

Challenges of BCLC stage C hepatocellular carcinoma

Results of a single-institutional experience on stereotactic body radiation therapy

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Abstract

In this study, we evaluated the feasibility and efficacy of stereotactic body radiation therapy (SBRT) in the treatment of Barcelona Clinic Liver Cancer (BCLC) stage C hepatocellular carcinoma (HCC).

This retrospective study evaluated 139 patients with BCLC stage C HCC who underwent CyberKnife SBRT between January 2009 and September 2017. All patients had BCLC-C, Child–Turcotte–Pugh score A-B. In-field control, overall survival (OS), progression free survival (PFS), and prognostic factors were evaluated.

An objective response rate was achieved in 81.5% patients (complete response, 36.2%, partial response, 45.3%). The median survival was 15.44 months, and the 1-, 3-, 5-year OS rates were 56%, 28%, and 20%, respectively. The median PFS was 6 months, the PFS rate at 1-, 3-, and 5-year were 35%, 14%, and 10%, respectively. In-field control of 1 to 2 years was achieved in 85.1% of patients. The major pattern of failure was out-field intrahepatic failure which comprised 42.9% of patients. Multivariate analysis revealed that the Child–Turcotte–Pugh score, macrovascular invasion, advance stage (III-IV), and tumor response rate were independent predictors of OS.

The result of our study shows that SBRT is a safe and effective therapeutic option for BCLC stage C HCC lesions that are unsuitable for standard loco-regional therapies. Moreover, SBRT has acceptable local control rates and low-treatment toxicity.

Abbreviations: AFP = alpha fetoprotein, AJCC = American Joint Committee on Cancer, BCLC = Barcelona Clinic Liver Cancer, BED = biological effective dose, CR = complete response, CT = computed tomography, CTP = child–turcotte–pugh, DP = disease progression, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, MRI = magnetic resonance imaging, OS = overall survival, PFS = progression free survival, PR = partial response, PTV = planning target volume, RFA = radiofrequency ablation, RILD = radiation induced liver disease, SBRT = stereotactic body radiation therapy.

Keywords: Barcelona clinic liver cancer stage C, hepatocellular carcinoma, stereotactic body radiation therapy

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide and the most common liver malignancy. Unfortunately >50% of cases are at an advanced stage upon diagnosis and show a dismal prognosis with a median survival of less than 12 months. Although there are numerous classification

systems for HCC, the Barcelona Clinic Liver Cancer (BCLC) staging system is the most widely used because of its simplicity.^[1] The BCLC staging system stratifies patients according to clinical condition and also provides information on appropriate treatment strategies.^[2] BCLC stage C HCC represents a large spectrum of disease with poor prognosis and constitutes the

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This work was approved by the Medicine Ethics Committee of Chi Mei Medical Center. The research reported in this paper was in compliance with the Helsinki Declaration. All patients provided written informed consent to participate.

All data are available without restriction. Researchers can obtain data by contacting the corresponding author.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files]. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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majority of HCC patients. The treatment options for this stage are limited, and sorafenib monotherapy is the standard of care; however, the 2% to 3.3% response rate and modest overall survival (OS) benefit of 2 to 3 months, raises the questions about whether its use is appropriate in all BCLC stage C patients.^[3,4,5]

Recently, several prospective and retrospective trials have showed promising results in patients treated with stereotactic body radiation therapy (SBRT) with high rates of local control and acceptable toxicity. Thus, SBRT could be considered as an alternative to radiofrequency ablation (RFA) and/or transarterial embolization techniques or in cases where these treatments have failed or were contraindicated.^[6,7,8] However, the majority of HCC SBRT studies have focused on small tumors with good liver functions. Nevertheless, there are limited data concerning the safety of SBRT for advanced stages of HCC. Therefore, in this study we focused our evaluation on the efficacy and toxicity of SBRT among patients with BCLC stage C HCC.

2. Methods and materials

2.1. Patients

This retrospective study evaluated 139 HCC patients who underwent CyberKnife SBRT between January 2009 and September 2017 at Chi Mei Medical Center, Tainan, Taiwan. The inclusion criteria were as follows:

- (1) BCLC stage C HCC, based on the presence of symptomatic tumors (e.g., Eastern cooperative oncology group performance status of 1–2) or vascular invasion/extrahepatic disease confirmed using computed tomography (CT) or magnetic resonance imaging (MRI);
- (2) Child–Turcotte–Pugh (CTP) class A to B liver function;
- (3) Uninvolved liver volume of ≥ 700 cc;
- (4) Any prior treatment was allowed except for previous liver irradiation; and
- (5) HCC diagnosis could be based on histological or radiological criteria^[9] and/or accompanied by a serum tumor marker alpha fetoprotein (AFP) level >200 ng/mL. All cases were re-staged according to the American Joint Committee on Cancer (AJCC) staging system (7th edition).

Each patient received a mandatory baseline examination of liver dynamic MRI and/or triphasic CT of the liver; complete blood study; liver function tests; hepatitis B and/or C antigens and viral titers; AFP level, and chest X-ray images. Prophylactic anti-retroviral therapy to all patients demonstrating positive hepatitis B surface antigen (HbsAg) and/or elevated hepatitis B viral (HBV) titers was prescribed from the initiation of SBRT to at least 6 months after treatment for the prevention of post-radiation therapy reactivation of HBV.^[10]

2.2. SBRT technique and dose

SBRT was performed using the CyberKnife, a robotic image-guided whole body radiosurgical system (Accuray Inc., Sunnyvale, CA) equipped with the synchrony system that is, a real-time respiratory tracking system for target volumes that move with respiration. Four gold fiducial markers were implanted percutaneously around the perimeter of the target volume using a sonographically-guided procedure 5 to 7 days before acquisition of the CT-scan used for planning. Thin-slice CT-scan and MRI were performed with a slice thickness of 1 mm, and the results

were transferred to the CyberKnife planning system. Tumor contouring was performed on the planning CT with contrast. All patients were positioned on individually shaped vacuum pillows and wore a treatment jacket on which the optical markers were fixed. Any displacement of the patient during treatment was detected by either internal or external fiducial markers with sub-millimeter accuracy.

The gross tumor volume (GTV) included the visible tumor in the portal vein on CT scan or MRI with contrast. No clinical target volume was further added. The gross tumor volume was directly expanded 5 mm in all directions to create the planning target volume (PTV). Modification of PTV was performed in cases where it extended into the dose-limiting organs, excluding the normal liver. The prescription dose ranged from 26 to 40 Gy to the PTV and was given in 3 to 5 fractions over 5 to 10 days. Treatment was delivered with the real-time tracking system using the fiducial as a guide, and planning was performed with the MultiPlan CyberKnife Treatment Planning System version 2.10 (Accuray Inc, Sunnyvale CA, USA).

2.3. Follow-up, response, and toxicity assessment

After completion of the treatment, vital status evaluation, physical examination, liver function test, and complete blood tests were performed to assess acute toxicity. The test was performed every 1 to 2 weeks in the first month and every 3 months thereafter. Imaging studies using 4-phase CT-scan or dynamic MRI of the liver and AFP were performed every 1 to 2 months and subsequently every 3- to 4-months after treatment. Toxicity grading was performed according to the Common Toxicity Criteria Adverse Events version 4.0. Acute toxicities were defined as adverse events that occurred within 3 months of SBRT, and late toxicities were defined that occurred after 3 months. Radiation-induced liver disease (RILD) was defined as either classic or non-classic RILD. Classification was defined according to Pan et al^[11] with typical occurrence within 4 months of irradiation completion or a decline in liver function. The diagnoses of both classifications of RILD could only be made in the absence of evidence of tumor progression. Toxicity grading was recorded based on the worst toxicity recorded.

The modified response evaluation criteria in solid tumors was used to evaluate the treatment responses.^[12] Macrovascular thrombosis responses were evaluated using the criteria proposed by Yoon et al^[13] in-field failure was defined as the development of new lesions or an increase in tumor size within the PTV. Intrahepatic out-field failure was defined as the development of new lesions in the liver outside the PTV. Extrahepatic failure was defined as recurrence or development of new lesions beyond the liver.

2.4. Statistical analysis

All analyses used the statistical software, SAS 9.4 (SAS Institute Inc., Cary, NC). The baseline information was presented using description statistics for categorical variables as frequency as percentage and the continuous variables as mean \pm SD or median with interquartile. The risk of OS and progression free survival (PFS) were estimated using a Cox regression model. The multivariable model was established using the significant variable ($P < .05$) among the univariate hazard ratio. Kaplan–Meier analysis was used to plot the trend of OS, PFS. Significance was set at $P < .05$.

3. Results

3.1. Patient and treatment characteristics

Between 2009 and 2017, a total of 139 BCLC stage C HCC patients were included in the analysis. Patient and treatment characteristics are summarized in Table 1. The median age of the patients was 70 years (range, 65–72 years), 100 patients (71.9%) were male, and the majority of the underlying liver disease was related to HBV infection (63 patients, 45.3%) follow by hepatitis C virus infection (52 patients, 36.9%). Other predominant features include CTP class A liver function (122 patients, 87.8%), 7th AJCC stage of IIIB (52 patients, 37.4%) and IV (29 patients, 20.6%), The tumor median diameter was 5.3 cm (range 3.4–8.6 cm), more than half of the tumors were greater than 4 cm (>4–<10 cm, 55 patients, 38.6% and ≥ 10 cm, 28 patients, 19.9%), and 57 patients (41.0%) have demonstrated macrovascular involvement. The median prescribed SBRT dose was 40 (IQR, 39–40) Gy in 3 to 5 fractions. The most common regimen was 40 Gy in 5 fractions (78 patients, 56.1%) while the median prescribed biological effective dose and equivalent dose (2Gy) were 72 (72–85) Gy and 60 (60–71) Gy, respectively. Sorafenib was given to 36 Stage IIIB to IV patients, 12 patients received sorafenib prior the start of SBRT, while 24 patients received sorafenib sequentially after SBRT.

3.2. Treatment outcomes

The median follow-up of all patients was 12.83 months (range: 1.74–107 months). The best primary tumor responses were complete response (CR) in 51 patients (36.2%), partial response (PR) in 63 patients (45.3%), stable disease in 20 patients (14.4%), and disease progression (DP) in 5 patients (3.6%). (Table 2) Intrahepatic out-field failure was the main cause of treatment failure comprising 54 patients (42.9%), followed by in-field failure in 20 patients (14.89%), and extrahepatic failure in 16 patients (12.7%). Simultaneous appearance of each pattern of failure was observed in 16 patients (12.7%) (Fig. 1). The 1 to 2 year in-field control rate was 85.1%.

At the time of analysis, 31 (22.3%) patients remained alive while 108 (77.6%) patients had died. The median OSR was 15.44 months (range 1.56–107.4 months) and the 1-, 3-, and 5-year OSR were 56%, 28%, and 20%, respectively. The median PFSR was 6 months, and the 1-, 3-, and 5-year PFSRs were 25%, 14%, and 10%, respectively (Table 3, Figs. 2A and 2B).

The results of the univariate and multivariate analysis in all patients for prediction of OS are summarized in Table 4. In univariate analyses, several factors were significantly associated with OS, including CTP score (A vs B), AJCC stage (I vs II, III, IV), number of tumor treated (1 vs ≥5), macrovascular invasion (no vs yes), radiation dose (lower dose vs higher dose), biological effective dose (<72 vs 89 Gy), tumor response (CR vs PR, stable, DP), and pattern of failure. However, multivariate analyses revealed that OS was independently associated with the CTP score, stage, macrovascular invasion, and tumor response after SBRT. Patients who had better responses to SBRT had a significantly longer survival and PFSR compared to those who did not respond. For CR patients, the mean OSR was 28.75 months, the 1-, 3-, and 5-year OSRs were 80.39%, 43.14%, and 21.56%, respectively. The mean for PFSR was 6.13 months, and the 1-, 3-, and 5-year PFSRs were 50.98%, 25.49%, and 21.57%, respectively. (*P* < .05). DP patients had the worse OSR and PFSR, among the 5 patients with DP, 1 patient survived 18.82 months, others survived less than 6.89 months (Table 2, Fig. 3A and 3B)

Table 1
Patient characteristic (n = 139).

	Frequency	%
Gender		
Male	100	71.9
Female	39	27.7
Age		
Median (IQR)	70 (65–72)	
≤ 49 yrs old	14	10
50–60 yrs old	12	8.6
>60 yrs old	113	81.3
ECOG		
0	24	17
1	97	69.8
2	18	12.8
Child Pugh score		
A	122	87.8
B	17	12.1
Etiology		
Hepatitis B	63	45.3
Hepatitis C	52	36.9
Non B non C hepatitis	16	11.5
Hepatitis B+C	7	5
Alcoholic	1	0.7
TNM		
T		
T1	26	18.4
T2	24	17
T3a	29	20.8
T3b	55	39.6
T3c	0	0
T4	5	3.5
N		
NO	124	89.2
N1	15	10.6
M		
M0	125	88.7
M1	16	11.3
AJCC Stage		
I	21	14.9
II	19	13.5
IIIA	18	12.9
IIIB	52	37.4
IV	29	20.6
Tumor number		
1	85	61.1
2	32	22.7
3	19	13.6
5	3	2.1
Tumor size		
Median (IQR)	5.30 (3.40–8.57)	
≤4cm	56	40.3
>4–<10 cm	55	38.6
≥10 cm	28	19.9
Macrovascular invasion		
No	82	59
Yes	57	41
AFP		
≤ 20	45	32.3
>20–400	36	25.5
>400–1000	16	11.3
>1000	42	29.8
Radiation dose		
Median (IQR)	40 (39–40)	
26–36	18	12.8
39	32	22.7
40	78	56.1
45	11	7.8
BED 10 Gy		
Median (IQR)	72 (72–85)	
<72 Gy	12	8.5
72–88 Gy	83	59.71
89 Gy	44	31.2
Nexavar therapy		
Prior SBRT		
No	127	91.4
Yes	12	8.5
Post SBRT		
No	115	82.7
Yes	24	17

AFP = alpha fetoprotein, AJCC = American Joint Committee on Cancer, BED = biological effective dose, ECOG = Eastern cooperative oncology group, SBRT = stereotactic body radiation therapy.

Table 2
Overall survival of tumor response (mRECIST).

Status	Frequency		1-yr OSR		3-yrs OSR		5-yrs OSR		P-value
	n	%	n	%	n	%	n	%	
Complete Response	51	36.2	41	80.4	22	43.1	11	21.6	<.0001
Partial Response	63	45.3	20	31.7	5	7.9	4	6.3	
Stable	20	14.4	10	50	3	1.5	0	0	
Disease progression	5	3.6	1	20	0	0	0	0	

mRECIST = modified response evaluation criteria in solid tumor, OSR = overall survival rate.

3.3. Toxicity

The acute toxicities are listed in Table 5. SBRT was generally tolerable in this group of patients. Grade 1 to 2 fatigue was the most common sequelae and developed in 66.9% of the patients followed by nausea 23% and abdominal pain 16%. Other common toxicities included liver enzyme alteration especially SGOT (86.7%) and SGPT (47.5%), and thrombocytopenia, which was found in 108 patients (77.7%). However, with exception of 1 patient, these toxicities were mostly transient and tended to recover to their previous levels 2 to 4 weeks later. Grade 1 to 2 diarrhea in 5 patients (3.6%) and dermatitis in 10 patients (7.2%) were commonly seen in patients (24 patients) who received sequential sorafenib therapy. The toxicities tended to be relieved after stopping or tapering the dose of sorafenib.

A total of 11 patients developed ≥ grade 3 liver dysfunction within 3 months of SBRT. Two of which were due to DP and 9 developed non-classic RILD. No classic RILD was observed. Most patients with RILD recovered within 3 months of supportive treatment, although 1 patient developed fatal non-

classic RILD. The fatal case was a 54-year-old, male, with T3bN0M0, Stage IIIB HCC, HBV liver cirrhosis, CTP score A, who underwent SBRT without prophylactic anti-HBV therapy. A dose of 40 Gy was delivered in 5 fractions to right liver tumor and the right portal vein tumor thrombosis. A week after completion of treatment, he exhibited CTP score deterioration (from A6 to B10) and progressive elevation of serum transaminase levels. Furthermore, his HBV DNA levels markedly increase from 1,560,000 to 1,610,000,000 copies/mL 3 weeks after SBRT. Follow-up MRI of the liver showed partial regression of previously treated liver tumor and portal vein tumor thrombosis, with no evidence of new lesions, this finding suggests the HBV reactivation rather than DP was the main reason leading to liver failure. Supportive treatment was given but the patient eventually died from liver decompensation 4 weeks after treatment.

4. Discussion

Previous prospective and retrospective studies have shown excellent results of SBRT on small and early stage HCC,¹⁴

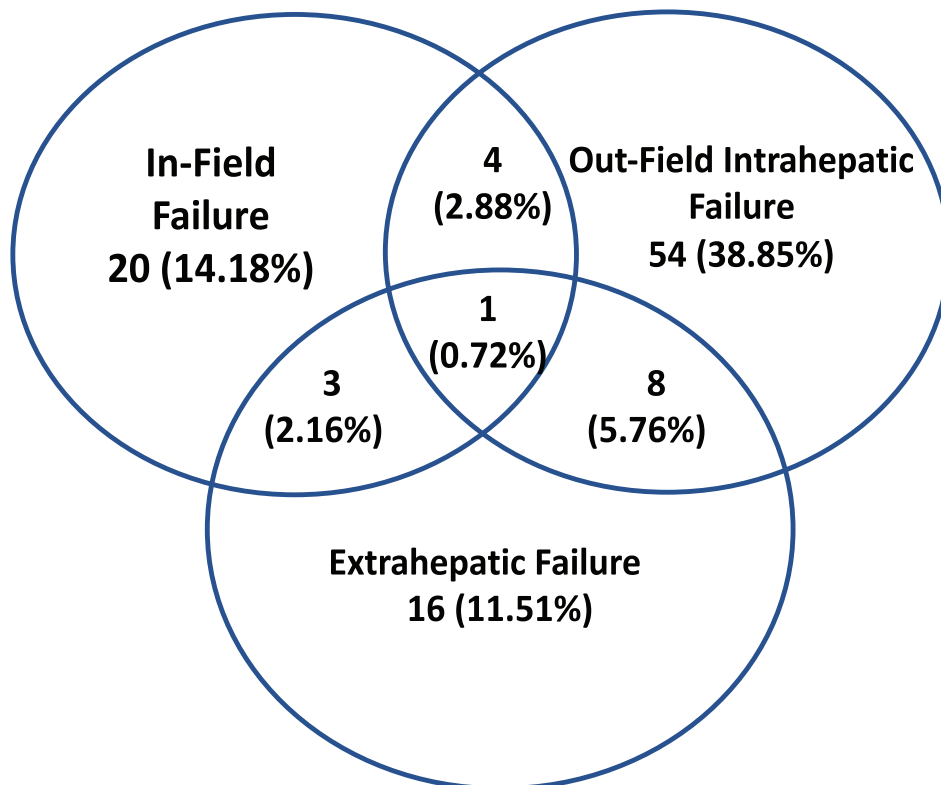


Figure 1. Failure Pattern of Barcelona Clinic Liver Cancer-C hepatocellular carcinoma after stereotactic body radiation therapy.

Table 3		
Summary of Efficacy.		
Median survival time	Overall survival rate 15.44 mo	Progression-free survival rate 6.00 mo
1-yr	56%	35%
2-yr	34%	22%
3-yr	28%	14%
4-yr	22%	11%
5-yr.	20%	10%

*restricted mean.

however, until now there was limited data of the use of SBRT on BCLC stage C HCC. As BCLC-C is a heterogenous population with various adverse features and a dismal prognosis, delivering high doses to this group of patients is often challenging as higher mean radiation doses to the liver might compromise the liver function and increase the risk for liver failure. Therefore, at present there was no optimal radiation dose for SBRT on this group of patients. In our study, we individualized our prescribe dose depending on the status of liver function, tumor volume and remaining liver normal volume available. The median radiation dose given was 40 Gy range from 26 to 45 Gy. Patients tolerated the whole SBRT treatment with minimal toxicity. At present, sorafenib, a multi-tyrosine kinase inhibitor is the standard therapy for patients with BCLC stage C HCC, however, the survival is modest and the tumor response is unsatisfactory.

Many ongoing research assessing the benefit of several other new tyrosine kinase-inhibiting agents (sunitinib, linifanib, levatinib) use as a first-line setting, either alone or in combination with sorafenib in Phase 3 trials did not demonstrated an improvement in survival over sorafenib. Options for patients who progress on sorafenib are limited^[15]; although recent data from the RESORCE Phase 3 trial indicated that regorafenib was efficacious for HCC patients who progressed on sorafenib, with a median OS of 10.6 and PFS of 3.2 months.^[16] The results of the current study show the survival of the patients with BCLC stage C disease treated with SBRT was comparative and not inferior to either target therapy. Other new medications such as Nivolumab, an anti-PD-1 monoclonal antibody, have been approved by FDA for patients with advance HCC. Although Nivolumab has shown promising efficacy and safety in Phase 1 and 2 trials, the impact on survival outcome remains unsatisfactory.^[17]

Bujold et al reported one of the largest series of prospective studies of patients with locally advanced HCC treated with SBRT.^[7] A total of 102 patients were evaluated. BCLC-C patients comprised 65.7% and 66% were TNM stage III. The 1-year local control rate was 87% (95% CI, 78.5 to 93%), and the median OSR was 17.0 months (95%CI, 10.4–21.3 months). The 1-year OSR was 55% and the 2-year OSR was 34%. Although the current study mainly comprised BCLC stage C HCC patients, we achieved results that were comparable to the above study, in that our 1- to 2-year local control rate was 85.11%, median OSR was 15.44 months, and the 1-, 2-, and 3-year OSR were 56%, 34%, and 28%, respectively. However, both studies compare favorably with the best supportive care, and even with sorafenib, the only other potential therapy available for these patients.

Consistent with other studies, CTP score, advance stage (Stage III and IV), macrovascular invasion, and tumor response were the major independent factors affecting OS after SBRT. This study demonstrates that advanced HCC patients with a large tumor burden and portal vein tumor thrombosis show a poorer outcome. This coincides with a recent study by Huang et al,^[18] in which 246 patients with nonmetastatic BCLC stage C patients was prospectively studied using a predictive nomogram. A median survival rate of 13.5 months, and a 1- and 2-year OSRs of 55% and 32.9%, respectively were achieved. Moreover, the number of tumors, largest tumor size, macrovascular invasion, CTP score, and biologically effective dose were significantly associated with OS ($P < .05$). Presence of an underlying liver condition was another major factor affecting OS, In our previous study.^[19] A total of 115 with unresectable HCC treated with CyberKnife SBRT were retrospectively analyzed. The results showed that the 1- and 2-year survival rate for HCC with CTP score A were 68.3% and 47.1%, while in patients with CTP score B, the survival rate were only 27.3% and 12.5%, respectively. Another study by Bae et al; demonstrated that the CTP score was the most significant prognostic factor among BCLC stage C patients after SBRT, with 1-year survival rates of 69% and 0% for CTP score A and B, respectively.^[20] Therefore, based on this clinical evidence, caution should be exerted when selecting SBRT for BCLC stage C patients with CTP score B liver function.

It was interesting to find that patients who achieved initial in-field CR maintained this status throughout follow-up, as this suggests that initial tumor response to SBRT is an important indicator for OSR and PFS (Figs. 1 and 2). Among the patients

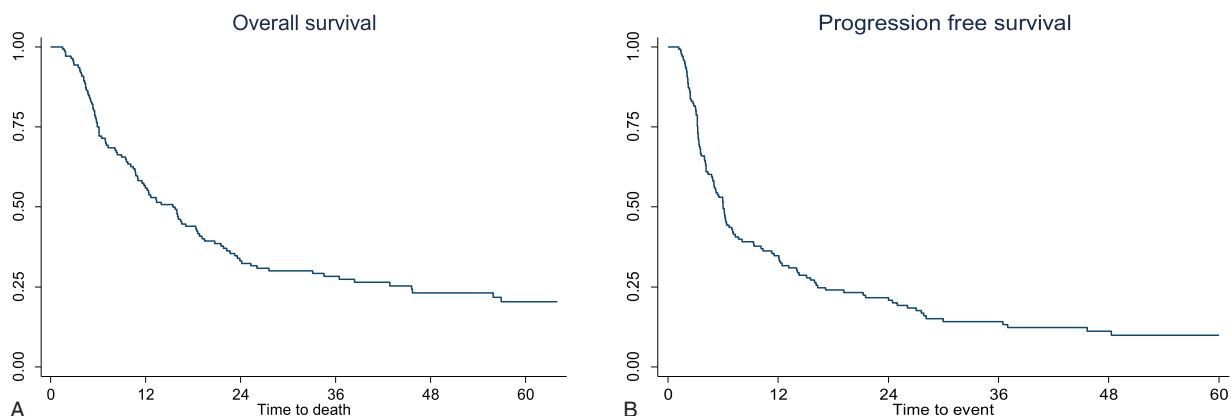


Figure 2. A and B. Kaplan–Meier of overall survival (OS) and progression-free survival. The 1-, 3- and 5-year OS rates were 56%, 28% and 20%, respectively. The median OS was 15.44 months. The 1-, 3- and 5-year PFS rates were 35%, 14% and 10%, respectively. And the median PFS was 6 months.

Table 4**Univariate and multivariate analysis for overall survival.**

Variables	Univariate HR (95% C.I.)	P-value	Multivariable HR (95% C.I.)	P-value
Gender				
Male	1.00 (ref.)			
Female	0.97 (0.63–1.48)	.8694		
Age				
≤ 49 yr old	1.00 (ref.)			
50–60 yr old	0.59 (0.26–1.37)	.2199		
>60 yr old	0.56 (0.30–1.06)	.0730		
ECOG				
0	1.00 (ref.)			
1	1.27 (0.76–2.13)	.3627		
2	1.27 (0.61–2.65)	.5179		
Child Pugh score				
A	1.00 (ref.)		1.00 (ref.)	
B	2.70 (1.55–4.72)	.0005	2.39 (1.27–4.50)	.0072
Etiology				
Hepatitis B	1.85 (0.91–3.76)	.0912		
Hepatitis C	1.69 (0.82–3.49)	.1560		
Non B non C hepatitis	1.00 (ref.)			
Hepatitis B+C	2.60 (0.92–7.32)	.0708		
Alcoholic				
TNM				
T				
T1	1.00 (ref.)			
T2	1.88 (0.93–3.80)	.0804		
T3a	2.44 (1.24–4.78)	.0094		
T3b	2.81 (1.51–5.23)	.0011		
T4	0.29 (0.04–2.21)	.2320		
N				
N0	1.00 (ref.)			
N1	1.01 (0.54–1.89)	.9713		
M				
M0	1.00 (ref.)			
M1	1.46 (0.83–2.56)	.1914		
AJCC Stage (7 th)				
I	1.00 (ref.)		1.00 (ref.)	
II	2.41 (1.06–5.52)	.0367	4.02 (1.65–9.82)	.0022
IIIA	2.46 (1.07–5.63)	.0335	4.29 (1.72–10.71)	.0018
IIIB	3.44 (1.66–7.12)	.0009	2.09 (0.90–4.87)	.0882
IV	2.97 (1.38–6.39)	.0054	4.62 (2.01–10.62)	.0003
Tumor number				
1	1.00 (ref.)			
2	1.10 (0.69–1.77)	.6822		
3	0.96 (0.55–1.70)	.8970		
5	5.66 (1.73–18.50)	.0041		
Tumor size				
≤4cm	1.00 (ref.)			
>4–<10 cm	1.27 (0.81–1.96)	.2957		
≥10 cm	1.50 (0.90–2.51)	.1226		
Macrovascular invasion				
No	1.00 (ref.)		1.00 (ref.)	
Yes	2.25 (1.52–3.33)	<.0001	2.14 (1.28–3.57)	.0035
AFP				
≤ 20	1.00 (ref.)			
>20–400	1.47 (0.88–2.46)	.1403		
>400–1000	1.70 (0.90–3.21)	.1035		
>1000	1.15 (0.70–1.91)	.5785		
Radiation dose				
26–36	1.00 (ref.)			
39	0.55 (0.28–1.05)	.0695		
40	0.70 (0.40–1.23)	.2153		
45	0.37 (0.14–0.96)	.0403		
BED 10 Gy				

(continued)

Table 4
(continued).

Variables	Univariate HR (95% C.I.)	P-value	Multivariable HR (95% C.I.)	P-value
<72 Gy	1.00 (ref.)			
72–88 Gy	0.56 (0.29–1.11)	.0964		
89 Gy	0.42 (0.20–0.86)	.0182		
Sorafenib therapy				
Prior SBRT				
No	1.00 (ref.)			
Yes	0.92 (0.43–1.98)	.8270		
Post SBRT				
No	1.00 (ref.)			
Yes	1.36 (0.83–2.22)	.2179		
Tumor response				
Complete response	1.00 (ref.)		1.00 (ref.)	
Partial response	3.40 (2.11–5.48)	<.0001	4.72 (2.81–7.94)	<.0001
Stable	2.94 (1.61–5.39)	.0005	4.14 (2.18–7.86)	<.0001
Disease progression	7.80 (2.95–20.65)	<.0001	21.20 (7.17–62.65)	<.0001
Failure Pattern				
None	1.00 (ref.)			
In-field failure	3.07 (1.43–6.55)	.0038		
Out-field intrahepatic	2.14 (1.24–3.70)	.0064		
Extra-hepatic	3.71 (1.87–7.38)	.0002		
In-field+Out-field	5.21 (1.74–15.62)	.0032		
In-field+Extrahep.	1.84 (0.43–7.95)	.4143		
Out-field+Extrahep.	6.73 (2.87–15.81)	<.0001		
In-field+Out-field+Extrahep	4.13 (0.54–31.33)	.1704		

*The multivariable model was established using the significant variable ($P < .05$) among univariate HR with the stepwise approach.

who achieved CR, 66.7% comprised of tumor size ≤ 4 cm, while the PR group, 76.2% had a tumor size > 4 cm to > 10 cm. Stage III and IV patient comprised 64.70% in CR group and 76.19% in the PR group. In a study by Yoon SM et al, a total of 93 HCC patients treated with SBRT were retrospectively analyzed. Median size of tumors was 2 cm (range: 1–6 cm). OSR at 1- and 3-years were 86.0% and 53.8%, respectively. Local recurrence-free survival rate was 92.1% at 3 years. Most local failures were found in > 3 cm tumor size, and local control rate at 3 years was 76.3% in patients with HCC > 3 cm, 93.3% in patients with tumors between 2.1 and 3 cm, and 100% in patients

with tumors ≤ 2 cm, respectively. The following results showed SBRT was effective in local control of small HCC.^[21] Furthermore, Huang et al,^[18] demonstrated that advanced HCC patients with a high tumor burden show a poor outcome after SBRT, in the larger tumor size and number were associated with worse OS. Reflecting intrahepatic disease tumor burden was an independent factor of OS in advanced HCC patients treated with SBRT. Therefore, we suggest early tumor stages (Stage I and II) and small tumor size are the best candidates for SBRT.

Intrahepatic out-field failure was the main pattern of disease failure in this study. As HCC is a multicentric disease by nature,

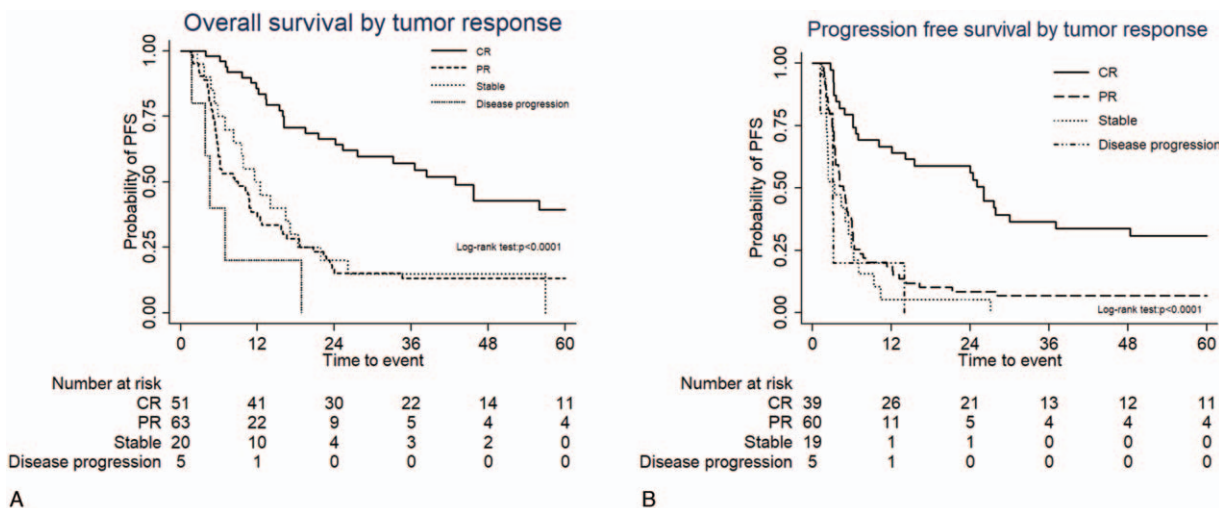


Figure 3. A and B. Kaplan–Meier of overall survival and progression-free survival according to tumor response.

Table 5
Toxicity CTCAE V4.

Toxicity	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Fatigue	83	59.7	10	7.2	0	0	0	0	0	0	93	66.9
Nausea	30	21.5	2	1.4	0	0	0	0	0	0	32	23.0
Vomiting	8	5.7	1	0.7	0	0	0	0	0	0	9	6.5
Abdominal pain	20	14.3	0	0	0	0	0	0	0	0	20	14.4
Diarrhea	2	2.2	2	1.4	0	0	0	0	0	0	5	3.6
R't chest pain	16	11.5	1	0.7	0	0	0	0	0	0	17	12.2
Dermatitis/rash	6	4.3	2	1.4	1	0.7	1	0.7	0	0	10	7.2
Biochemical changes												
SGOT	105	75.5	8	5.7	6	4.3	0	0	1	0.7	120	86.3
SGPT	53	38.1	7	5.0	5	3.6	0	0	1	0.7	66	47.5
T-bilirubin	16	11.5	9	6.5	4	2.9	0	0	1	0.7	30	21.6
Albumin	48	34.5	13	9.3	1	0.7	0	0	0	0	62	44.6
Hematologic changes												
Thrombocytopenia	61	43.9	32	23.0	15	10.8	0	0	0	0	108	77.7
Leukopenia	7	5	10	7.2	3	2.1	0	0	0	0	20	14.4

*CTCAE = Common Terminology Criteria for Adverse Events Version-4; SGOT = aspartate aminotransferase; SGPT = alanine aminotransferase; T-Bilirubin = Total-Bilirubin.

and disease outside the treatment field remain the dominant pattern of relapse after SBRT. The implication is that close monitoring of target lesions and metastases is essential and the combination of SBRT with other treatment modalities such as transcatheter arterial chemoembolization, radiofrequency ablation, and/or systemic therapy may potentially increase the OSR and local control.

The toxicity profile in the present study was acceptable and a similar profile has been reported in previous studies.^[20,22,23,24] In our study, grade ≥ 3 toxicities were observed in 11 patients (7.9%), and 9 (6.5%) patients developed non-classic RILD within 3 months of SBRT. Unlike previous studies, that stated HBV status and CTP score B liver cirrhosis have a greater chance of RILD,^[10] in our 9 cases of RILD, the underlying etiology was hepatitis C (HCV) in 6 patients and 3 patients were HBV respectively. All 9 patients were CTP score A before SBRT. Among the 11 cases developing grade ≥ 3 toxicities, 10 patients had a tumor size larger than 6 cm, which resulted in a limited amount of normal liver being available, and increased the risk of liver toxicity and DP. However, all RILD patients recover within 1 month, with the exception of one who eventually succumbed to uncontrolled RILD due to reactivation of HBV. These findings highlight the importance of strict patient selection and personalized treatment in cases of HCC.

The major limitation of this study was the single-institutional retrospective analysis. Therefore, patients with a better prognosis among BCLC-C patients might be selected previously before SBRT. However, despite the limitations, the results warrant a prospective trial.

5. Conclusion

In conclusion, SBRT for BCLC stage C patients showed 1-, 3-, 5-year OSRs of 56%, 28%, and 20%, respectively. SBRT is a viable treatment option for BCLC stage C patients, especially for those with smaller tumors and with stage I and II. The occurrence of treatment related toxicity requiring prompt therapeutic response was moderate. Finally, CTP score, macrovascular invasion, advance stage (III-IV) were independent predictors of OSR and may therefore be useful when selecting patients to undergo SBRT for HCC.

Author contributions

JQ reviewed, analyzed, interpreted the data, and wrote the manuscript. CHL, LCL provided significant intellectual contribution and reviewed the manuscript. CHH performed statistical analysis. All authors gave the final approval of the manuscript's submission for publication

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