Advances in Radiation Oncology (2024) 9, 101631

advances in radiation oncology

www.advancesradonc.org

Clinical Investigation - Gastrointestinal Cancers

Outcomes After Stereotactic Body Radiation for Hepatocellular Carcinoma in Patients With Child-Pugh A Versus Child-Pugh B/C Cirrhosis

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Received 13 February 2024; accepted 2 July 2024

Purpose: For patients with hepatocellular carcinoma (HCC), stereotactic body radiation therapy (SBRT) has emerged as a locoregional treatment. Our purpose was to report outcomes in patients with HCC with Child-Pugh A (CP A) versus Child-Pugh B or C (CP B/C) liver dysfunction treated with SBRT.

Methods and Materials: A retrospective analysis of 80 patients with HCC, with a total of 94 tumors treated with SBRT, was conducted at a single institution. Outcomes were compared between patients with CP A (n = 51) and CP B/C (n = 29) liver dysfunction. Outcomes of interest included local control, overall survival (OS), and toxicity.

Results: Median tumor size was 3.2 cm. There were 59 tumors included in the CP A cohort and 35 tumors in the CP B/C cohort. Median radiation dose was 50 Gy in 5 fractions for the CP A cohort and 40 Gy in 5 fractions for the CP B/C cohort. The rates of pathologic complete response were similar between the 2 groups at 63% for the CP A group and 61% for the CP B/C group. The estimated 1-year local control rates were similar between the 2 groups at 93% for the CP A group and 91% for the CP B/C group (P = .59). The 1-year OS for the CP A group was 85%, whereas the 1-year OS for the CP B/C group was 61% (P = .19). There was a 5.9% rate of grade 3+ toxicity in the CP A group and a 20.7% rate of grade 3+ toxicity in the CPB/C group.

Conclusions: Our findings suggest that SBRT is feasible and effective in patients with both CP A and CP B/C liver dysfunction with similar rates of local control and pathologic complete response despite lower radiation doses in the CP B/C cohort. In patients with more advanced CP B/C cirrhosis, toxicities were higher and must be weighed against possible treatment benefits. Further studies characterizing the optimal role of SBRT in patients with advanced cirrhosis are warranted.

Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and represents both the sixth leading cause of cancer death in the United States and the third leading cause of cancer death worldwide.[1-4] In the

Sources of support: This work had no specific funding.

Research data are stored in an institutional repository and will be shared on request to the corresponding author.

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https://doi.org/10.1016/j.adro.2024.101631

United States, a rise in the incidence of hepatitis C infection has been linked to the rise in HCC.[5] Less than 30% of patients with HCC are eligible for surgical treatment including liver transplantation and tumor resection.[6] Stereotactic body radiation therapy (SBRT) has emerged as a safe and effective local ablative treatment to complement other available treatments, including transarterial chemoembolization (TACE), radiofrequency ablation, microwave ablation, transarterial radioembolization, systemic therapy, and immunotherapy.[7-9]

HCC most commonly develops in the setting of chronic liver disease.[4] Management options for HCC largely depend on the patient's underlying liver dysfunction. In the past, treatment of HCC with radiation therapy was limited because of concerns of liver toxicity. However, the development of SBRT has allowed for highly conformal, ablative treatment, which spares the uninvolved, functional portion of the liver.[7] Multiple studies have established SBRT as a safe treatment option for appropriately selected patients with high local control (LC) rates of >90%.[7,10,11] In patients with HCC, indications for SBRT include definitive treatment of unresectable disease, downstaging tumors to meet liver transplantation criteria, and providing LC to bridge patients to liver transplantation.[8,12-14] Few studies exist characterizing the safety and efficacy of locoregional treatments including SBRT in patients with advanced cirrhosis.[10,11,15,16] Reports suggesting an increased risk of toxicity in patients with Child-Pugh (CP) B cirrhosis have led to recommendations for more stringent liver dose constraints.[7,11,15,16] For patients with advanced cirrhosis, HCC treatment decisions must be balanced carefully with these patients' life expectancy because of their baseline cirrhosis. The purpose of our study was to characterize the safety and efficacy of SBRT in patients with HCC with CP A versus CP B/C liver dysfunction.

Methods and Materials

Study design

This prospective registry database was approved by the institutional review board of University of Massachusetts Memorial Medical Center. From 2012 to 2021, a total of 80 patients with HCC were treated with SBRT, including 51 classified as CP A and 29 classified as CP B/C. HCC was diagnosed either by biopsy or imaging according to the Barcelona criteria.[17] There were 94 total HCC tumors with 59 in the CP A group and 35 in the CP B/C group. Eligibility criteria included patients with a diagnosis of HCC treated with SBRT and included CP A, B, or C liver dysfunction. Patients were allowed to have prior therapy including systemic therapy, and other prior HCC therapies including TACE, transarterial radioembolization, radiofrequency ablation, and systemic therapy. All cases were discussed prospectively during weekly multidisciplinary tumor board conferences to determine if SBRT would be used in the management of their HCC.

Radiation treatment

During simulation, a vacuum cushion was custom-molded for the patients, and a treatment planning helical computed tomography (CT) followed by a 4-dimensional computed tomography (4D-CT) was performed. Diagnostic imaging, including 4-phase CT or magnetic resonance imaging, was fused to the planning CT to aid with target delineation. 4D-CT was used to account for respiratory motion. Patients were treated with a total dose of 30 to 60 Gy (range) prescribed in 3 to 6 fractions (range). Radiation treatment planning objectives included limiting the mean liver dose (MLD) defined as liver-clinical target volume to MLD <13 Gy for patients with CP A liver dysfunction, MLD <9 Gy for CP B liver dysfunction, and MLD <6 Gy for CP C liver dysfunction. Additionally, at least 700 cc of the uninvolved liver received <15 Gy for all patients. Radiation planning was performed using volumetric modulated arc therapy. Prior to each radiation treatment, cone beam CT and kilovoltage orthogonal films were used for image guidance.

Follow-up

All patients were seen weekly during SBRT, at 1 month post-SBRT, 3 months post-SBRT, and then every 3 months thereafter in a multidisciplinary HCC clinic. Abdominal imaging with 4-phase abdominal magnetic resonance imaging or 4-phase abdominal CT was obtained at 3-month intervals or as clinically indicated. Tumor response was evaluated with imaging based on the modified Response Evaluation Criteria in Solid Tumors as well as using pathologic data obtained from liver explant and/or autopsy.[18] LC was defined as complete response (CR), partial response (PR), or stable disease, whereas local recurrence (LR) was defined as progressive disease within the SBRT-treated region of the liver. Pathologic complete response (pCR) was determined based on autopsy or explant pathology review. Distant metastasis was defined as metastatic lesions outside of the liver. Elsewhere liver recurrence was defined as recurrence in the liver outside of the SBRT-treated radiation field. Patients were listed for orthotopic liver transplantation (OLT) as clinically indicated and previously established criteria including Milan criteria were used to help determine institutional eligibility for OLT.[19]

Statistical analysis

Descriptive statistics were used to characterize the patient cohort. Overall survival (OS) and LC were calculated from the completion of SBRT. OS and LC were evaluated using the Kaplan-Meier method. Patients who underwent OLT were censored for LC at the time of liver transplantation. Cox proportional Hazards models were used to compare survival outcomes based on the patient's baseline characteristics. *P* values were considered significant if ≤.05. Data analysis was performed using SPSS version 22 and R Studio version 4.2.1.

Results

Patient demographics and tumor variables

Baseline characteristics of patients treated with SBRT are summarized in Table 1. In total, 80 patients with HCC were treated with SBRT including 51 patients with CP A and 29 patients with CP B/C. There were 94 total HCC tumors treated with 59 in patients with CP A and 35 in patients with CP B/C. The median age of patients among the entire cohort was 67 years with an interquartile range (IQR) of 61 to 74 years for CP A and 62 years (IQR, 56-65 years) for CP B/C. The median tumor size was 3.35 cm (IQR, 2.7-4.4 cm) for the CP A group and 3.1 cm (IQR, 2.6-4.0 cm) for the CP B/C group. Portal vein tumor thrombus (PVTT) was present in 9.8% (5/51) of the patients in the CP A group and 3.4% (1/29) of patients in the CP B/C group. In the CP A group, 70.1% (36/51) of patients met Milan criteria for liver transplantation, whereas in the CP B/C group, 65.6% (19/29) met Milan criteria. Patients were listed for OLT as clinically indicated, and 29.4% (15/51) patients with CP A were listed with 11 of 15 ultimately receiving transplants, and 65.6% (19/29) patients with CP B/C listed with 12 of 19 receiving OLT during the study period. There were 51 patients with CP A, 23 patients with CP B, and 6 patients with CP C. Chronic liver disease was often multifactorial and was attributed to alcohol in 47.5% of patients, hepatitis C in 42.5% of patients, hepatitis B in 7.5% of patients, and nonalcoholic steatohepatitis in 16.3% of patients. Patients in our treatment cohort were also heavily pretreated with 63.8% (51/80) receiving prior TACE, 8.8% (7/80) receiving prior Yttrium-90 (y-90) radioembolization, and only 16.3% (13/80) with no prior liver-directed local treatments.

Treatment details

Treatment details are summarized in Table 2. The median radiation dose of the overall cohort was 47.5 Gy (IQR, 40-50 Gy) delivered over a median of 5 fractions (range, 3-6 fractions) with a median equivalent dose in 2 Gy fractions [EQD2] of 80.3 Gy2 (IQR, 60-83.3 Gy2), and a median BED_{10} of 96.3 Gy (IQR, 72-100 Gy). Patients in the CP A group had a median radiation dose of 50 Gy (IQR, 50-51.25 Gy) delivered over a median of 5 fractions (range, 3-5 fractions), a median EQD2 of 83.3 Gy2 (83.3-95 Gy2), and a median BED_{10} of 100 Gy (IQR, 100-114 Gy). Patients in the CP B/C group had a median radiation dose of 40 Gy (IQR, 37.5-40 Gy) delivered over a median of 5 fractions (range, 4-6 fractions), a median EQD2 of 60 Gy2 (IQR, 54.5-60 Gy2), and a median BED_{10} of 72 Gy (IQR, 65.5-72 Gy). The median MLD in the CP A group was 8 Gy (IQR, 5.5-10.3 Gy), and in the CP B/C group, the MLD was 7 Gy (IQR, 4.8-8.8 Gy).

Treatment outcomes

At a median follow-up time of 11 months, the estimated 1- and 2-year LC was similar between the 2 groups with a 1-year LC of 92.5% and 2-year LC of 86.9% for the CP A group and 90.9% and 90.9% for the CP B/C group (P = .59) (Fig. 1A). For LC, the median follow-up for patients with CP A was 14 months, whereas the median follow-up for CP B/C patients was 7 months. On univariable analysis, only PVTT was associated with worse LC (hazard ratio [HR], 11.568; 95% confidence interval [CI], 2.224-60.185; P = .004). On multivariable analysis, only the presence of PVTT conferred worse LC (HR, 11.581; 95% CI, 1.679-79.873; P = .013). Other factors such as age, tumor size, alpha fetoprotein, imaging within Milan criteria, listing for OLT, CP group, radiation EQD2, MLD, and CP progression did not affect LC on univariable or multivariable analysis (Table 3).

Similarly, at a median follow-up of 28 months, the estimated 1- and 2-year OS was similar between the 2 groups but trended worse but was not statistically different for the CP B/C group. The estimated 1- and 2-year OS for the CP A group was 85% and 66.4%, whereas the 1- and 2-year OS for the CP B/C group was 61.4% and 50.3% (P = .19) (Fig. 1B). For OS, the median follow-up for the CP A group was 32 months and for the CP B/C group was 17 months. On univariable analysis, PVTT (HR, 3.41; 95% CI, 1.187-9.803; P = .023) and CP progression (HR, 2.762; 95% CI, 1.548-4.929; P = .001) were both associated with worse OS. Conversely, on univariable analysis listing for OLT (HR, 0.499; 95% CI, 0.271-0.900; P = .021) was associated with improved OS. On multivariable analysis, PVTT (HR, 3.960; 95% CI, 1.285-12.204; P = .017), CP group B/C (HR, 2.649; 95% CI, 1.081-6.492; P = .033), and CP progression (HR, 3.442; 95% CI, 1.604-7.387; P =.002) were associated with worse OS. Conversely, on multivariable analysis, imaging within Milan criteria (HR, 0.460; 95% CI, 0.220-0.961; P = .039) and listing for OLT (HR, 0.404; 95% CI, 0.209-0.779; P = .007) were associated with improved OS. Factors such as age, tumor size, alpha

Table 1 Baseline characteristics of patients and HCC tumors treated with SBRT

	Total	CP A	CP B/C
No. of patients	80	51	29
No. of tumors	94	59	35
Median age (IQR)	64 (59-70.25)	67 (61-74)	62 (56-65)
Median tumor size (IQR)	3.2 (2.5-4.1)	3.35 (2.7-4.4)	3.1 (2.6-4.0)
PVTT	6	5	1
Median AFP (IQR)	8.4 (4.5-39.8)	6.1 (4-30.6)	10.7 (6-74.9)
Imaging within Milan Criteria (n, %)	55 (68.8%)	36 (70.1%)	19 (65.6%)
Listed for OLT (n, %)	34 (42.5%)	15 (29.4%)	19 (65.6%)
CP score prior to SBRT			
A5	32	32	0
A6	19	19	0
B7	5	0	5
B8	6	0	6
B9	12	0	12
C10	5	0	5
C11	1	0	1
Comorbid liver disease (n, %)			
Alcohol	38 (47.5%)	24 (47%)	14 (48.3%)
Hepatitis B	6 (7.5%)	3 (5.8%)	3 (10.3%)
Hepatitis C	34 (42.5%)	18 (35.3%)	16 (55.2%)
NASH	13 (16.3%)	10 (19.6%)	3 (10.3%)
Other	12 (15%)	6 (11.8%)	6 (20.7%)
Previous liver-directed therapies (n, %)			
TACE	51 (63.8%)	34 (66.7%)	17 (58.6%)
y-90	7 (8.8%)	4 (7.8%)	3 (10.3%)
TAE	8 (10%)	5 (9.8%)	3 (10.3%)
MWA	3 (3.8%)	3 (5.9%)	0 (0%)
RFA	2 (2.5%)	2 (3.9%)	0 (0%)
None	13 (16.3%)	7 (13.7%)	6 (20.7%)

Abbreviations: AFP = alpha fetoprotein; CP A = Child-Pugh A; CP B/C = Child-Pugh B/C; IQR = interquartile range; MWA = microwave ablation; NASH = nonalcoholic steatohepatitis; PVTT = portal vein tumor thrombus; RFA = radiofrequency ablation; TACE = transarterial chemo-embolization; TAE = transarterial embolization; y-90 = Yttrium-90 radioembolization.

fetoprotein, EQD2, and MLD were not found to be associated with a difference in OS on univariable or multivariable analysis (Table 3).

There were similar rates of elsewhere liver recurrence at 43.1% (22/51) for the CP A group and 41.4% (12/29) for the CP B/C group (P = .808). There were also similar rates of distant metastasis at 15.7% (8/51) in the CP A group and 10.3% (3/29) in the CP B/C group (P = .505) (Table 4).

Given that OLT has been shown to improve OS, we compared the rates of LC and OS among our cohort excluding patients who proceeded to OLT. Excluding patients who proceeded to OLT, LC was similar between the 2 groups. The estimated 1- and 2-year LC for the CP A group was 90% and 83% compared with 88% and 88% for the CP B/C group (Fig. 1C). Excluding patients who proceeded to OLT, OS was worse for the CP B/C group than for the CP A group. The estimated 1- and 2-year OS CP A group was 80.4% and 58.5% and 39.2% and 17.4% for the CP B/C group (P = .008) (Fig. 1D).

Table 2 Treatment details for patients treated with SBRT

Variable	Overall (n = 94)	CP A (n = 59)	CP B/C (n = 35)
Tumor size (median, IQR)	3.2 (2.5-4.1)	3.35 (2.7-4.4)	3.1 (2.6-4.0)
GTV volume (cm^3) (median, IQR)	26.1 (24.6-44.1)	25.7 (10-40.6)	30 (17.1-46.2)
PTV volume (cm^3) (median, IQR)	87.4 (56-139.5)	82.8 (53.3-137)	89.1 (65.9-145.35)
Prescribed dose (Gy) (median, IQR)	47.5 (40-50)	50 (50-51.25)	40 (37.5-40)
No. of fractions (median, range)	5 (3-6)	5 (3-5)	5 (4-6)
EQD2 (Gy) (median, IQR)	80.3 (60-83.3)	83.3 (83.3-95)	60 (54.5-60)
BED_{10} (Gy)	96.3 (72-100)	100 (100-114)	72 (65.5-72)
Mean liver dose (Gy), (median, IQR)	8 (5.5-10.3)	8.6 (6.1-11.2)	7 (4.8-8.8)

Abbreviations: cm = centimeters; EQD2 = equivalent dose in 2 Gy fractions; GTV = gross tumor volume; Gy = gray; IQR = interquartile range; PTV = planning target volume.

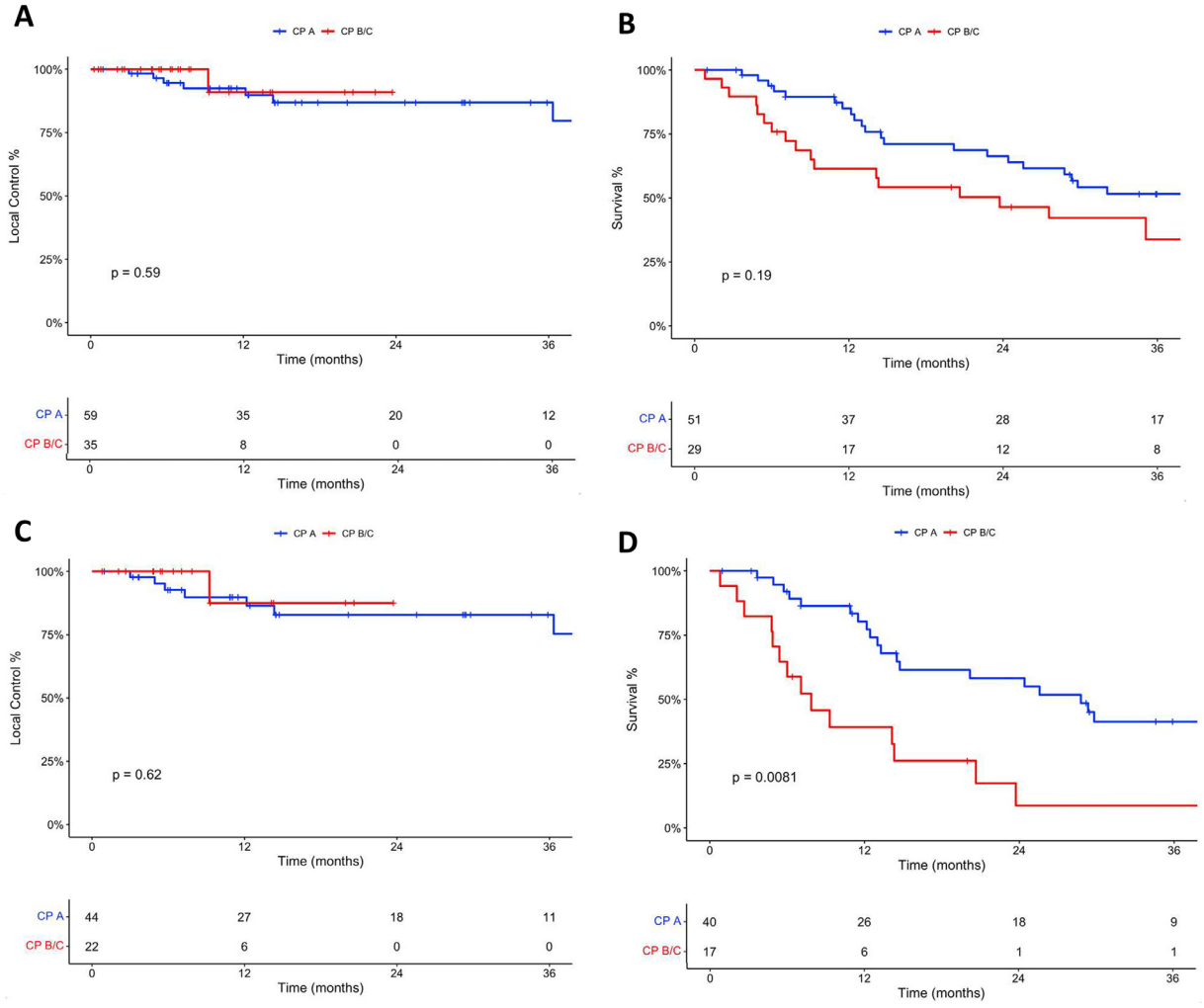

Figure 1 Kaplan-Meier plots displaying the LC (A) and OS (B) for patients with HCC and CP A versus CP B/C cirrhosis. (C) LC excluding patients who proceeded to OLT. (D) OS excluding patients who proceeded to OLT. *Abbreviations:* CP A = Child-Pugh A; CP B/C = Child-Pugh B/C; HCC = hepatocellular carcinoma; LC = local control; OLT = orthotopic liver transplantation; OS = overall survival.

Table 3 Cox regression univariable and multivariable analysis of factors associated with local control and overall survival

	Local control						Overall survival					
	Univariable			Multivariable			Univariable			Multivariable		
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (y)	1.017	0.956-1.082	.591	1.001	0.928-1.080	.972	1.008	0.978-1.038	.624	1.009	0.977-1.041	.586
Tumor size (cm)	0.946	0.629-1.425	.792	0.908	0.491-1.679	.759	1.016	0.855-1.207	.856	0.804	0.651-1.194	.144
PVTT	11.568	2.224-60.185	.004	11.581	1.679-79.873	.013	3.411	1.187-9.803	.023	3.960	1.285-12.204	.017
AFP (ng/mL)	1.000	0.998-1.002	.877	1.000	0.999	.998-1.002	1.000	0.999-1.001	.808	1.00	0.999-1.001	.490
Imaging within Milan criteria	1.759	0.365-8.489	.482	1.287	0.191-8.659	.795	0.585	0.327-1.045	.070	0.460	0.220-0.961	.039
Listed for OLT	0.851	0.209-3.467	.822	0.837	0.166-4.229	.829	0.494	0.271-0.900	.021	0.404	0.209-0.779	.007
CP B/C vs CP A (ref)	0.534	0.064-4.482	.563	1.000	0.062-16.190	.999	1.454	0.818-2.584	.202	2.649	1.081-6.492	.033
EQD2 (Gy)	1.006	0.974-1.038	.722	1.003	0.957-1.052	.888	0.992	0.978-1.006	.261	1.003	0.982-1.024	.792
Mean liver dose (Gy)	1.005	0.817-1.235	.966	1.023	0.804-1.302	.852	1.058	0.961-1.164	.249	1.100	0.980-1.235	.107
CP progression vs Stable/improved (ref)	1.869	0.433-8.071	.402	1.558	0.283-9.811	.572	2.762	1.548-4.929	.001	3.442	1.604-7.387	.002

Abbreviations: 95% CI = 95% confidence interval; AFP = alpha fetoprotein; cm = centimeters; CP A = Child-Pugh A; CP B/C = Child-Pugh B or C; EQD2 = equivalent dose in 2 Gy fractions; Gy = gray; HR = hazard ratio; mL = milliliters; ng = nanograms; OLT = orthotopic liver transplant; PVTT = portal vein tumor thrombus; ref = referent.

Clinical and pathologic response rates

Treatment response rates are listed in Table 4. Among the entire cohort, combined radiographic and pathologic CR rates were not different (P = .111). Response data were available for 89 tumors. Overall, there was a CR rate of 65.2% (58/89) with a CR rate of 68.4% (39/57) for the CP A group and a CR rate of 59.4% (19/32) for the CP B/C group. We observed PR rates of 20.2% (18/89) for the entire cohort with PR in 14% (8/57) for the CP A group and 31.3% (10/32) for the CP B/C group. There were 9 total LRs with 14% (8/57) for the CP A group and 3.1% (1/32) rate of LR for the CP B/C group. Of the 32 total tumors with pathology available either at liver explant or autopsy, there was a pCR rate of 62.5% (20/32) for the entire cohort. Rates of pCR were similar between groups with a pCR rate of 63.2% (12/19) for the CP A group and 8/13 (61.5%) for the CP B/C group (P = .952) (Table 4).

Toxicity rates

Toxicity rates are summarized in Table 5. Toxicity rates were relatively low with a rate of 11.3% (9/80) of grade 3+ toxicity overall. Of the 9 patients who experienced grade 3+ toxicity attributed to treatment, there were 5 patients with grade 3+ alterations of liver function laboratory values, 2 patients developed new or significantly worsened grade 3 ascites, 2 patients developed grade 3 upper gastrointestinal bleeds, 1 patient developed new-onset PVTT, and 1 patient developed grade 3 pain. There were higher rates of grade 3+ toxicity in the CP B/C cohort at 20.7% (6/29) and 5.9% (3/51) for the CP A cohort (P = .044). We assessed CP score to determine if patients had progression, stability, or improvement at 6 months following SBRT treatment. There were 30% (24/80) of patients overall who had progression of their CP score by 1 or more points with a higher rate in the CP B/C group at 44.8% (13/29) compared with the CP A group at 21.6% (11/51) (P = .004). Among the 11 patients in the CP A group who experienced CP score progression, 9 patients had an increase in CP score by 1 point, 1 patient had an increase in CP score by 3 points, and 1 patient had an increase in CP score by 4 points. Among the 13 patients in the CP B/C group who experienced CP score progression, 8 patients had an increase in CP score by 1 point, 3 patients had an increase in CP score by 2 points, and 2 patients had an increase in CP score by 3 points. Overall, 61.3% (49/80) patients had stable CP scores after SBRT with 74.5% (38/51) patients with CP A and 37.9% (11/29) of patients with CP B/C with a stable CP score following SBRT. Finally, CP score was improved in 8.8% (7/80) with 3.9% (2/51) of patients with CP A and 17.2% (5/29) of patients with CP B/C with an improvement in CP

Table 4 Treatment outcomes following SBRT

	Overall	CP A	CP B/C	*P* value
CR (n = 89)	58 (65.2%)	39 (68.4%)	19 (59.4%)	.111
PR (n = 89)	18 (20.2%)	8 (14%)	10 (31.3%)	
SD (n = 89)	4 (4%)	2 (4%)	2 (6%)	
PD (n = 89)	9 (10.1%)	8 (14%)	1 (3.1%)	
pCR (n = 32)	20 (62.5%)	12 (63.2%)	8 (61.5%)	.952
Distant metastases (n = 80)	11 (13.8%)	8 (15.7%)	3 (10.3%)	.505
Elsewhere liver recurrence (n = 80)	34 (42.5%)	22 (43.1%)	12 (41.4%)	.878

Abbreviations: CP = Child-Pugh; CR = complete response; pCR = pathologic complete response; PD = progressive disease; PR = partial response; SD = stable disease.

score following SBRT. No patients in our cohort exhibited signs of classic radiation-induced liver disease.

Discussion

In patients with both HCC and severe liver dysfunction, treatment options are limited, and it is important to balance the overall poor prognosis of their advanced cirrhosis with any potential HCC treatment benefit. The CP class was initially used to predict the survival of patients with cirrhosis following portosystemic shunting and was later found to predict survival after other liver-directed therapies.[20-22] Although the CP scoring system is limited by subjectivity and variations in liver function are often difficult to attribute to treatment versus the natural progression of advanced cirrhosis, the CP score is the most studied measure of liver function in the SBRT literature. This study suggests that SBRT for HCC is a feasible and effective treatment option in patients with both CP A and CP B/C liver dysfunction with similar rates of LC between the 2 groups despite lower RT doses in the CP B/C group.

Limited data exist regarding the optimal use of locoregional therapy including SBRT in patients with advanced cirrhosis. In fact, many clinical trials exclude patients with CP B/C liver dysfunction. Lee et al[16] previously reported favorable LC of a smaller cohort of patients with CP B/C from University of Massachusetts Memorial Medical Center with a 1-year LC rate of 92%. Similarly, Gresswell et al[23] reported a favorable rate of radiographic response at 80% and pCR of 46% in a small case series of 12 patients with CP B/C cirrhosis. Culleton et al[15] reported a poor median OS of 7.9 months in a cohort of patients with CP B/C cirrhosis with HCC; however, it primarily included patients with CP B7 and patients treated with overall lower radiation doses of 30 Gy in 5 fractions. Our current study bolsters these findings showing excellent rates of 1-year LC in both early and advanced cirrhosis at 93% for the CP A group and 91% for the CP B/C group as well as 1-year OS of 85% for the CP A group and 64.1% for the CP B/C group. Additionally, our rate of pCR of 62.5% compares favorably with previously reported rates ranging from 14% to 62.5% in prior case series.[16,24-28] Interestingly, our excellent rates of pCR were similar between cohorts with a rate of 63.2% for the CP A group, which was similar to the pCR rate of 61.5% in the CP B/C group despite lower radiation doses.

When treating patients with advanced cirrhosis, strategies to preserve remaining liver function are essential to deliver SBRT safely. Jackson et al[29] proposed an approach for patients with CP B cirrhosis using adaptive planning and pre- and midtreatment liver function testing using indocyanine green. In our patient population, we used a CP-based adaptive approach to MLD, which we previously described in Lee et al[16] with a constraint of 8 Gy for CP B7-B8, 5 Gy for B9-C10, and kept our MLD as low as possible at 2.5 Gy for our single CP C11 patient. Despite these stringent RT dose constraints and in turn lower RT doses, we observed similar rates of LC between patients

Table 5 Treatment-related toxicities including CP score change after treatment and grade 3+ toxicities

CP score and adverse events	Overall (n = 80)	CP A (n = 51)	CP B/C (n = 29)	*P* value
CP Progression	24 (30%)	11 (21.6%)	13 (44.8%)	.004
CP Stability	49 (61.3%)	38 (74.5%)	11 (37.9%)	
CP Improvement	7 (8.8%)	2 (3.9%)	5 (17.2%)	
Grade 3+ Adverse Events	9 (11.3%)	3 (5.9%)	6 (20.7%)	.044

Abbreviation: CP = Child-Pugh.

with CP A and CP B/C. In patients with a progression of CP score, we observed worse OS, which is in line with a previous study by Chapman et al[30] and highlights the importance of preserving baseline liver function. Further studies to define the optimal dosimetry for patients with advanced cirrhosis will be helpful to ensure safe and effective treatment.

It is important to note that at our institution's multidisciplinary HCC conference, we use a comprehensive approach to assess a patient's liver function including factors such as the CP trend over time, performance status, comorbidities, model for end-stage liver disease score, tolerance of previous treatments, and history of prior liver-related decompensations. These complex decisions are difficult to capture in a study and highlight the importance of multidisciplinary involvement in the care of HCC patients.

Our study is limited by the small number of subjects, particularly in the advanced cirrhosis CP B/C group. Additionally, although CP score is a commonly used metric in radiation literature to assess liver function, it is limited, and other clinical factors are important in understanding a patient's baseline liver function. Finally, patients with more advanced cirrhosis are more likely to proceed to liver transplantation and have additional competing mortality risks relating to their cirrhosis, which can confound comparisons between our 2 study cohorts. Further studies to define the optimal role of SBRT in patients with advanced cirrhosis as well as studies to define dose volume correlates of liver toxicity in these patients are essential.

Conclusions

Our study demonstrates that for patients with HCC, SBRT is a feasible and effective treatment option for patients with both CP A and CP B/C liver dysfunction. We observed similar rates of LC, CR, and pCR rates despite lower radiation doses in the CP B/C cohort. In patients with more advanced CP B/C cirrhosis, treatment-related toxicities were higher and must be weighed with the possible treatment benefit. Providers must take caution in treating patients with advanced cirrhosis and use strict liver dose constraints to preserve remaining liver function. Importantly, OS trended worse in patients with more advanced cirrhosis and was worse when patients who proceeded to OLT were excluded, highlighting the importance of appropriately selecting patients with HCC for SBRT treatment. Additional studies are needed to further characterize the optimal role of locoregional therapy including SBRT in patients with HCC and advanced cirrhosis.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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