereotactic body radiation therapy in treating patients with liver cancer. https://clinicaltrials.gov/ct2/show/NCT01730937.

[29] Meng MB, Cui YL, Lu Y, She B, Chen Y, Guan YS, *et al.* Transcatheter arterial chemoembolization in combination with radiotherapy for unresectable hepatocellular carcinoma: a systematic review and meta-analysis. *Radiother Oncol* 2009; 92:184–194.

[30] Paik EK, Kim MS, Jang WI, Seo YS, Cho CK, Yoo HJ, *et al.* Benefits of stereotactic ablative radiotherapy combined with incomplete transcatheter arterial chemoembolization in hepatocellular carcinoma. *Radiat Oncol* 2016;11:22.

[31] Choi BO, Choi IB, Jang HS, Kang YN, Jang JS, Bae SH, *et al.* Stereotactic body radiation therapy with or without transarterial chemoembolization for patients with primary hepatocellular carcinoma: preliminary analysis. *BMC Cancer* 2008; 8:351.

[32] Shim SJ, Seong J, Han KH, Chon CY, Suh CO, Lee JT. Local radiotherapy as a complement to incomplete transcatheter arterial chemoembolization in locally advanced hepatocellular carcinoma. *Liver Int* 2005;25:1189–1196.

[33] Honda Y, Kimura T, Aikata H, Kobayashi T, Fukuhara T, Masaki K, *et al.* Stereotactic body radiation therapy combined

with transcatheter arterial chemoembolization for small hepatocellular carcinoma. *J Gastroenterol Hepatol* 2013;28:530–536.

[34] Moon DH, Wang AZ, Tepper JE. A prospective study of the safety and efficacy of liver stereotactic body radiotherapy in patients with and without prior liver-directed therapy. *Radiother Oncol* 2018;126:527–533.

[35] O'Connor JK, Trotter J, Davis GL, Dempster J, Klintmalm GB, Goldstein RM. Long-term outcomes of stereotactic body radiation therapy in the treatment of hepatocellular cancer as a bridge to transplantation. *Liver Transpl* 2012;18:949–954.

[36] Facciuto ME, Singh MK, Rochon C, Sharma J, Gimenez C, Katta U, *et al*. Stereotactic body radiation therapy in hepatocellular carcinoma and cirrhosis: evaluation of radiological and pathological response. *J Surg Oncol* 2012;105:692–698.

[37] Moore A, Cohen-Naftaly M, Tobar A, Kundel Y, Benjaminov O, Braun M, *et al*. Stereotactic body radiation therapy (SBRT) for definitive treatment and as a bridge to liver transplantation in early stage inoperable hepatocellular carcinoma. *Radiat Oncol* 2017;12:163.

[38] Sapisochin G, Barry A, Doherty M, Fischer S, Goldaracena N, Rosales R, *et al*. Stereotactic body radiotherapy vs. TACE or RFA as a bridge to transplant in patients with hepatocellular carcinoma. An intention-to-treat analysis. *J Hepatol* 2017;67:92–99.

[39] Global Burden of Disease Liver Cancer Collaboration, Akinyemiju T, Abera S, Ahmed M, Alam N, Alemayohu MA, *et al*. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the global burden of disease study 2015. *JAMA Oncol* 2017;3:1683–1691.

[40] Weiner AA, Olsen J, Ma D, Dyk P, DeWees T, Myerson RJ, *et al*. Stereotactic body radiotherapy for primary hepatic malignancies - Report of a phase I/II institutional study. *Radiother Oncol* 2016;121:79–85.