Whitmill *et al. Hepatoma Res* 2024;10:35
DOI: 10.20517/2394-5079.2024.19

Hepatoma Research

Original Article

Open Access

Oncologic outcomes and rates of hepatotoxicity following stereotactic body radiotherapy for hepatocellular carcinoma

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How to cite this article: Whitmill M, Young M, Tan X, Zhang X, Thapa D, Kim HP, Danquah F, Moon AM, Tepper JE, Yanagihara TK. Oncologic outcomes and rates of hepatotoxicity following stereotactic body radiotherapy for hepatocellular carcinoma. *Hepatoma Res* 2024;10:35. https://dx.doi.org/10.20517/2394-5079.2024.19

Received: 30 Jan 2024 **First Decision:** 24 Jun 2024 **Revised:** 16 Aug 2024 **Accepted:** 30 Aug 2024 **Published:** 7 Sep 2024

Academic Editor: Georgios Tsoulfas **Copy Editor:** Ting-Ting Hu **Production Editor:** Ting-Ting Hu

Abstract

Aim: Hepatocellular carcinoma (HCC) localized to the liver has various treatment options, including external beam radiotherapy (EBRT). Despite many prospective and retrospective reports showing excellent local control (LC) and favorable toxicity, EBRT has not been widely adopted in the first-line setting and this may be due to a perceived lack of evidence. This study aims to share a decade of experience with Stereotactic Body Radiotherapy (SBRT) for HCC, leveraging a homogenous treatment technique.

Methods: This retrospective study at a single institution included patients with HCC treated with SBRT, with a standardized treatment protocol. Freedom from local progression (FFLP), overall survival (OS), and rates of hepatotoxicity post-treatment using child-pugh (CP) and albumin-bilirubin (ALBI) scores were analyzed. A mixed-effects multivariable analysis (MVA) was also performed to assess various factors' impact on outcomes.

Results: A total of 138 lesions in 106 patients were treated between 2009 and 2020. FFLP was 91% at one year and 86% at three years. OS was 80% and 46% at 1 and 3 years, respectively. Baseline liver function was a significant

predictor of FFLP and OS on MVA. CP scores and ALBI grades were stable 3 months after treatment in ≥ 70% of patients.

Conclusion: SBRT provides excellent LC and low toxicity for HCC patients. While long-term survival remains challenging, treatment decisions should consider overall clinical status. Multidisciplinary review and forthcoming prospective trial results will further clarify radiotherapy's role in HCC management.

Keywords: Radiation, SBRT, hepatocellular carcinoma, liver

INTRODUCTION

For patients with hepatocellular carcinoma (HCC) localized to the liver, numerous locoregional therapies are available[1]. External beam radiotherapy (EBRT), including conventional fractionation, hypofractionation, and stereotactic body radiotherapy (SBRT), has been used successfully to treat patients with HCC for palliation[2], as a bridge to transplant[3], or for tumor ablation (i.e., when the intent is complete eradication of localized disease)[4]. Results from many institutional series and early results from prospective clinical trials demonstrate excellent local control (LC) and favorable toxicity following EBRT[5]. However, some international consensus guidelines have not adopted EBRT due to a lack of higher-level evidence[6,7].

While prospective trials comparing EBRT to other modalities have begun to report results and others are underway, much of the published experience is retrospective, and the largest series are from a few select institutions. In addition to inherent limitations of retrospective analyses, including bias in patient selection and incomplete follow-up assessment, there are several additional limitations that particularly affect studies of EBRT for HCC. First, radiotherapy techniques have evolved rapidly over time and this increases heterogeneity in the treatment of patients within retrospective datasets. Second, patient follow-up is often limited due to poor prognosis, competing medical comorbidities, and health disparities that affect patients with HCC[8]. Finally, the child-pugh (CP) score has been the most prevalent measure of clinical disease status in patients with cirrhosis, but the albumin-bilirubin (ALBI) score is more objective and may be a superior toxicity assessment tool in the post-radiation setting[9,10].

Here, we present our experience with SBRT for HCC over a 10-year period where essentially all patients were treated with a standardized SBRT technique that was defined by a prospective institutional trial[11] and were prospectively followed using a standardized protocol that included routine laboratory analysis and assessment of both CP score and ALBI.

METHODS

Patients with HCC treated with SBRT at a single institution were included in this Institutional Review Board(IRB)-approved retrospective institutional database (UNC IRB 23-1226). Based on a multidisciplinary discussion, patients were deemed unsuitable for resection or thermal ablation and SBRT was recommended. Baseline patient characteristics of age, gender, etiology of cirrhosis, and Eastern Cooperative Oncology Group (ECOG) performance status, along with SBRT dose, fractionation, and laboratory data, were collected by chart review. Freedom from local progression (FFLP) and overall survival (OS) were calculated using the Kaplan-Meier method starting from the date of the pre-SBRT MRI. Patients were treated with SBRT in the de novo setting or as salvage therapy for locally recurrent disease. All patients had pretreatment diagnostic abdominal MRIs and lesion size was defined as the largest cross-sectional measurement. A biopsy for pathologic confirmation of HCC was not required if imaging characteristics met liver imaging reporting and data systems (LI-RADS) criteria[12] for HCC and there were no concerns about the diagnosis

following multidisciplinary review. MRIs were also evaluated for the presence of extrahepatic metastasis. Patients were followed until the study end date (11/8/2022), death, or loss to follow-up. If a patient was lost to follow-up, the last date of any clinical contact was used as the censoring date.

Radio-opaque fiducials were placed adjacent to the target adjacent to the target lesion at least one week prior to CT simulation. Patients were simulated in a supine position and immobilized with a full-length vacuum cushion. CT-based planning was used for all patients and four-dimensional motion tracking was performed throughout the free breathing cycle. Treatments were delivered using non-coplanar 6MV photon beams using the CyberKnife delivery system (Accuray, Inc., Sunnyvale, CA). Gross tumor volume (GTV) was defined on a fused, contrast-enhanced MRI and no expansion was created for a clinical target volume (CTV). No internal target volume (ITV) was applied due to the use of real-time target tracking during treatment. The planning target volume (PTV) was typically generated with a uniform expansion of 5 mm radially and 8 mm in the craniocaudal direction[11]. When necessary to achieve planning goals, adjustments were made to this technique based on physician discretion.

Dose, fractionation, and dosimetric parameters were based on CP Class and expected post-treatment functional liver remnant, considering any previously treated areas (e.g., prior ablation). The goal of treatment was to deliver a dose of 4,500 cGy over three fractions, with 48 hours between each fraction, while maintaining a liver GTV mean dose < 1,500 cGy and a minimum of 700 cc of liver receiving less than 1,500 cGy. Other planning goals included restricting the heart, esophagus, stomach, and duodenum D1cc to < 3,000 cGy, each kidney D50% < 1,400 cGy, and spinal cord point max < 1,500 cGy. In cases where these planning goals could not be achieved due to organ at risk (OAR) constraints, dose and fractionation were altered, typically to a dose of 3,500–5,000 cGy over five fractions.

FFLP (at lesion level) was computed with a cumulative incidence function cumulative incidence function with death treated as a censoring event. Local progression was defined by the interpreting radiologist as part of routine clinical care (i.e., images were not re-reviewed for this research study), interdisciplinary review, or any decision to intervene with salvage therapy. A mixed-effects multivariable analysis (MVA) using a Cox proportional hazards model was performed using patient age, performance status, gender, HCC diameter (maximum length per lesion), biologically effective dose (alpha/beta = 10), number of prior treatments to the target lesion, and pretreatment CP score as regression variables. Patients with multiple lesions treated metachronously were treated as independent events. CP score and ALBI were used to quantify hepatotoxicity following SBRT at 3 and 6 months post-treatment.

RESULTS

Patient characteristics

Between the years 2009 and 2020, a total of 138 lesions were treated in 106 patients. Patient characteristics are summarized in Table 1. The patient cohort comprised 76% males (n = 81) and 24% females (n = 25). The median age was 65 years (range 50-87). ECOG performance status was 0-1 in 89% (n = 94), ECOG 2 in 10% (n = 11), and ECOG 3 in 1% (n = 1). The most common etiology of underlying liver disease was hepatitis C, accounting for 42% (n = 45), followed by metabolic dysfunction-associated steatotic liver disease (MASLD) at 20% (n = 21) and hepatitis C with concurrent alcohol-associated liver disease at 14% (n = 15). A total of 55% (n = 58) of patients underwent a prior HCC-directed therapy before treatment with radiation (this count excludes patients with metachronous lesions who were treated with re-irradiation).

Treatment Characteristics

Out of all 138 treated lesions, 42 (30%) had received prior treatment to the lesion of interest and SBRT was

Table 1. Patient demographics and clinical characteristics

	All	CP-A	CP-B
Total patients	106	79	23
Follow-up, median (range), years	2.5 (0.3-10.2)	2.8 (0.3-7.4)	1.1 (0.3-10.2)
Gender			
Female	25 (24)	20 (25)	5 (22)
Male	81 (76)	59 (75)	18 (78)
Age	65 (50-87)	65 (51-86)	56 (66-87)
ECOG			
0-1	94 (89)	72 (91)	19 (83)
2	11 (10)	6 (8)	4 (17)
3	1 (1)	1 (1)	0 (0)
Treated Lesions			
1	79 (75)	58 (73)	17 (74)
2	23 (22)	20 (27)	3 (13)
3	3 (3)	1 (1)	2 (9)
4	1 (1)	0 (1)	1 (4)
Cirrhosis			
None	10 (9)	9 (11)	1 (4)
MASLD	22 (21)	15 (19)	7 (29)
EtOH-associated	7 (7)	5 (6)	2 (8)
Hepatitis B	5 (5)	4 (5)	0 (0)
Hepatitis C	43 (41)	33 (42)	9 (38)
Hepatitis B & C	1 (1)	1 (1)	0 (0)
Hepatitis C-& EtOH-associated	15 (14)	10 (13)	4 (17)
Other	3 (3)	2 (3)	0 (0)
Prior treatment (any lesion)			
None	48 (45)	35 (44)	13 (57)
1	27 (25)	17 (22)	8 (35)
2	16 (15)	13 (16)	2 (9)
3	11 (10)	10 (13)	0 (0)
4+	4 (4)	4 (5)	0 (0)

Data are presented as *n* (%) or median (range). Four patients are excluded from CP subgroups due to either insufficient data (3) or being child-pugh class C (1). CP-A/B: Child-pugh class of A or B; ECOG: Eastern Cooperative Oncology Group Performance Status Scale; EtOH: ethanol; MASLD: metabolic-associated steatotic liver disease.

used as salvage therapy for residual disease or local progression [Table 2]. Of these 42 lesions, 25 (60%) had 1 prior therapy and 17 (40%) had ≥ 2 prior therapies, with the most common prior treatment being radiofrequency ablation (RFA) (n = 18; 43%), followed by transarterial chemoembolization (TACE) (n = 13; 31%), and microwave ablation (MWA) (n = 7; 17%). The median biological effective dose using an alpha/beta of 10 (BED_{10}) was 113 Gy with a range of 43–188 Gy. Lesion size ranged from 1.0 to 7.0 cm with a median of 2.3 cm.

Clinical outcomes

Median follow-up was 2.5 years (range 0.3-10.2 years). OS for the entire cohort was 79% at 1 year and 55% at 3 years [Figure 1]. FFLP, where death was a censoring event, was 91% at 1 year and 86% at 3 years [Figure 2]. OS for patients with CP scores 5-6 *vs.* CP scores 7-9 were 83% *vs.* 64% at 1 year, 73% *vs.* 37% at 2 years, and 60% *vs.* 32% at 3 years [Figure 3].

Table 2. Treated lesion characteristics

Total lesions		138
Diameter (cm)		2.3 (1.0-7.0)
BED10		113 (38-188)
Prior treatment (lesion-specific)		
	None	96 (70)
	1	25 (18)
	2	11 (8)
	3	5 (4)
	4	1 (1)
Salvage tx		
	Yes	17 (12)
	No	121 (88)

Data are presented as *n* (%) or median (range). BED10: Biologically effective dose using an alpha/beta ratio of 10.

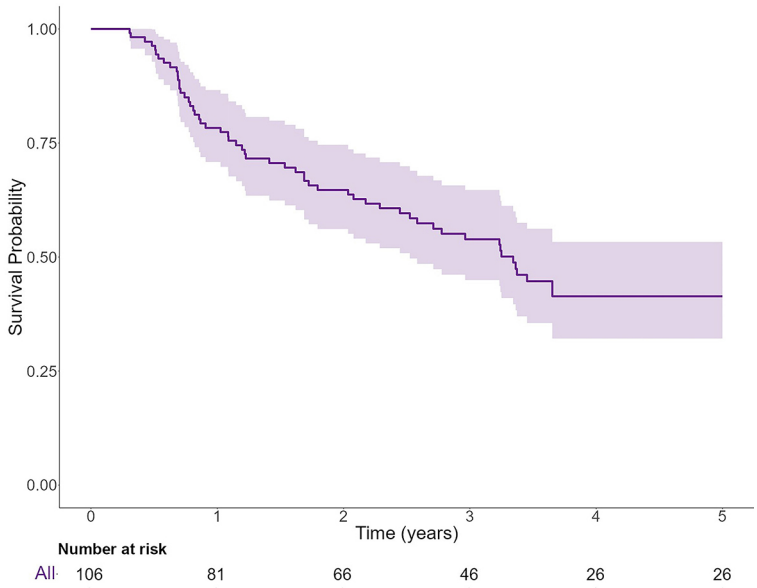

Figure 1. Overall survival of the entire cohort.

Salvage therapy for local progression after SBRT was delivered to 17 lesions (13%) and treatments included TACE for 8 lesions (44%), RFA for 7 lesions (39%), MWA for 1 lesion (6%), Bevacizumab/Atezolizumab for 1 lesion (6%), and combination of TACE/MWA for 1 lesion (6%).

Univariate analysis was performed on maximum lesion diameter, gender, age, BED_{10}, ECOG, number of prior treatments to the liver lesion, and pretreatment CP score. The pretreatment CP score was found to be significantly associated with FFLP, with CP-A being associated with improved FFLP compared to CP-B [HR = 2.82 (1.15–6.96, 95%CI), $P = 0.026$], with no other significant associations ($P > 0.05$). Multivariate analysis was performed with the same variables [Table 3]. Pretreatment CP class A was again significantly associated with improved FFLP [HR = 2.82 (1.15–6.96, 95%CI), $P = 0.024$] and OS [HR = 2.48 (1.3–4.74, 95%CI), $P = 0.006$]. No other significant associations were found with FFLP or OS in MVA.

Table 3. Multivariate associations with FFLP and OS

		FFLP			OS		
Variable		HR	95%CI	*P*-value	HR	95%CI	*P*-value
Max lesion diameter	Continuous	1.11	0.84-1.47	0.45	1.14	0.93-1.41	0.20
Gender	Male	1.00	-	-	1.00	-	-
	Female	1.52	0.63-3.70	0.35	1.10	0.56-2.15	0.80
Age	Continuous	0.98	0.93-1.02	0.30	1.00	0.97-1.03	> 0.9
BED10	Continuous	0.99	0.97-1.01	0.53	1.00	0.98-1.02	0.70
ECOG	0-1	1.00	-	-	1.00	-	-
	2-3	0.91	0.25-3.31	0.89	1.20	0.46-3.15	0.70
# of prior treatments	Continuous	0.94	0.61-1.45	0.77	1.15	0.82-1.62	0.40
CPS	CP-A	1.00	-	-	1.00	-	-
	CP-B	2.82	1.15-6.96	0.03	2.48	1.3-4.74	0.006

FFLP: Freedom from local progression; OS: overall survival; BED10: biologically effective dose using an alpha/beta ratio of 10; ECOG: Eastern Cooperative Oncology Group Performance Status Scale; CPS: child-pugh score.

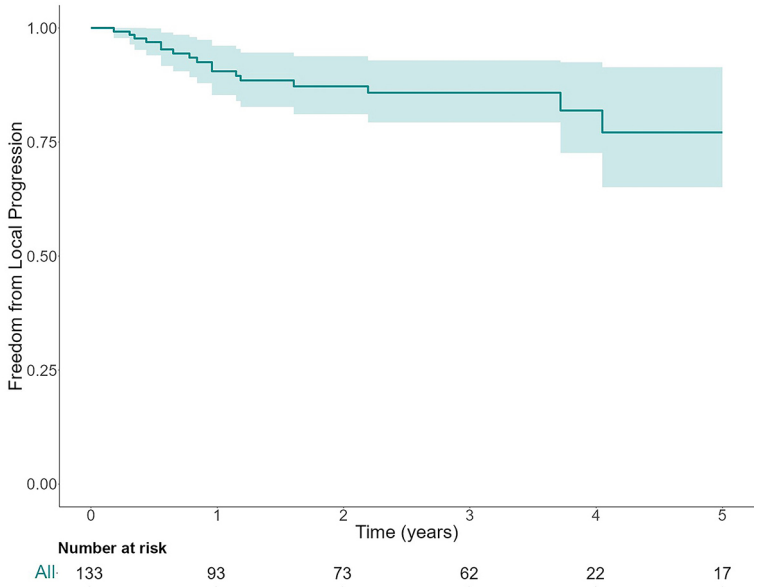

Figure 2. Freedom from local progression of the entire cohort. Data reported per lesion. Five lesions excluded due to incomplete data. Deaths are censored.

Change in liver function

CP Scores were calculated and stratified into CP classes of CP-A (5-6 points), CP-B (7-9 points), and CP-C (10-15 points). Pretreatment CP-A, -B, and -C classes were observed in 79 (75%), 24 (23%), and 0 of treated patients, with 3 patients not having sufficient data to score [Table 4]. At 3 months [Figure 4], among the 77 (73%) patients with sufficient follow-up data to compute CP scores, CP-A, -B, and -C were observed in 51 (66%), 21 (29%), and 5 (8%) of treated lesions, respectively. In the 75 patients whose change in CPS during this interval can be calculated, 4 (5%) had a decrease (improvement) of one class level, 57 (74%) had no change, 13 (17%) had a one-class increase (worsening), and 1 (1%) had a two-class increase. At six months, of the 74 scorable patients, CP-A, -B, and -C classes were seen in 47 (64%), 23 (30%), and 4 (5%) patients. Compared to the pretreatment baseline, 6 (8%) of patients had a CPS improvement, 52 (71%) remained unchanged, 13 (18%) had a one-class CPS increase, and 2 (3%) had a two-class CPS increase (CP-A to CP-

Table 4. Pre- and post-treatment liver function

CPS	Baseline (*n* = 103)	3 months (*n* = 78)	6 months (*n* = 74)
5A	53 (50)	31 (29)	31 (29)
6A	26 (25)	20 (19)	16 (15)
7B	16 (15)	11 (10)	11 (10)
8B	4 (4)	5 (5)	9 (9)
9B	4 (4)	6 (6)	3 (3)
10C	0 (0)	2 (2)	3 (3)
11C	0 (0)	3 (3)	1 (1)
NA	3 (3)	28 (26)	32 (30)
ALBIX	**Baseline (*n* = 104)**	**3 months (*n* = 82)**	**6 months (*n* = 78)**
1	44 (42)	30 (37)	32 (41)
2	58 (56)	45 (55)	39 (50)
3	2 (2)	7 (9)	7 (9)
NA	2	24	28

Data are presented as *n* patients (% scored patients) with available data. CPS: Child-pugh score; ALBI: albumin-bilirubin score; NA: data not available; Baseline: prior to SBRT.

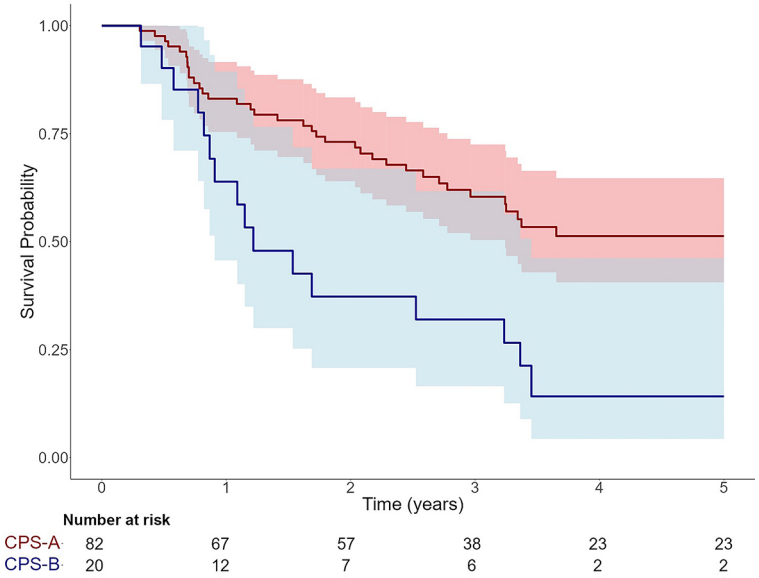

Figure 3. Overall survival by pretreatment child-pugh Score. Four patients were excluded from this analysis: three due to having insufficient data to compute a pretreatment CPS, and one due to a pretreatment CPS of C. CPS: Child-pugh score.

C).

Pretreatment ALBI grade 1, 2, and 3 scores were observed in 44 (42%), 58 (56%), and 2 (2%) of patients, with 2 patients having insufficient data to score. At three months, of the 82 scorable patients, ALBI grades 1, 2, and 3 were seen in 30 (37%), 45 (55%), and 7 (9%) of patients, respectively. Over this interval, 70% (*n* = 57) of scored patients had no change in ALBI grade, while 9% (*n* = 7) had an improvement by one grade, and 22% (*n* = 18) had a one-grade worsening. The median change in ALBI score was +0.14, with a range of -1.37 to +1.04. At six months, of the 78 scorable patients, ALBI grades 1, 2, and 3 were seen in 32 (41%), 39 (50%), and 7 (9%) of patients, respectively. Compared to baseline, at six months, 64% (*n* = 50) of scored patients had no change in ALBI grade, while 14% (*n* = 11) had a one-grade improvement and 19% (*n* = 15)

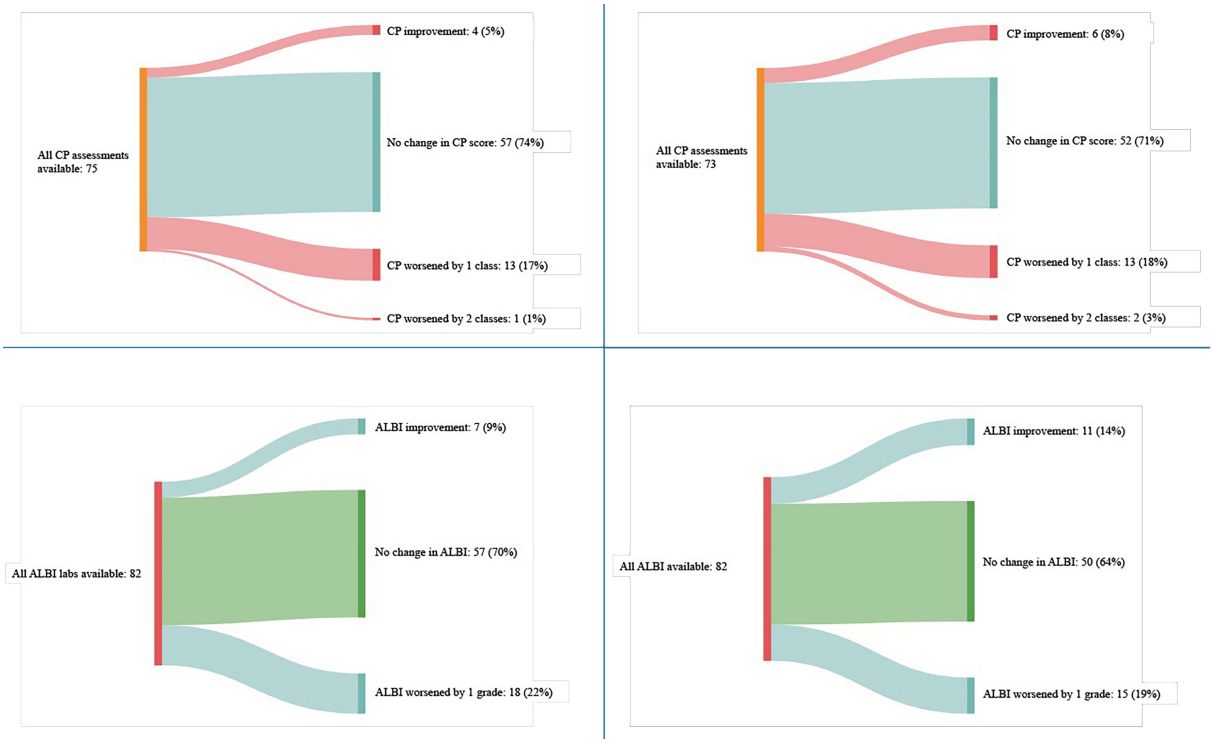

Figure 4. Change in liver function after SBRT. Change in CP score is displayed for patients with available data at 3 (A) and 6 months (B) following SBRT. Change in ALBI grade is displayed at 3 (C) and 6 months (D) following SBRT. ALBI: Albumin-bilirubin Score; CP: child-pugh; SBRT: stereotactic body radiotherapy.

had a one-grade worsening. Only one patient had a two-grade worsening (1%). The median change in ALBI score was +0.07, with a range of -1.84 to +1.64.

DISCUSSION

Experience with SBRT in the treatment of HCC has grown substantially over the past 10 years and American Society for Radiation Oncology (ASTRO) clinical practice guidelines have endorsed the use of radiation as first-line treatment for many patients[13]. Further, the American Association for the Study of Liver Disease (AASLD) guidelines endorse radiation as an alternative to thermal ablation, alongside radiation segmentectomy (with transarterial radioembolization)[14]. Still, SBRT is not included as a primary recommendation for first-line treatment in some international guidelines[6,7], citing a lack of evidence. Our institutional practice is to determine treatment modality in a multidisciplinary setting, weighing the toxicities and limitations of all available options, with determining factors often including size, location, vascular proximity (considering the heat sink effect limiting thermoablative modalities), OAR proximity (impacting SBRT toxicity), and compounding toxicities from prior treatments. Here, we share our institution's experience with SBRT to add to the growing literature characterizing its outcomes.

This report is limited by its retrospective nature and the population treated was from a single institution. Yet, these data add to the experience described in the literature by providing long-term outcomes in patients treated with a consistent and homogenous technique over 10 years with high-fidelity toxicity assessments using both traditional CP categorization and ALBI grading in the majority of patients. Patients were treated with a uniform treatment technique, so caution is required when interpreting these results when patient selection and treatment delivery methods are different. For example, Cyberknife treatment planning

involves unique aspects, such as heterogeneous dose distributions and non-coplanar beams, which differ from techniques such as linear accelerator-based treatment. The immortal time bias in our analyses should be minimal given the short time between the pre-radiation MRI and the start date of radiation (median of 19 days). We did not account for the effects of liver transplant after radiation, which removes the possibility of local progression and could impact OS. However, only one patient received a liver transplant in our study, so the impact on results is minimal.

In our overall cohort, OS was 79% at 1 year and 55% at 3 years [Figure 1]. Disease control after SBRT was excellent, with FFLP for the entire cohort of 91% at 1 year and 86% at 3 years [Figure 2]. As has been reported consistently in HCC, clinical outcomes were best for patients with good baseline liver function [Figure 3]. Specifically, at three years following SBRT, patients with CP-A5 or A6 cirrhosis at baseline had a 3-year OS of 60% compared to a 3-year OS of 32% among patients with CP-B7-9 at baseline. We found that baseline CP score was also associated with FFLP on both univariate [HR = 2.8 (1.13-6.79, 95%CI), P = .026] and multivariate [HR = 2.82 (1.15–6.96, 95%CI), P = 0.024] analyses.

The rates of OS and LC reported here demonstrate consistency with the existing literature. After treatment with primary radiotherapy for HCC, OS at 1 and 3 years has generally been reported in the range of 60%-90% and 40%-80%, respectively, and LC at 2 and 3 years has ranged from 80%-95% and 65%-95%, respectively[4]. Technical parameters that define ablative radiotherapy have recently been described[15] and when this technique is used, LC rates parallel those of thermal ablation[16]. Data beyond 3 years of follow-up are limited, but studies show a variable OS at 5 years of 10%–60%[17,18], likely owing to competing risks for death from liver disease and non-liver related comorbidities. Referencing data from prospective trials, clinical outcomes again appear consistent with our findings. For example, in a Phase II multicenter study of proton beam radiotherapy for patients with primary liver cancer[19], OS at 1 and 2 years was 77% and 63%, respectively, and LC at 2 years was 95%. In another Phase II multicenter study of SBRT for HCC in CP-A cirrhosis[20], patients were treated with the same photon-based technique and dose as our report and OS was 72% at 18 months and 69% at 24 months. Meanwhile, LC was 98% and 94% at 18 and 24 months, respectively.

To evaluate treatment toxicity to the liver, we utilized CP and ALBI scores [Figure 4]. CP scores historically have been used to measure toxicity, but this metric is very subjective (i.e., categorizing mild, moderate, and severe ascites or hepatic encephalopathy). There is also ambiguity in how the timing of ascites or hepatic encephalopathy should be counted. For example, a patient with a single episode of hepatic encephalopathy in the setting of recent infection receives the same "points" as a patient with chronic fluctuations in mental status. Therefore, an assessment tool based strictly on laboratory data would be more objective. Recent studies suggest ALBI scores are a better overall indicator of treatment toxicity compared with CP scores[9,10]. In our study, at 3 months, 17% of patients experienced a worsening of their CP class by 1 level, while fewer than 2% experienced a worsening of two levels. A worsening of 1 ALBI grade was seen in 22% of patients, and no patient had a worsening of 2 ALBI grades. These data support a generally low incidence of hepatotoxicity secondary to SBRT, which is consistent with other studies.

For example, in a randomized Phase III comparison of proton beam radiotherapy to RFA[21], the rate of a 1-point increase in CP after proton radiation or RFA was 7.5% and 19.6%, respectively, and no patient in the study experienced a 2-point increase. Interestingly, the incidence of an improvement in CP class or ALBI grade was higher than the incidence of worsening by the same proportion. At 6 months post-treatment, the incidence of a 2-point CP score worsening and 2-grade ALBI worsening remained low, 3% and 1%, respectively. We acknowledge that with longer post-treatment follow-up, it becomes difficult to determine if

hepatic decompensation is attributable to treatment and/or natural progression of underlying liver disease. Nonetheless, the low rate of late (6-month) worsening of liver disease is encouraging and suggests that our study includes a favorable cohort of patients and the rates of hepatotoxicity we describe are similar to previous reports[4]. The results for CP and ALBI were very similar. Perhaps the subjectivity and ambiguity of CP score discussed above do not have a major impact on the validity of CP as a measure of hepatotoxicity. This is consistent with our MVA analysis, where baseline CP score was the only variable that correlated with FFLP and OS. However, for reasons mentioned previously, we encourage reporting of both CP score and ALBI on subsequent larger datasets.

Our data build on prior experience and demonstrate LC and risks of toxicity that compare favorably with other ablative locoregional treatment modalities. Still, long-term OS in this patient population remains poor. Ongoing prospective trials will be informative regarding the ultimate role of radiotherapy in the management of HCC.

DECLARATIONS

Authors' contributions

Drafted manuscript: Whitmill M, Young M
Revised and approved manuscript: Whitmill M, Young M, Tan X, Zhang X, Thapa D, Kim HP, Danquah F, Moon AM, Tepper JE, Yanagihara TK
Data acquisition: Whitmill M, Young M
Statistical analysis: Whitmill M, Young M, Tan X

Availability of data and materials

Data and materials are available upon reasonable request.

Financial support and sponsorship

None.

Conflicts of interest

AMM reports grants or contracts from the American Association for the Study of Liver Diseases (AASLDs), the American College of Gastroenterology, the National Institutes of Health, and DCN diagnostics; and consulting feeds from Target RWE and Intercept Pharmaceuticals; and serves on the AASLDs Practice Guidelines Committee. TKY reports grants or contracts from the Radiation Oncology Institute and Lineberger Comprehensive Cancer Center.

Ethical approval and consent to participate

This study was approved by The Institutional Review Board of The University of North Carolina at Chapel Hill as a retrospective study, which did not require informed consent. The IRB information is: UNC-CH IRB 23-1226 "Disease outcomes and toxicities in patients with gastrointestinal and sarcomatous malignancies: A retrospective database".

Consent for publication

Not applicable.

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