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ORIGINAL ARTICLE

Application of Stereotactic Ablative Radiotherapy in Hepatocellular Carcinoma Patients with Child–Turcotte–Pugh Class B Liver Function

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Background: The aim of this study is to evaluate the outcomes and prognostic factors in patients with hepatocellular carcinoma (HCC) and Child–Turcotte–Pugh (CTP) class B liver function after stereotactic ablative radiotherapy (SABR). **Materials and Methods:** This retrospective study evaluated patients with HCC and impaired liver function who underwent SABR between December 2007 and August 2016. All patients had CTP class B liver function before treatment. Local control (LC) rate, overall survival (OS) rate, prognostic factors, and radiation-related toxicity were evaluated. **Results:** This study included 34 patients. The majority had a CTP score of B7 (52.9%) and advanced HCC (91.2%). The median survival time was 4.8 months, and the 1-year OS rate was 21.4%. Only the tumor number (multiple vs. single) was identified as an independent predictor of survival. The 1-year LC rate was 95.8%. Eight patients (23.5%) developed the radiation-induced liver disease, and 15 (44.1%) had a CTP score decline of ≥2 within 3 months. Other toxicities were generally tolerable. **Conclusion:** SABR may be considered as an alternative option for patients with HCC and CTP class B liver function, particularly for those with a single lesion.

Key words: Hepatocellular carcinoma, stereotactic ablative radiotherapy, stereotactic body radiotherapy, Child–Turcotte–Pugh class B

INTRODUCTION

Stereotactic ablative radiotherapy (SABR) has been used to treat hepatocellular carcinoma (HCC) with minimal toxicity and sustained local control (LC). Limited prospective studies have demonstrated 75%–100% LC and 55%–94% survival at 1 year after liver SABR.[1-5] SABR was an accepted treatment choice for early- and advanced-stage HCC. However, most patients in previous studies had favorable Child–Turcotte–Pugh (CTP) class A liver function with 1–3 lesions. SABR feasibility in patients with impaired liver function has not been well studied. We aimed to evaluate the outcomes of patients with HCC and CTP class B after liver SABR.

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MATERIALS AND METHODS

Patients

This study was the Institutional Review Board (IRB) approved for analysis of HCC patients who underwent SABR at our institution between December 2007 and August 2016. This was a retrospective study, and therefore, IRB approval was obtained for waiver of consent. Our inclusion criteria were as follows: (1) noninfiltrative HCC, (2) CTP class B liver function, (3) nontumor liver volume ≥700 cc, (4) no previous history of liver radiotherapy, and (5) no other active cancer within the 5 years before SABR. The diagnosis of HCC was

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made according to the histological or radiological criteria.[6] All previous liver-directed therapies were accepted, except for liver transplantation.

Radiotherapy technique and dose

All SABR were carried out using CyberKnife® image-guided radiosurgery system (Accuray Incorporated, Sunnyvale, CA, USA). The details regarding the preparation, simulation, and dose volume constraints followed the published report.[7] Synchrony respiratory motion tracking (Accuray Inc., Sunnyvale, CA, USA) and abdominal compression to reduce tumor motion were used in the majority of the patients. The most recent multiphase dynamic magnetic resonance imaging (MRI) scans were loaded for image fusion to facilitate target delineation. The gross target volume (GTV) was delineated on the simulation computed tomography (CT) images. The planning target volume (PTV) was based on the motion management strategy. For patients with implanted fiducials, a margin of 0–8 mm was expanded from GTV. For patients without fiducials, asymmetrical margins of 3–8 mm in the axial direction and 8–20 mm in the longitudinal direction were adopted, which were based on organ motion.

The prescribed dose was limited by normal liver volume, tumor volume, and the tolerance of adjacent luminal gastrointestinal organs.

Treatment response and toxicity assessments

Clinical evaluations, liver function test, abdominal CT, and/or MRI were conducted at 1–3 months after the completion of SABR and then at 3–4-month intervals. The modified response evaluation criteria in solid tumors were adopted to evaluate radiotherapy response.[8] LC was defined as the absence of progressive disease (PD) within or at the margin of PTV. All other recurrences within the liver were classified as an intrahepatic out-field failure. All diseases at any nonliver site were defined as extrahepatic failure.

Toxicities were graded based on the worst episode after treatment, according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).[9] Liver toxicity including radiation-induced liver disease (RILD) and CTP score decline was diagnosed after the exclusion of intrahepatic progression and was censored at the time of liver-directed therapies or transplant.

Statistical analysis

All analyses were performed using SPSS version 17 software (SPSS Inc., Chicago, IL, USA). Overall survival (OS) was calculated as the time from the last fraction of SABR until death from any cause or last follow-up. Survival data were censored at the time of liver transplantation. The Kaplan–Meier method was used to compare the OS and LC rates; the differences between subsets were evaluated using the log-rank test. The univariable Cox proportional-hazards model was used to determine the predictors for OS. Variables with $P < 0.1$ in univariable analysis were included in the multivariable model using a backward stepwise logistic regression model. Treatment response and liver toxicity events were compared between different subgroups using Fisher's exact test. Differences were defined as statistically significant at $P < 0.05$.

RESULTS

Patients and radiotherapy dose

A total of 21 men and 13 women were reviewed and analyzed in this study. The median age was 67.5 years. Most patients had underlying viral hepatitis (88.2%), with hepatitis B virus (HBV) infection being predominant. Most patients had a CTP score of B7 (52.9%). Moreover, 91.2% had advanced HCC (Barcelona clinic liver cancer [BCLC] stage C or D), 55.9% had a macrovascular invasion, and 38.2% had the extrahepatic disease. Other patient characteristics are summarized in Table 1.

Doses of 25–52 Gy (median, 40 Gy) in 4–5 fractions were prescribed to 64%–78% isodose lines. The most common regimen was 40 Gy in five fractions (7 patients), followed by 45 Gy (6 patients) and 35 Gy (5 patients) in five fractions.

Response and survival

During the analysis, 28 patients died and six remained alive. Most patients died of HCC recurrence/progression ($n = 18$), other causes included esophageal variceal bleeding ($n = 3$), gastrointestinal bleeding ($n = 2$), liver failure ($n = 2$), intra-abdominal infection/sepsis ($n = 2$), and hemorrhagic brain metastasis ($n = 1$). The median follow-up for all patients was 3.9 months (range: 0.6–72.5 months) and 4.2 months for living patients. The median survival time was 4.8 months, and the 1-year OS rate was 21.4% [Figure 1]. There was no difference in survival between patients with and without macrovascular invasion [$P = 0.335$, Figure 2a], with a median survival of 4.2 and 5.8 months, respectively. Patients with CTP B7 had a trend toward better OS compared with those with CTP ≥ B8 [$P = 0.095$, Figure 2b], with a median survival of 6.5 and 3.5 months, respectively. Only the tumor number (multiple vs. single) was identified as an independent predictor of survival in both univariable and multivariable analyses [Table 2]. Patients with a single tumor had a significantly longer survival than those with multiple tumors, with a median survival of 8.5 and 4.2 months, respectively [$P = 0.018$, Figure 2c].

Table 1: Patient and treatment characteristics

Number of patients	34 (100)*
Gender	
Male/female	21 (61.8)/13 (38.2)
Age (years)	
Median (range)	67.5 (36-86)
Recurrent HCC	
Yes/no	15 (44.1)/19 (55.9)
Viral hepatitis	
HBV	15 (44.1)
HCV	12 (35.3)
Both	3 (8.8)
None	4 (11.8)
Tumor size (cm)	
Median (range)	6.8 (2-16)
Total tumor volume (cc)	
Median (range)	193.8 (3.6-1440.2)
Tumor number	
Single/multiple	9 (26.5)/25 (73.5)
Nontumor liver volume (cc)	
Median (range)	1278 (736-2535)
MVI	
Present/absent	19 (55.9)/15 (44.1)
Extrahepatic spread	
Present/absent	13 (38.2)/21 (61.8)
Performance status	
0	8 (23.5)
1	14 (41.2)
2	10 (29.4)
3	2 (5.8)
AFP (ng/ml)	
<400/≥400	18 (52.9)/16 (47.1)
CTP score	
7/8/9	18 (52.9)/13 (38.2)/3 (8.8)
BCLC stage	
0-A	3 (8.8)
B	0
C	29 (85.3)
D	2 (5.9)
SABR total dose (Gy)	
Median (range)	40 (25-52)
Combination of Sorafenib	
Present/absent	9 (26.5)/25 (73.5)
Prior liver directed therapies	
Liver resection	3 (8.8)
RFA	1 (2.9)
TACE	15 (44.1)

*With percentages in parentheses unless indicated otherwise. HCC=Hepatocellular carcinoma; HBV=Hepatitis B virus; HCV=Hepatitis C virus; AFP=α-fetoprotein; CTP=Child-Turcotte-Pugh liver function scale; BCLC=Barcelona clinic liver cancer; SABR=Stereotactic ablative radiotherapy; RFA=Radiofrequency ablation; TACE=Transarterial chemoembolization, MVI=Macrovascular invasion

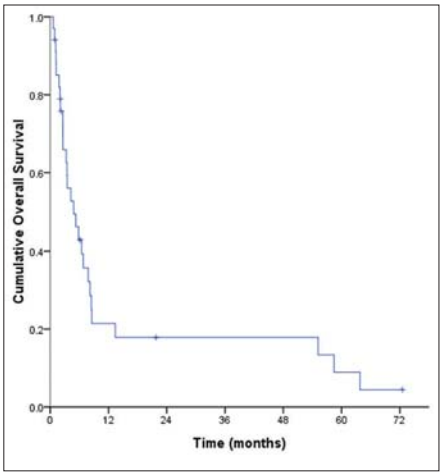

Figure 1: Kaplan–Meier curve for overall survival. The median survival time was 4.8 months, and the 1-year overall survival rate was 21.4%

A total of 26 patients were evaluable for treatment response. The best responses of the primary tumor were a complete response (CR) in 7 patients (26.9%), partial response (PR) in 12 (46.2%), stable disease (SD) in 6 (23.1%), and PD in 1 (3.8%). Figure 3 illustrates one patient who had CR after the SABR. Factors associated with treatment response (CR + PR vs. SD + PD) are shown in Table 3; none was identified as an independent predictor. Intrahepatic out-field recurrence was the main cause of treatment failure and was observed in 14 patients (53.8%). The 1-year LC rate was 95.8%.

Toxicity

All patients received the planned SABR without interruption because of radiation-related toxicity. Acute toxicities are listed in Table 4. SABR was generally tolerable, with no Grade 4 or higher toxicity, except for RILD. Fatigue and abdominal pain were the most common adverse effects experienced.

Eight patients (23.5%) developed RILD, which included nonclassic RILD (7 patients), and 1 patient fulfilled the criteria for both classic and nonclassic types. Patients with CTP B7

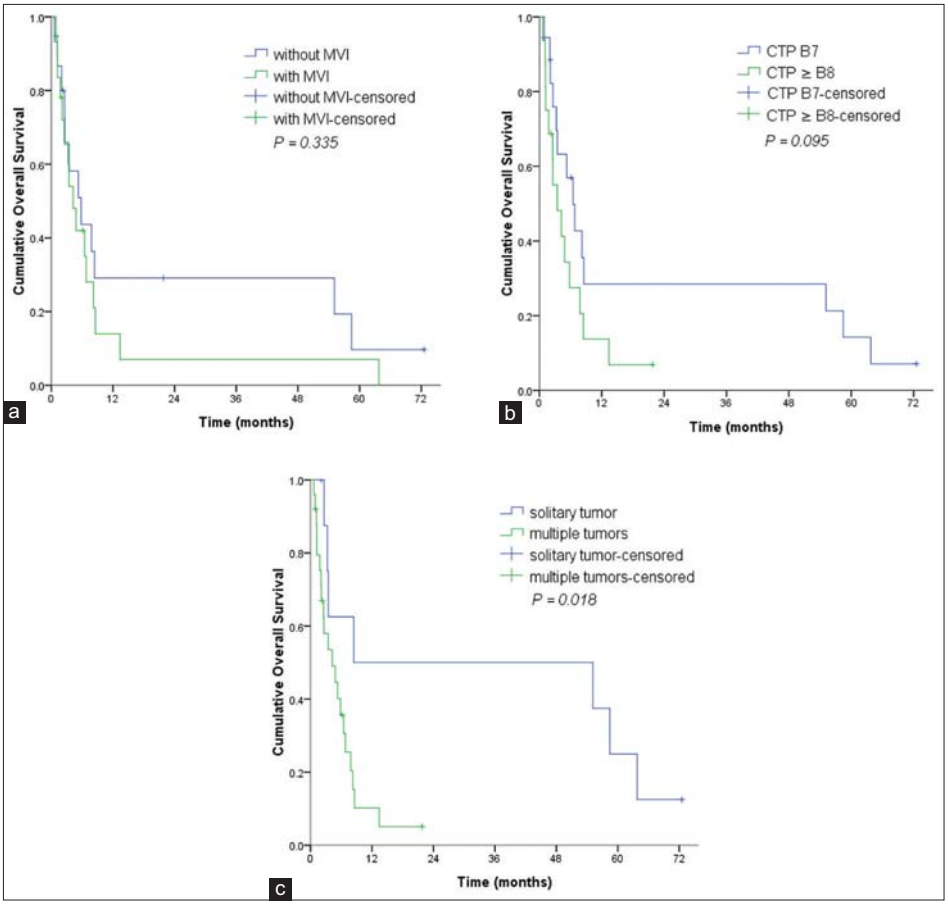

Figure 2: Overall survival of patients with hepatocellular carcinoma. (a) With macrovascular invasion versus without macrovascular invasion (1-year overall survival, 13.8% vs. 28.5%). (b) Child-Turcotte-Pugh B7 versus Child–Turcotte–Pugh ≥ B8 (1-year overall survival, 29.1% vs. 14.0%). (c) Single tumor versus multiple tumors (1-year overall survival, 50.0% vs. 10.2%)

were less likely to develop RILD than those with CTP ≥B8, but the difference was not statistically significant (CTP B7: 3/18, CTP ≥B8: 5/16; $P = 0.317$). CTP score decline within 3 months was observed in 18 patients, among which 13 progressed to CTP class C. Patients with CTP B7 were less likely to progress to CTP class C after liver SABR compared with patients with CTP ≥B8 (CTP B7: 4/18, CTP ≥B8: 9/16; $P = 0.042$). The magnitudes of the declines in CTP score were 1 point ($n = 3$), 2–3 points ($n = 8$), and ≥4 points ($n = 7$); only four patients achieved their baseline CTP score after conservative care.

DISCUSSION

The present study provides the outcomes of SABR for patients with HCC, CTP class B liver function, and most advanced disease. The suggested treatment in this population is sorafenib based on BCLC algorithm, with an expected survival of 4.5–5 months in patients with CTP class B.[10,11] Other options of limited evidence included transarterial chemoembolization, radiotherapy, and multimodality management.[12-15] The best outcome was achieved using SABR. A prospective study by Cárdenes *et al*. reported that SABR for 11 patients with HCC and CTP class B liver function provided a median OS of 12.5 months.[16] Culleton *et al*. revealed that the median survival of 29 patients with CTP B/C HCC treated with SABR was 7.9 months.[12] The median survival in our series was 4.8 months, which is consistent with the outcome of historic control treated with sorafenib.[10,11] Notably, portal vein tumor thrombosis, an essential prognostic factor, may determine the outcome after SABR. It presented in three of the 11 (27.3%) patients in the study by Cárdenes *et al*., compared with 24 of the 29 (82.8%) in the study by Culleton *et al*., and 19 of the 34 (55.9%) in our series.

Patients with HCC and CTP class A liver function were appropriate candidates for SABR. It is one of the inclusion criteria in the largest prospective study.[1] Although a higher proportion of toxicity was noted, patients with CTP Class B disease were successfully treated; lower doses were adopted

Table 2: Prognostic factors on overall survival by cox proportional-hazards model (***n***=34)

Variables	Univariable		Multivariable	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age, years >60 versus ≤60	1.04 (0.47-2.32)	0.918		
Female versus male	1.37 (0.62-3.03)	0.442		
Viral hepatitis				
HBV versus no	2.63 (0.69-10.06)	0.157		
HCV versus no	3.05 (0.76-12.24)	0.115		
Recurrent versus new diagnosis	1.20 (0.56-2.58)	0.643		
Total tumor volume (cc)				
≥200 versus <200	2.03 (0.94-4.39)	0.073		
Tumor number				
Multiple versus single	3.47 (1.17-10.32)	0.025	3.39 (1.13-10.12)	0.029
MVI	1.64 (0.75-3.61)	0.215		
Extrahepatic spread	1.05 (0.47-2.32)	0.914		
Performance status				
≥2 versus 0-1	2.17 (0.97-4.85)	0.058		
AFP level				
≥400 versus <400	2.05 (0.96-4.36)	0.064	1.98 (0.93-4.23)	0.079
Combination with Sorafenib				
Yes versus no	0.87 (0.35-2.17)	0.760		
Total dose (Gy)				
≥40 versus <40	0.60 (0.28-1.31)	0.199		
CTP B8-9 versus B7	1.94 (0.88-4.30)	0.101		

HR=Hazard ratio; HBV=Hepatitis B virus; HCV=Hepatitis C virus; AFP=α-fetoprotein; CTP=Child-Turcotte-Pugh liver function scale; CI=Confidence interval, MVI=Macrovascular invasion

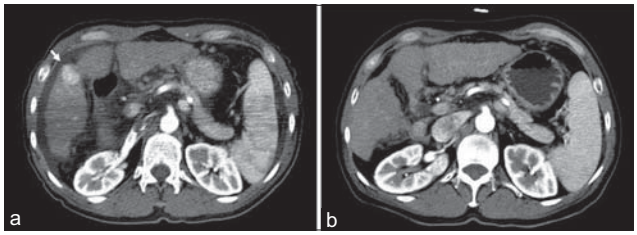

Figure 3: An example of complete response after the stereotactic ablative radiotherapy in a patient with Child–Turcotte–Pugh class B liver function. (a) The initial abdominal computed tomography with the hepatocellular carcinoma lesion indicated by the arrow. Note the irregularity of the external contour of the liver and presence of perihepatic ascites, which are consistent with impaired liver function. (b) The abdominal computed tomography conducted 12 months after the stereotactic ablative radiotherapy demonstrated no evidence of residual tumor

for these patients in some series.[3,17] A phase I/II trial by Lasley *et al*. reported the outcome of unresectable HCC after SABR.[3]

Table 3: Analysis of factors associated with treatment response after stereotactic ablative radiotherapy

Variables	Response (CR + PR, *n*=19)	No response (SD + PD, *n*=7)	*P*
Age (years)			
≤60	6	3	0.592
>60	13	4	
Gender			
Male	13	4	0.592
Female	6	3	
HBV carrier			
Yes	10	4	0.838
No	9	3	
HCV carrier			
Yes	8	4	0.495
No	11	3	
Recurrent HCC			
Yes	7	5	0.117
No	12	2	
Total tumor volume (cc)			
<200	9	3	0.838
≥200	10	4	
Tumor number			
Single	6	0	0.090
Multiple	13	7	
MVI			
Present	11	4	0.973
Absent	8	3	
AFP level			
<400	12	4	0.780
≥400	7	3	
Combination with Sorafenib			
Present	7	2	0.694
Absent	12	5	
Total dose (Gy)			
<40	5	2	0.908
≥40	14	5	

SABR=Stereotactic ablative radiotherapy; HBV=Hepatitis B virus; HCV=Hepatitis C virus; HCC=Hepatocellular carcinoma; AFP=α-fetoprotein; CR=Complete response; PR=Partial response; SD=Stable disease; PD=Progressive disease, MVI=Macrovascular invasion

This study involved 38 patients with CTP class A and 21 with CTP class B with 65 lesions, and patients with up to three lesions with a total diameter of ≤6 cm were eligible. The initial prescription doses were 36–48 Gy in three fractions for all patients despite CTP scores. After the observation of

Table 4: Acute toxicities after treatment

Toxicity	Number of patients (%)		
	Grade 1	Grade 2	Grade 3
Fatigue	7 (20.6)	3 (8.8)	0
Anorexia	4 (11.8)	2 (5.9)	0
Nausea/vomiting	1 (2.9)	2 (5.9)	0
Abdominal pain	6 (17.6)	4 (11.8)	1 (2.9)
Duodenal ulcer	0	1 (2.9)	0
Diarrhea	1 (2.9)	2 (5.9)	0

increased toxicity in patients with CTP class B, the planned dose for the following CTP B patients was reduced to 40 Gy in five fractions, and patients with a CTP score of ≥8 were excluded from this study. A similar policy of dose prescription was seen in the study by Sanuki *et al*.[17] They included 185 patients (CTP A, $n = 158$; CTP B, $n = 27$) unfeasible for surgery or percutaneous ablative therapies, with a single lesion of ≤5 cm. The planned prescription doses were 40 and 35 Gy in five fractions for patients with CTP class A and B liver function, respectively, with dose modification acceptable to meet constraints. More acute toxicities occurred in the 35-Gy group, which probably reflected a higher proportion of patients with CTP class B (52%) than the 40-Gy group (1%).

Selecting appropriate patients with CTP class B liver function who may benefit from SABR is essential. In theory, radiotherapy is more tolerable for patients with baseline CTP B7 compared with those with CTP ≥ B8. This was reflected in improved survival and less toxicity in patients with CTP B7. Culleton *et al*., reported that the CTP score was an independent predictor of OS among patients with CTP class B liver function after SABR. The median survival of patients with CTP B7 was 9.9 months versus 2.8 months for those with CTP ≥ B8 ($P = 0.011$).[12] In the aforementioned study by Cárdenes *et al*., the only factor associated with severe liver toxicity or death within 6 months was CTP ≥ B8 ($P = 0.03$).[16] In the present study, patients with CTP B7 had a trend toward better OS compared with those with CTP ≥ B8 (median survival, 6.5 months vs. 3.5 months; $P = 0.095$). They were also less prone to progress to CTP class C liver disease compared with those with CTP ≥ B8 ($P = 0.042$). Accordingly, patients with HCC and mild liver impairment (CTP B7) may undergo SABR and such population warrant inclusion in future prospective studies.

In the present study, only the tumor number (multiple vs. single) was identified as an independent predictor of survival. In our opinion, at least two rationales may explain this result. First, patients with a single tumor indeed had lower tumor burden than those with multiple tumors, which may transform into the survival difference between two groups. Second, the more spared nontumor liver volume may be achieved by treatment planning in cases with a single tumor, which may result in better tolerability and less liver toxicity.

Despite favorable response and LC rates after SABR, intrahepatic out-field recurrence was the main cause of treatment failure in our series and most studies involving SABR or other local therapies. This finding provided the rationale for combination therapies involving SABR and systemic therapies. The feasibility of concurrent SABR and Sorafenib had been investigated in a phase I trial.[18] Given the observation of significant toxicity, it suggested that concurrent use of SABR and sorafenib is not recommended, particularly in patients with large tumor burden. Other strategy such as the sequential use of SABR and sorafenib or development of new drugs is being investigated.[19,20]

Toxicity is always the main concern when considering the treatment. It is well known that patients with CTP class B liver function frequently developed liver toxicity. In the study by Cárdenes *et al*., RILD developed in three of the 11 (27.2%) patients with CTP class B.[16] Another prospective study reported that five of the 20 (25%) patients with CTP class B experienced ≥ Grade 3 liver enzyme elevation with ascites (nonclassic RILD) after SABR.[5] Culleton *et al*. reported that three of the 29 (10.3%) patients developed ≥ Grade 3 liver enzyme elevation 1 month after treatment and 63% had a decline in CTP score by ≥2 points at 3 months.[12] Our data are consistent with these studies: eight of the 34 (23.5%) patients developed RILD and 15 of the 34 (44.1%) had a CTP score decline of ≥2. These results stress the importance of patient selection, and more attention should be paid to patients with CTP class B after SABR.

There are some limitations in our study. The single-institute retrospective design is prone to selection bias. Besides, most patients had advanced-stage HCC and HBV infection, which limit the extrapolation of the result to early-stage disease and nonhepatitis B endemic area. The heterogeneous dose range without strict dose prescription was partly due to the diverse position or size of liver tumors and variable normal liver volume or function in individual patients. Last but not least, short-term survival of our patients prohibits long-term image follow-up. The 1-year LC rate of 95.8% might be overestimated with only one or two series image follow-up.

CONCLUSION

SABR may be considered as an alternative option for patients with HCC and CTP class B liver function, particularly for those with a single lesion. Further prospective studies are warranted to define optimal candidates for SABR.

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Conflicts of interest
There are no conflicts of interest.

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