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Stereotactic body radiotherapy versus lenvatinib for hepatocellular carcinoma with portal vein tumor thrombosis: a propensity matching score analysis

Xiaoquan ji[1,2†], Aimin Zhang[1†], Xuezhang Duan[1,2*] and Quan Wang[1*]

Abstract

Background and objectives The purpose of this study was to investigate the survival benefit of Stereotactic Body Radiotherapy (SBRT) versus lenvatinib as first-line therapy in the treatment of hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT).

Materials and methods 147 HCC patients with PVTT were included in this retrospective study, 70 were treated with SBRT and 77 of were treated with lenvatinib. Propensity score matching (PSM) analysis was employed to balance the differences in baseline characteristics between the two groups. Overall survival (OS), progression-free survival (PFS) and objective response rate (ORR) were compared between the two groups. In addition, the safety of patients in both groups was also evaluated.

Results After PSM, 38 patients were matched in each of the two groups. The median OS was 14.5 (95% CI: 10.1–18.9) and 11.1 (95% CI: 9.3–12.9) months in the SBRT and lenvatinib groups, respectively ($P=0.014$). The median PFS was 6.8 (95% CI: 5.1–8.5) and 5.0 (95% CI: 3.0–7.0) months, respectively ($P=0.010$). The 1-, 2-years OS rates in the two groups were 65.8% vs. 39.5% and 31.6% vs. 10.5%, respectively. The 6-, 12-months PFS rates in the two groups were 57.9% vs. 44.7% and 28.9% vs. 10.5%, respectively. In addition, the SBRT group had a better ORR than the lenvatinib group (52.6% vs. 23.7%, $P=0.009$). Patients with good response to SBRT had better survival. Cox proportional hazard model showed that SBRT was an important prognostic factor for OS and PFS. The incidence of hypertension (34.2% vs. 0%) was higher in the LEN group, however, both treatment modalities were well tolerated in the two groups of patients.

Conclusion In HCC patients with PVTT, SBRT had a better survival benefit than Lenvatinib treatment as first-line therapy.

Keywords Hepatocellular carcinoma, Portal vein tumor thrombosis, Stereotactic body radiotherapy, Lenvatinib

†Xiaoquan ji and Aimin Zhang contributed equally to this work.

*Correspondence:
Xuezhang Duan
duanxuezhang2006@163.com

Quan Wang
quanwang1987@163.com
[1]Department of Radiation Oncology, Senior Department of Oncology, the Fifth Medical Center of PLA General Hospital, Beijing, China
[2]The Second School of Clinical Medicine, Southern Medical University, Guangzhou, China

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide and the third leading cause of cancer deaths [1]. Approximately 10–40% of patients with HCC have portal vein tumor thrombosis (PVTT) at diagnosis, and was considered to be in advanced stage leading to a poor prognosis, with a median survival of only 2.7–4.0 months [2, 3].

However, there is currently no widely-accepted consensus for the management of HCC complicated with PVTT. European Association for the Study of the Liver (EASL) guidelines, which is based on Barcelona Clinic Liver Cancer (BCLC) staging system, recommends systemic therapy as the only evidence-based treatment option for HCC patients with PVTT [4]. In Chinese and Korean guidelines, transarterial chemoembolization (TACE), surgery, systemic therapy or radiotherapy (RT) are all recommended to treat this patient group [5, 6].

With the rapid development in radiotherapy technology, stereotactic body radiotherapy (SBRT) has emerged as a feasible standalone or adjunct management for HCC [7]. SBRT maximizes treatment efficacy by focusing high doses precisely on the tumor in a short period of time [7, 8], achieving results comparable to those of hepatectomy, radiofrequency ablation, and TACE in early-stage HCC [9–11]. Meanwhile, the value of SBRT in the treatment of HCC with PVTT has also begun to attract attention. A multicenter retrospective trial investigating the efficacy of SBRT in patients with recurrent HCC combined with extensive PVTT showed a 100% clinical benefit rate and 38.7% 1-year OS rate, subgroup analysis showed that SBRT was effective in any location of the tumor thrombus [12]. Furthermore, a mete-analysis showed that SBRT had an effective rate of 70.7% in the treatment of PVTT, which was much higher than that of other radiotherapy methods [13]. Although such findings clearly suggest the efficacy of RT in HCC with PVTT, comparative studies with systemic therapy have been limited.

For advanced HCC, Bettinger et al. [14] found that SBRT had a considerable survival benefit compared to sorafenib, extending median OS to 9.3 months. In a recent phase III noninferiority trial, lenvatinib was found to be noninferior to sorafenib in overall survival (OS) in untreated advanced HCC [15]. Therefore, lenvatinib was established as an alternative to sorafenib as first-line treatment option in patients with advanced HCC [16]. However, it is unclear whether SBRT has better survival benefit than lenvatinib in treating HCC patients complicated by PVTT. Therefore, the purpose of this study is to compare the survival benefit of SBRT versus lenvatinib as first-line therapy in unresectable HCC with PVTT.

Materials and methods

Study design and patient population

Patients with unresectable HCC diagnosed from August 2014 to August 2021 were included in this retrospective study. The eligibility criteria were: (1) Diagnosed with HCC by radiological or histological, (2) presence of PVTT and PVTT was identified by the existence of a low attenuation intraluminal filling defect during the portal phase and a filling defect enhancement during the arterial phase, (3) at least one measurable lesion ≥ 1 cm in solid liver lesion or vascular tumor thrombosis > 1 cm, (4) Child-Pugh classification A and B, (5) Eastern Cooperative Oncology Group performance status score (ECOG PS) 0–1. Exclusion criteria were as follows: (1) concomitant with other malignancy, (2) presence of extrahepatic metastases, (3) previously received any systemic therapy, (4) lost to follow-up. We classified PVTT into five types based on the type of PVTT classification proposed by the Japanese Hepatocellular Carcinoma Research Group [17], based on the severity of tumor thrombosis and anatomical structure: Vp0, no PVTT; Vp1, PVTT distal to but not involved in second-order branches of the PV; Vp2, PVTT invasive to second-order branches; Vp3, PVTT present in first-order branches; Vp4, PVTT extends into the main portal trunk and/or contralateral portal vein branches. Patients in this study who were treated with SBRT had a contraindication to, or declined upfront sorafenib and lenvatinib. The study protocol complied with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by our medical center's Human Research Committee.

Treatment

After locating the treatment location using computed tomography (CT) simulation, an oncologist contoured the gross tumor volume (GTV) and outlined organs at risk (OARs). The GTV was conventionally defined as the total volume of PVTT and parenchymal HCC. However, in patients with large tumors and severe liver cirrhosis or numerous intrahepatic metastases, only the PVTT was delineated as the GTV. The planning target volume (PTV) expanded 3–5 mm of the GTV and avoided the OARs. SBRT was delivered using the CyberKnife® G4 image-guided robotic stereotactic radiosurgery system (Accuray inc., Sunnyvale, CA, USA), after implanting 2 to 4 fiducial markers in each patient. The prescribed doses were 45–55 Gy/5–10 fx. The plans were calculated using CyberKnife® Multiplan® Treatment Planning System software (version 4.0.2), and the tolerance doses of OARs were determined based on the American Association of Physicists in Medicine (AAPM) TG-101 report [18]. In our multidisciplinary management for HCC patients, SBRT is recommended for HCC patients with PVTT and those with contraindication for

transarterial chemoembolization (TACE). If the patient's lesion showed rich blood supply on enhanced imaging and no TACE contraindication, they were treated with transcatheter arterial embolization between the fiducial marker implantation and SBRT treatment.

For patients with Child-Pugh classification A, the regular starting dose of lenvatinib is 12 mg/d for patients weighing > 60 kg and 8 mg/d for patients weighing ≤ 60 kg. For patients with Child-Pugh classification B, the regular starting dose is 8 mg/d, regardless of weight [19, 20]. The dose was reduced (to 8 mg/day, 4 mg/day, or 4 mg every other day) because of lenvatinib related toxicities until the adverse events (AEs) were alleviated or eliminated. If the AEs continued even after dose adjustment, lenvatinib treatment was interrupted until it alleviated or disappeared.

Evaluation

Tumor response was assessed using the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria [21, 22]. The response of PVTT was evaluated by dynamic contrast enhanced CT and/or magnetic resonance imaging (MRI). OS was defined as the time from the date of initiation of SBRT or lenvatinib to the date of death from any cause or the date of last follow-up (Sep 30, 2022). progression-free survival (PFS) was defined as the time from the date of initiation of SBRT or lenvatinib to the date of first detection of tumor progression or death from any cause, based on the mRECIST. Objective response rate (ORR) = complete response (CR) + partial response (PR), and disease control rate (DCR) = CR + PR + stable disease (SD).

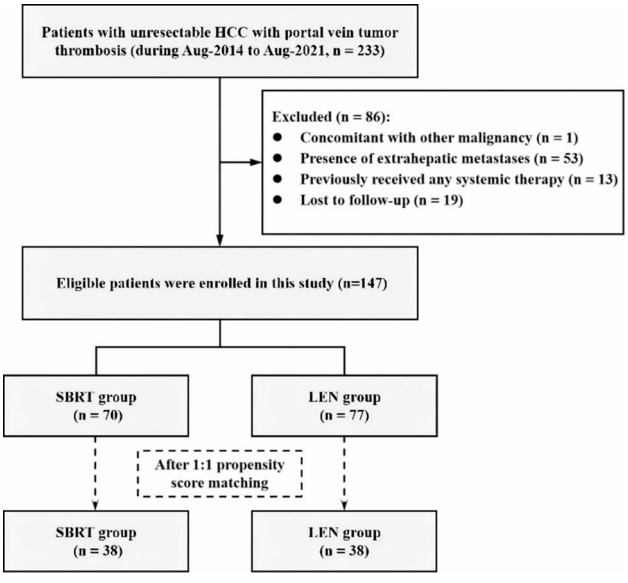

Fig. 1 Flow chart of the study design. SBRT, stereotactic body radiotherapy. PSM, propensity score matching

Follow up and safety evaluation

The time of first follow-up was 4–8 weeks after treatment and every 2–3 months thereafter until Sep 30, 2022, or the patient died. Follow-up tests included blood routine, liver function, coagulation function, serum tumor markers, contrast-enhanced CT or MRI of the upper abdomen, and lung CT. The toxicity reaction was evaluated according to the Common Terminology Criteria for Adverse Events version 5.0 [23]. In addition, radiation-induced liver disease (RILD) diagnostic criteria was used in the SBRT groups [24, 25].

Statistical analysis

All statistical analyses were performed using SPSS software (Version 26.0; IBM Corp., Armonk, NY) and R version 4.1.3 (Stanford University, CA, USA). The propensity score model included age, sex, etiology, cirrhosis, Child–Pugh classification, number of tumors, tumor size (defined as the largest tumor's diameter), alpha-fetoprotein (AFP), ECOG PS, PVTT, grade albumin-bilirubin grade (ALBI), platelet counts (PLT), white blood cell counts (WBC) and previous treatments. The cases were matched using 1:1 nearest neighbor matching. The standardized mean difference (SMD) was used to measure the covariate balance. An independent t-test was used to evaluate differences between groups for numerical variables, while chi-square test or Fisher's exact test was used to examine differences between groups for categorical variables. The Kaplan-Meier technique was used to estimate survival rates. Univariate and multivariate analyses based on Cox regression models were applied to OS and PFS. The variables of the multivariate model included variables with a p-value < 0.1 in the univariate model analysis. A p-value < 0.05 was considered statistically significant. GraphPad 8.0 software is used to drawing figures.

Results

Overall, 147 eligible patients were included in the study. 70 patients were treated with SBRT (SBRT group) and 77 patients were treated with Lenvatinib (LEN group) (Fig. 1). The baseline characteristics of the SBRT group and the LEN group were shown in Table 1. Before PSM, the proportion of patients with adverse baseline characteristics was higher in the LEN group than in the SBRT group, including number of tumors > 3, maximum tumor diameter ≥ 10 cm, and PVTT of Vp3-4. However, more patients in the SBRT group received previous local treatments. After PSM, 38 patients were matched in each of the two groups. In the SBRT group, there are 11(28.9%) patients combined with transcatheter arterial embolization. The patient characteristics were well balanced in the matched cohort. The changes in SMD between the two

Table 1 Baseline characteristics of the study population

Parameter	Before PSM		P[a] value	SMD	After PSM		p[a] value	SMD
	SBRT group (*n* = 70)	LEN group (*n* = 77)			SBRT group (*n* = 38)	LEN group (*n* = 38)		
Gender, n (%)								
Male	58 (82.9)	68 (88.3)	0.345	0.169	32 (84.2)	32 (84.2)	1	0
Female	12 (17.1)	9 (11.7)			6 (15.8)	6 (15.8)		
Age, years, n (%)								
< 60 years	26 (37.1)	38 (49.4)	0.136	0.243	18 (47.4)	18 (47.4)	1	0
≥ 60 years	44 (62.9)	39 (50.6)			20 (52.6)	20 (52.6)		
Cirrhosis, n (%)								
Presence	69 (98.6)	77 (100)	0.476	0	38 (100)	38 (100)	1	0
Absence	1 (1.4)	0 (0)			0 (0)	0 (0)		
HBV infection, n (%)								
Yes	64 (91.4)	73 (94.8)	0.628	0.151	36 (94.7)	37 (94.7)	1	0
No	6 (8.6)	4 (5.2)			2 (5.3)	2 (5.3)		
Child-Pugh classification, n (%)								
A	64 (91.4)	65 (84.4)	0.195	-0.192	36 (94.7)	34 (89.5)	0.674	-0.169
B	6 (8.6)	12 (15.6)			2 (5.3)	4 (10.5)		
ECOG PS score, n (%)								
0	34 (48.6)	32 (41.6)	0.393	-0.141	18 (47.7)	18 (47.7)	1	0
1	36 (51.4)	45 (58.4)			20 (52.6)	20 (52.6)		
Number Of Tumors, n (%)								
≥ 3	19 (27.1)	40 (51.9)	**0.002**	0.493	13 (34.2)	13 (34.2)	1	0
< 3	51 (72.9)	37 (48.1)			25 (65.8)	25 (65.8)		
Tumor size, cm, n (%)								
< 5	12 (17.1)	16 (20.8)	**0.005**		8 (21.1)	10 (26.3)	0.79	
≥ 5 and < 10	48 (68.6)	34 (44.2)		-0.488	21 (55.3)	21 (55.3)		0
≥ 10	10 (14.3)	27 (35.1)		0.433	9 (23.7)	7 (18.4)		-0.134
PVTT, n (%)								
Vp1	4 (5.7)	6 (7.8)	**0.024**		2 (5.3)	3 (7.9)	0.939	
Vp2	43 (61.2)	28 (36.4)		-0.581	16 (42.1)	15 (39.5)		-0.053
Vp3	20 (28.6)	36 (46.8)		0.362	17 (44.7)	16 (42.1)		-0.053
Vp4	3 (4.3)	7 (9.1)		0.166	3 (7.9)	4 (10.5)		0.085
ALBI grade, n (%)								
1	20 (28.6)	21 (27.3)	0.861	-0.029	14 (36.8)	12 (31.6)	0.629	-0.112
2	50 (71.4)	56 (72.7)			24 (63.2)	26 (68.4)		
AFP, n (%)								
< 200 ng/mL	33 (47.1)	40 (51.9)	0.561	0.096	21 (55.3)	21 (55.3)	1	0
≥ 200 ng/mL	37 (52.9)	37 (48.1)			17 (44.7)	17 (44.7)		
PLT, n (%)								
$< 100 \times 10^9$/L	26 (37.1)	19 (24.7)	0.101	-0.287	9 (23.7)	9 (23.7)	1	0
$\geq 100 \times 10^9$/L	44 (65.9)	58 (75.3)			29 (76.3)	29 (76.3)		
WBC, n (%)								
$< 4 \times 10^9$/L	20 (28.6)	24 (31.2)	0.731	0.056	9 (23.7)	9 (23.7)	1	0
$\geq 4 \times 10^9$/L	50 (71.4)	53 (68.8)			29 (76.3)	29 (76.3)		
Previous treatment, n (%)								
Absence	50 (71.4)	68 (88.3)	**0.01**	-0.522	32 (84.2)	31 (81.6)	0.761	0.067
Presence								
Tace	9 (12.9)	3 (3.9)			3 (7.9)	3 (7.9)		
Ablation	7 (10.0)	2 (2.6)			2 (5.3)	1 (2.6)		
Argon–Helium cryosurgical	4 (5.7)	4 (5.2)			1 (2.6)	3 (7.9)		

HBV, hepatic B virus; HCV, hepatic C virus; ECOG, Eastern Cooperative Oncology Group; PS, performance status; PVTT, Portal Vein Tumor Thrombosis; ALBI, grade albumin-bilirubin grade; AFP, alpha-fetoprotein; PLT, platelet; WBC, white blood cell; TACE, transarterial chemoembolization; LEN, lenvatinib; SBRT, Stereotactic Body Radiotherapy

[a] Bold values indicate statistical significance

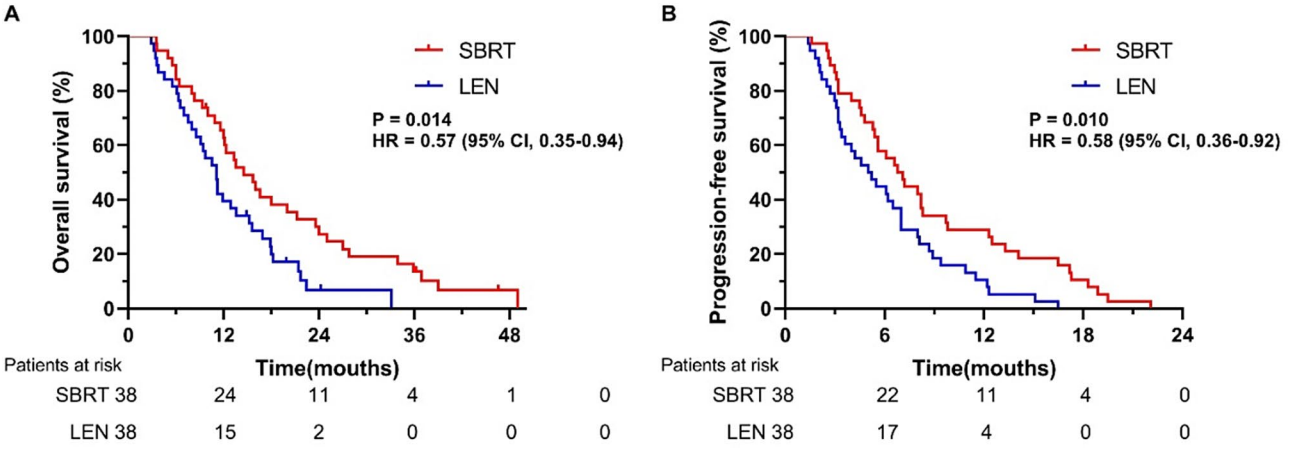

Fig. 2 Kaplan–Meier curves of **(A)** overall survival and **(B)** progression-free survival in patients in the SBRT and LEN groups after propensity score matching. LEN, lenvatinib; SBRT, Stereotactic Body Radiotherapy; CI, confident interval

Table 2 Best tumor response evaluated by mRECIST

mRECIST	SBRT group (*n* = 38)	LEN group (*n* = 38)	*P*[a] value
Complete response, n (%)	2 (5.3)	1 (2.6)	1
Partial response, n (%)	18 (47.4)	8 (21.1)	**0.016**
Stable disease, n (%)	12 (31.6)	17 (44.7)	0.238
Progressive disease, n (%)	6 (15.9)	12 (31.6)	0.106
ORR, n (%)	20 (52.6)	9 (23.7)	**0.009**
DCR, n (%)	32 (81.6)	26 (68.4)	0.106

mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate = complete response rate + partial response rate; DCR, disease control rate = complete response rate + partial response rate + stable disease rate

a. Bold values indicate statistical significance

groups before and after the PSM was shown in supplementary Fig. 1.

The median follow-up time was 22.1 months (range 9.8–46.6 months). During follow-up, the median OS in the SBRT group (14.5 months, 95% CI: 10.1–18.9) was longer than in the LEN group (11.1 months, 95% CI: 9.3–12.9) (HR = 0.57, 95% CI: 0.35–0.94, $p = 0.014$) (Fig. 2A). The OS rates at 1- and 2-years were 65.8% and 31.6% in the SBRT group and 39.5% and 10.5% in the LEN group, respectively. The median PFS in the SBRT group (6.8 months, 95% CI: 5.1–8.5) was longer than in the LEN group (5.0 months, 95% CI: 3.0–7.0) (HR = 0.58, 95% CI: 0.36–0.92, $p = 0.010$) (Fig. 2B). The PFS rates at 6 and 12 months were 57.9% and 28.9% in the SBRT group and 44.7% and 10.5% in the LEN group, respectively.

Tumor response evaluated according to mRECIST criteria are shown in Table 2. CR, PR, SD, and PD were observed in 2 (5.3%), 18 (47.4%), 12 (31.6%), and 6 (15.9%) of cases in the SBRT group, respectively, whereas in the LEN group these parameters were 1 (2.6%), 8 (21.1%), 17 (44.7%), and 12 (31.6%), respectively. The ORR in the SBRT group were higher than those in the LEN group (52.6% vs. 23.7%, $P = 0.009$). Furthermore, patients who showed treatment response in the SBRT group ($p < 0.001$, Fig. 3A) and LEN group ($p < 0.001$, Fig. 3B) had significantly higher OS than those who did not respond to treatment.

Forest plot analysis of OS related factors showed that the benefit of SBRT exceeded that of lenvatinib in the patients of male, age ≥ 55, HBV infection, Child-Pugh class A, ECOG score 1, number of tumors ≤ 3, tumor size ≥ 5 cm and < 10 cm, PVTT Vp3-4, ALBI grade 1, and AFP ≤ 200 (Fig. 4A). PFS was significantly longer in the SBRT group than in the LEN group for patients of male, HBV infection, Child-Pugh class A, number of tumors ≤ 3, tumor size ≥ 5 cm and < 10 cm, PVTT Vp3-4 and ALBI grade 1 (Fig. 4B).

The incidence of all AEs in both groups is shown in Table 3. No treatment-related deaths were observed in either group. The most frequently observed AEs in the LEN group were hypertension (34.2%), abdominal pain (26.3%) and diarrhea (21.1%), while in the SBRT group were anorexia (25.7%), nausea/vomiting (21.1%) and AST/ALT elevation (21.1%). In the LEN group, 2 patients (5.3%) occurred with grade ≥ 3 hypertension, 1 patient (2.6%) with grade ≥ 3 nausea/vomiting, 1 patient (2.6%) with grade ≥ 3 abdominal pain and 1 patient (2.6%) with grade ≥ 3 AST/ALT elevation. In the SBRT group, 2 patients (5.3%) occurred with grade ≥ 3 thrombocytopenia/leukopenia, 1 patient (2.6%) occurred with RILD. No other serious treatment-related toxicity was reported during follow-up.

The results of the univariable and multivariable analyses of probable prognostic factors for survival outcomes are shown in Table 4. Univariate analysis showed that treatment modality ($p = 0.015$), number of tumors ($p < 0.001$) and degree of PVTT ($p < 0.001$) were significantly associated with OS, and treatment modality ($p = 0.012$), number of tumors ($p < 0.001$) and degree of PVTT ($p = 0.001$) were also significantly associated

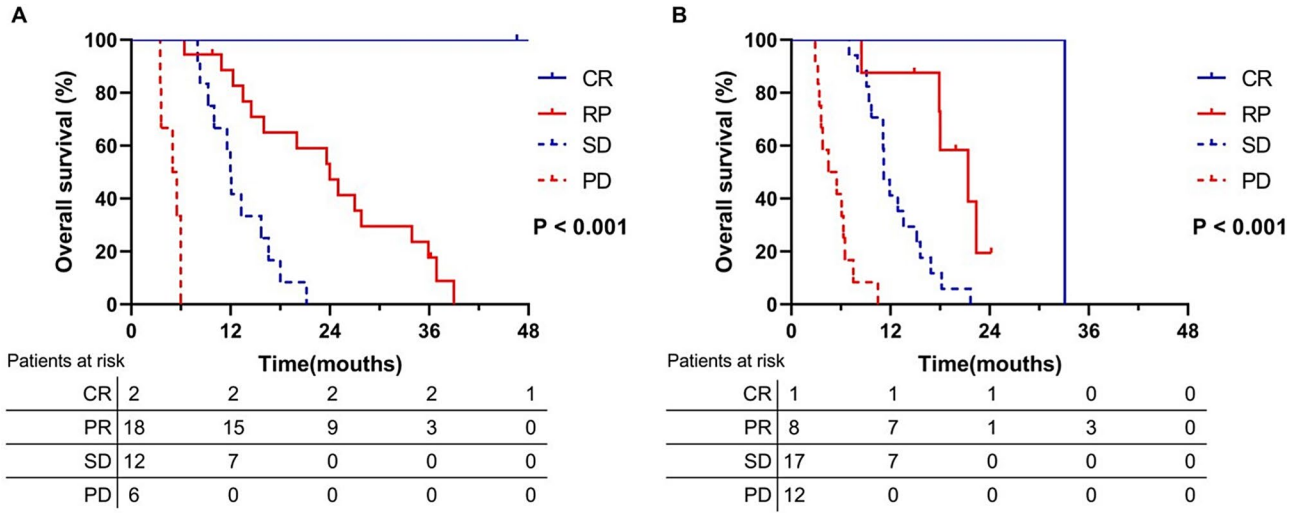

Fig. 3 Kaplan-Meier survival curves for overall survival in **(A)** stereotactic body radiotherapy group and **(B)** lenvatinib group according to treatment response

with PFS. In multivariate cox regression analysis, treatment modality (HR=0.38, $p<0.000$), number of tumors (HR=3.00, $p<0.000$) and degree of PVTT (HR=2.39, $p<0.000$) were independent predictors of OS, and treatment modality, number of tumors and degree of PVTT were independent predictors of PFS (HR=0.46, $p=0.002$; HR=2.58, $p=0.001$; HR=1.62, $p=0.002$, respectively).

All patients in both groups showed tumor progression during the follow-up period. The subsequent treatments received by the patients in both groups are shown in Table 5. In the LEN group, 14 patients (36.8%) received best supportive care, 13 patients (34.2%) received single treatment, and 11 patients (28.9%) received multiple treatments. In the SBRT group, 13 patients (34.2%) received best supportive care, 16 patients (42.1%) received single treatment, and 9 patients (23.7%) received multiple treatments. Overall, there was no statistically significant difference in the subsequent treatment between the two groups.

Discussion

The prognosis of HCC patients with PVTT is extremely poor, and the optimal treatment option remains controversial [26]. Sorafenib was the first drug to demonstrate a survival benefit in patients with advanced HCC based on the SHARP and Asia-Pacific trials [27, 28], whereas the efficacy for patients with PVTT were limited. Two studies showed that the median OS of sorafenib for patients with PVTT was only 4.3 months [29, 30]. REFLECT trial is the first global phase 3 trial in over 10 years showed lenvatinib, current another standard of treatment in HCC, to be non-inferior to sorafenib for OS [15], and lenvatinib had better PFS, ORR and time to progression. Hence, lenvatinib has been listed as the first-line of treatment for HCC with PVTT by the China Food and Drug Administration [31]. However, the REFLECT study excluded Vp4 PVTT patients. To date, there are fewer studies on lenvatinib for the treatment of HCC with PVTT. In a study by Yu et al. [32], lenvatinib treatment of HCC patients with macroscopic tumor thrombosis had a 1-year OS rate of 37.7%. In our study, the 1-year OS rate for lenvatinib treatment of HCC with PVTT was 39.5%, similar to the result of the study by Yu.

Recently, some breakthroughs in the systemic treatment of advanced HCC, especially antivascular endothelial growth factor–targeted therapy combined with immune checkpoint inhibitors in the IMbrave150 study [33]. The IMBrave150 study showed that atezolizumab in combination with bevacizumab achieved better OS and PFS than sorafenib in unresectable HCC. However, immune checkpoint inhibitors are not covered by the National Health Insurance in China, which would place a greater financial burden on patients than sorafenib or lenvatinib.

Historically RT was previously considered unsuitable for HCC because the liver is a radiation-sensitive organ and high doses of radiation can cause severe hepatotoxicity [24]. However, with the development of radiotherapy technology, intensity-modulated radiotherapy and SBRT have gradually evolved effective for HCC [3]. SBRT can accurately deliver larger single fraction particle sizes with fewer fractions and without excessive hepatotoxicity [7]. A growing number of retrospective studies showed the management of HCC patients with PVTT consistently showed positive efficacy with favorable toxicity profiles [34–36]. In our study, the median OS was 14.5 months and patients were also well tolerated after SBRT. In the SBRT group we observed 2 patients (5.3%) occurred with grade≥3 thrombocytopenia/leukopenia, 1 patient (2.6%)

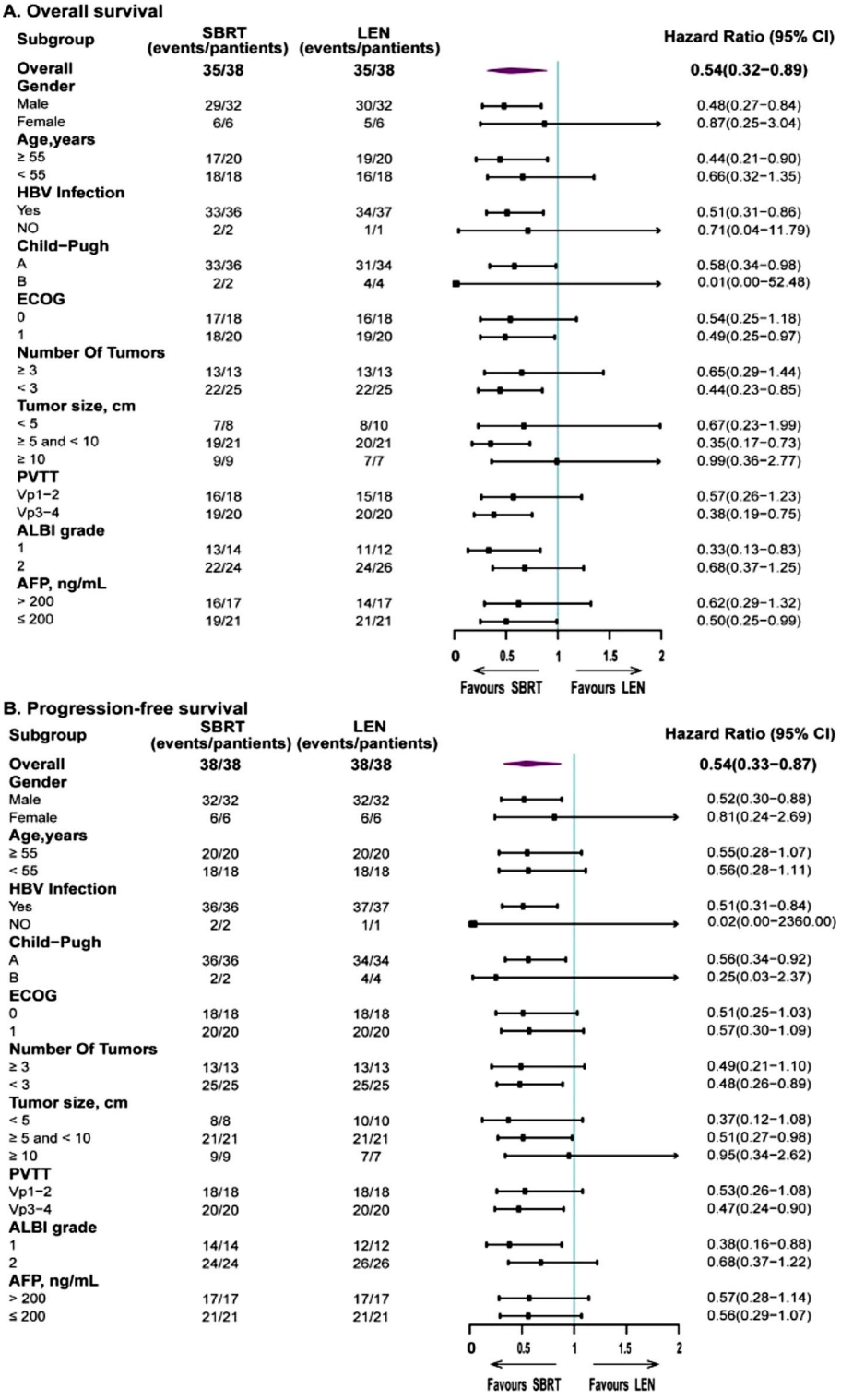

Fig. 4 Subgroup analyses of **(A)** overall survival and **(B)** progression-free survival in the patient subgroups. ECOG, Eastern Cooperative Oncology Group (performance status); PVTT, Portal Vein Tumor Thrombosis; ALBI, grade albumin-bilirubin grade; AFP, alpha-fetoprotein; LEN, lenvatinib; SBRT, Stereotactic Body Radiotherapy

Table 3 Treatment-related adverse events

Adverse events	LEN($n=38$)	SBRT($n=38$)	P^a value
Hypertension, n (%)			
Grade 1–2	11 (28.9)	0 (0)	**0.001**
Grade ≥ 3	2 (5.3)	0 (0)	0.493
Diarrhea, n (%)			
Grade 1–2	8 (21.1))	2 (5.3)	0.09
Nausea/vomiting, n (%)			
Grade 1–2	6 (15.8)	8 (21.1)	0.554
Grade ≥ 3	1 (2.6)	0 (0)	1
Proteinuria, n (%)			
Grade 1–2	4 (10.5)	0 (0)	0.115
Fatigue, n (%)			
Grade 1–2	6 (15.8)	6 (15.8)	1
Anorexia, n (%)			
Grade 1–2	5 (13.2)	9 (23.7)	0.375
Abdominal pain, n (%)			
Grade 1–2	9 (23.7)	4 (10.5)	0.223
Grade ≥ 3	1 (2.6)	0 (0)	1
Rash, n (%)			
Grade 1–2	2 (5.3)	0 (0)	0.493
Hand-foot syndrome, n (%)			
Grade 1–2	2 (5.3)	0 (0)	0.493
AST/ALT elevation, n (%)			
Grade 1–2	5 (13.2)	8 (21.1)	0.542
Grade ≥ 3	1 (2.6)	0 (0)	1
Thrombocytopenia/Leukopenia, n (%)			
Grade 1–2	3 (7.9)	6 (15.8)	0.478
Grade ≥ 3	0 (0)	2 (5.3)	0.493
Patients with RILD, n (%)	0 (0)	1 (2.6)	1

AST, aspartate aminotransferase; ALT, alanine aminotransferase; SBRT, Stereotactic Body Radiotherapy; LEN, lenvatinib. RILD, radiation-induced liver disease

[a]Bold values indicate statistical significance

occurred with RILD, but no treatment-related deaths or other serious AEs were seen within 3 months after SBRT.

There are no studies directly comparing SBRT versus lenvatinib for HCC with PVTT at present. However, a study by Nakazawa et al. [29] showed that better survival was noted in the radiotherapy group than in the sorafenib group (median survival, 10.9 vs. 4.8 months; $P=0.025$) after PSM ($n=28$ per group). Our study investigated the survival benefit of SBRT versus lenvatinib in the treatment of HCC with PVTT as first-line therapy. The results showed that SBRT significantly improved OS and PFS in HCC patients presenting with PVTT compared to lenvatinib. In this study, the median OS was 14.5 months after SBRT and 11.1 months after lenvatinib treatment ($p=0.014$). In addition, the SBRT group had a better ORR (based on mRECIST criteria) than the lenvatinib group (52.6% vs. 23.7%, $P=0.009$). Compared with lenvatinib, SBRT reduced the risk of death by 62% (HR = 0.38, 95% CI 0.22–0.65) and reduced the risk of tumor progression by 54% (HR = 0.46, 95% CI 0.28–0.75).

In the cox regression analysis of our study, treatment modality, number of tumors and degree of PVTT were independent predictors of OS and PFS. Furthermore, in subgroup analysis, the advantages of SBRT over lenvatinib were more obvious in HCC patients with Vp3-4 compared to HCC patients with Vp1-2. A meta-analysis comparing the efficacy of hepatic arterial infusion (HAIC) versus sorafenib also found a more obvious advantage of HAIC in HCC patients with type III-IV PVTT compared to HCC patients with type II-IV PVTT [37]. The study by Kim et al. [30] also found that patients with a higher degree of PVTT benefited more from liver-directed concurrent chemoradiotherapy (LD-CCRT) than sorafenib in terms of OS. Therefore, aggressive local treatments including SBRT, HAIC and LD-CCRT are more appropriate than sorafenib or lenvatinib monotherapy for the treatment of HCC with a high degree of PVTT. The advantages of SBRT over lenvatinib were also more obvious in HCC patients with tumor number < 3 compared to HCC patients tumor number ≥ 3. The reason for this result is that in patients with more intrahepatic metastases, we received radiotherapy targeting only PVTT. A multicenter study in Korea that included 985 HCC patients with PVTT showed that the median OS was longer in the group that received PVTT and the primary lesion as a target than in the group that only received PVTT as a target (11.6 vs. 8.9 months, $P=0.016$) [38].

In clinical practice, treatment decisions for each patient are made based on evidence of tumor response to therapy. Tumor response to treatment is often thought to improve patient survival outcomes. In addition, slower tumor progression may result in slower progression of tumor-related symptoms. In this study, we found that patients who responded to treatment had longer survival in either SBRT or LNE groups. This finding is supported by two other studies [34, 39]. These results suggest that study investigators may consider using objective response status by mRECIST shortly after commencing treatment as an early indicator of survival in clinical trials for advanced HCC. Meanwhile, this analysis may also support using objective response status by mRECIST as an endpoint for early clinical trials in advanced HCC. Assessing OS requires a longer follow-up time than objective response, hence, objective response could be used as a supportive or primary endpoint in clinical trials to provide a more rapid assessment of therapeutic activity. This may allow for faster results from clinical trials, which may speed up approval and increase the availability in turn of new treatment options for patients with advanced HCC. However, caution is warranted, and alternative endpoints should be adequately validated for

Table 4 Univariate and multivariate Cox regression analysis on OS and PFS

Variable	OS (*N* = 76, events = 70)				PFS (*N* = 76, events = 76)			
	Univariable model		Multivariable model		Univariable model		Multivariable model	
	HR (95% CI)	*P*[a]	HR (95% CI)	*p*[a]	HR (95% CI)	*p*[a]	HR (95% CI)	*p*[a]
Group (refer to LEN)	0.54(0.32–0.89)	**0.015**	0.38(0.22–0.65)	**0.000**	0.54(0.33–0.87)	**0.012**	0.46(0.28–0.75)	**0.002**
Gender (refer to Male)	1.04(054 – 2.00)	0.901			1.13(0.60–2.11)	0.702		
Age (refer to < 55 years)	1.12(0.70–1.80)	0.635			1.18(0.75–1.87)	0.476		
Etiology (refer to HBV)	2.08(0.64–6.74)	0.223			2.99(0.91–9.82)	0.071	2.55(0.74–8.78)	0.138
Child-Pugh classification (refer to A)	1.57(0.67–3.66)	0.297			1.28(0.55–2.98)	0.567		
ECOG PS (refer to 0)	1.39(0.86–2.25)	0.174			1.30(0.82–2.06)	0.261		
Number Of Tumors (refer to < 3)	3.00(1.77–5.07)	**0.000**	3.00(1.72–5.26)	**0.000**	2.75(1.64–4.60)	**0.000**	2.58(1.51–4.40)	**0.001**
Tumor size (refer to < 5 cm)	1.41(0.98–2.02)	0.065	1.34(0.91–1.98)	0.136	1.15(0.83–1.59)	0.416		
PVTT (refer to Vp1)	2.45(1.71–3.50)	**0.000**	2.39(1.62–3.53)	**0.000**	1.63(1.21–2.20)	**0.001**	1.62(1.19–2.20)	**0.002**
ALBI grade (refer to 1)	1.43(0.87–2.37)	0.164			1.34(0.83–2.17)	0.236		
AFP (refer to ≤ 200 ng/mL)	0.75(0.47–1.22)	0.244			0.88(0.56–1.39)	0.586		
PLT (refer to $< 100 \times 10^9$/L)	0.68(0.39–1.20)	0.188			0.68(0.40–1.17)	0.165		
WBC (refer to $< 4 \times 10^9$/L)	0.98(0.56–1.72)	0.945			0.97(0.57–1.66)	0.924		
Previous local treatment (refer to Absence)	0.73(0.39–1.37)	0.324			0.62(0.34–1.13)	0.115		

HBV, hepatic B virus; HCV, hepatic C virus; ECOG, Eastern Cooperative Oncology Group; PS, performance status; MVI, macrovascular invasion; ALBI, grade albumin-bilirubin grade; AFP, alpha-fetoprotein; PLT, platelet; WBC, white blood cell; LEN, lenvatinib; TAE, transcatheter arterial embolization; SBRT, Stereotactic Body Radiotherapy; LEN, lenvatinib. PFS, progression-free survival; OS, overall survival; IHPFS, intrahepatic progression-free survival

[a] Bold values indicate statistical significance

Table 5 Subsequent treatment

Subsequent therapies	Groups		*P* value
	LEN group (*n* = 38)	SBRT group (*n* = 38)	
Single treatment, n (%)	13 (34.2)	16 (42.1)	0.479
TACE, n (%)	8 (21.1)	4 (10.5)	0.345
RFA, n (%)	0 (0)	2 (5.3)	0.493
SBRT, n (%)	2 (5.3)	7 (18.4)	0.156
Argon–Helium cryosurgical, n (%)	2 (5.3)	0 (0)	0.493
lenvatinib, n (%)	0 (0)	2 (5.3)	0.493
ICIs, n (%)	1 (2.6)	1 (2.6)	1
Multiple treatments, n (%)	11 (28.9)	9 (23.7)	0.602
SBRT + TACE, n (%)	2 (5.3)	5 (13.2)	0.428
SBRT + ICIs, n (%)	2 (5.3)	1 (2.6)	1
TACE + ICIs, n (%)	4 (10.5)	1 (2.6)	0.358
lenvatinib + ICIs, n (%)	1 (2.6)	1 (2.6)	1
TACE + Lenvatinib + ICIs, n (%)	2 (5.3)	0 (0)	0.493
SBRT + Lenvatinib + ICIs, n (%)	0 (0)	1 (2.6)	1
Best Supportive Care, n (%)	14 (36.8)	13 (34.2)	0.811

TACE, Transarterial chemoembolization; RAF, Radio-frequency ablation; ICIS, Immune checkpoint inhibitors; SBRT, Stereotactic Body Radiotherapy; LEN, Lenvatinib

prospective studies to prevent inaccurate interpretation of risk-benefit profiles [40].

To our knowledge, this is the first article to investigate the survival benefit of SBRT versus lenvatinib in the treatment of HCC with PVTT as first-line therapy. The results demonstrated that SBRT had a better survival benefit than lenvatinib treatment in patients with HCC with PVTT. However, there are some limitations to our study. Firstly, our study was retrospective and our sample was limited. Secondly, although we used PSM analysis to balance possible confounders for a more accurate analysis between the two groups, it was not possible to control for all confounding variables. Thirdly, there are no clear recommendations for subsequent treatment after tumor progression of advanced HCC treated with lenvatinib or RT. Although there was no statistically significant difference in the subsequent treatment between the two groups after tumor progression in our study, more patients in the SBRT group received local therapy, while more patients in the lenvatinib group received a combination therapy that included systemic therapy. Finally, HBV infection was present in 94.7% of the patients in our study, therefore, the efficacy needs to be further confirmed in other etiologies.

Conclusion

In conclusion, our study shows that SBRT had a better survival benefit than lenvatinib treatment in HCC patients with PVTT as first-line therapy and SBRT was well tolerated in our patients. Patients with good response to SBRT or lenvatinib had better survival. Further larger patient cohorts and large sample randomized controlled trials are necessary to better assess the feasibility and effectiveness.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13014-024-02527-1.

Supplementary Material 1

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Not applicable.

Author contributions
XJ: Study design, data acquisition, data analysis and manuscript editing. AZ: data acquisition, data analysis, review and editing the manuscript. XD: Study design, review and editing the manuscript. QW: Study concepts, study design, quality control of data and manuscript editing. All authors reviewed the manuscript.

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Data availability
The datasets used during the current study are available from the Corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of the Fifth Medical Center of the PLA General Hospital. Written informed consents were obtained from all patients prior to treatment.

Consent for publication
All patients provided written informed consent.

Competing interests
The authors declare no competing interests.

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References

1. Vogel A, Meyer T, Sapisochin G, Salem R, Saborowski A. Hepatocellular carcinoma. Lancet. 2022;400:1345–62. https://doi.org/10.1016/S0140-6736(22)01200-4.
2. Lu J, Zhang X-P, Zhong B-Y, Lau WY, Madoff DC, Davidson JC, et al. Management of patients with hepatocellular carcinoma and portal vein tumour thrombosis: comparing east and west. Lancet Gastroenterol Hepatol. 2019;4:721–30. https://doi.org/10.1016/S2468-1253(19)30178-5.
3. Liu P-H, Huo T-I, Miksad R. Hepatocellular Carcinoma with Portal Vein Tumor involvement: best management strategies. Semin Liver Dis. 2018;38:242–51. https://doi.org/10.1055/s-0038-1666805.
4. Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. J Hepatol. 2022;76:681–93. https://doi.org/10.1016/j.jhep.2021.11.018.
5. Korean Liver Cancer Association (KLCA) and National Cancer Center (NCC) Korea. 2022 KLCA-NCC Korea Practice guidelines for the management of Hepatocellular Carcinoma. Korean J Radiol. 2022;23:1126. https://doi.org/10.3348/kjr.2022.0822.
6. Zhou J, Sun H, Wang Z, Cong W, Wang J, Zeng M, et al. Guidelines for the diagnosis and Treatment of Hepatocellular Carcinoma (2019 Edition). Liver Cancer. 2020;9:682–720. https://doi.org/10.1159/000509424.
7. Klein J, Dawson LA. Hepatocellular Carcinoma Radiation Therapy: review of evidence and Future opportunities. Int J Radiation Oncology*Biology*Physics. 2013;87:22–32. https://doi.org/10.1016/j.ijrobp.2012.08.043.
8. Park HC, Yu JI, Cheng JC-H, Zeng ZC, Hong JH, Wang MLC, et al. Consensus for Radiotherapy in Hepatocellular Carcinoma from the 5th Asia-Pacific Primary Liver Cancer Expert Meeting (APPLE 2014): current practice and future clinical trials. Liver Cancer. 2016;5:162–74. https://doi.org/10.1159/000367766.
9. Sun J, Wang Q, Hong Z-X, Li W-G, He W-P, Zhang T, et al. Stereotactic body radiotherapy versus hepatic resection for hepatocellular carcinoma (≤ 5 cm): a propensity score analysis. Hepatol Int. 2020;14:788–97. https://doi.org/10.1007/s12072-020-10088-0.
10. Su T-S, Liang P, Zhou Y, Huang Y, Cheng T, Qu S, et al. Stereotactic body Radiation Therapy vs. Transarterial Chemoembolization in Inoperable Barcelona Clinic Liver Cancer Stage a Hepatocellular Carcinoma: a retrospective, propensity-matched analysis. Front Oncol. 2020;10:347. https://doi.org/10.3389/fonc.2020.00347.
11. Wahl DR, Stenmark MH, Tao Y, Pollom EL, Caoili EM, Lawrence TS, et al. Outcomes after stereotactic body radiotherapy or Radiofrequency ablation for Hepatocellular Carcinoma. JCO. 2016;34:452–9. https://doi.org/10.1200/JCO.2015.61.4925.
12. Lou J, Li Y, Liang K, Guo Y, Song C, Chen L, et al. Hypofractionated radiotherapy as a salvage treatment for recurrent hepatocellular carcinoma with inferior vena cava/right atrium tumor thrombus: a multi-center analysis. BMC Cancer. 2019;19:668. https://doi.org/10.1186/s12885-019-5870-3.
13. Rim CH, Kim CY, Yang DS, Yoon WS. Comparison of radiation therapy modalities for hepatocellular carcinoma with portal vein thrombosis: a meta-analysis and systematic review. Radiother Oncol. 2018;129:112–22. https://doi.org/10.1016/j.radonc.2017.11.013.
14. Bettinger D, Pinato DJ, Schultheiss M, Sharma R, Rimassa L, Pressiani T, et al. Stereotactic body Radiation Therapy as an alternative treatment for patients with Hepatocellular Carcinoma Compared to Sorafenib: a propensity score analysis. Liver Cancer. 2019;8:281–94. https://doi.org/10.1159/000490260.
15. Kudo M, Finn RS, Qin S, Han K-H, Ikeda K, Piscaglia F, et al. Lenvatinib versus Sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018;391:1163–73. https://doi.org/10.1016/S0140-6736(18)30207-1.
16. Al-Salama ZT, Syed YY, Scott LJ, Lenvatinib. A review in Hepatocellular Carcinoma. Drugs. 2019;79:665–74. https://doi.org/10.1007/s40265-019-01116-x.
17. Ikai I, Yamamoto Y, Yamamoto N, Terajima H, Hatano E, Shimahara Y, et al. Results of hepatic resection for hepatocellular carcinoma invading major portal and/or hepatic veins. Surg Oncol Clin N Am. 2003;12:65–75. https://doi.org/10.1016/S1055-3207(02)00082-0.
18. Benedict SH, Yenice KM, Followill D, Galvin JM, Hinson W, Kavanagh B, et al. Stereotactic body radiation therapy: the report of AAPM Task Group 101: stereotactic body radiation therapy: the report of TG101. Med Phys. 2010;37:4078–101. https://doi.org/10.1118/1.3438081.
19. Ikeda M, Okusaka T, Mitsunaga S, Ueno H, Tamai T, Suzuki T, et al. Safety and Pharmacokinetics of Lenvatinib in patients with Advanced Hepatocellular Carcinoma. Clin Cancer Res. 2016;22:1385–94. https://doi.org/10.1158/1078-0432.CCR-15-1354.
20. Tamai T, Hayato S, Hojo S, Suzuki T, Okusaka T, Ikeda K, et al. Dose finding of Lenvatinib in subjects with Advanced Hepatocellular Carcinoma based on Population Pharmacokinetic and exposure-response analyses: the Journal of Clinical Pharmacology. J Clin Pharmacol. 2017;57:1138–47. https://doi.org/10.1002/jcph.917.
21. Llovet JM, Lencioni R. mRECIST for HCC: performance and novel refinements. J Hepatol. 2020;72:288–306. https://doi.org/10.1016/j.jhep.2019.09.026.
22. Lencioni R, Llovet J. Modified RECIST (mRECIST) Assessment for Hepatocellular Carcinoma. Semin Liver Dis. 2010;30:052–60. https://doi.org/10.1055/s-0030-1247132.
23. Freites-Martinez A, Santana N, Arias-Santiago S, Viera A. CTCAE versión 5.0. Evaluación De La Gravedad De Los eventos adversos dermatológicos de las terapias antineoplásicas. Actas Dermosifiliogr. 2021;112:90–2. https://doi.org/10.1016/j.ad.2019.05.009.
24. Lawrence TS, Robertson JM, Anscher MS, Jirtle RL, Ensminger WD, Fajardo LF. Hepatic toxicity resulting from cancer treatment. Int J Radiation Oncology*Biology*Physics. 1995;31:1237–48. https://doi.org/10.1016/0360-3016(94)00418-K.
25. Liang S-X, Huang X-B, Zhu X-D, Zhang W-D, Cai L, Huang H-Z, et al. Dosimetric predictor identification for radiation-induced liver disease after hypofractionated conformal radiotherapy for primary liver carcinoma patients with child–pugh Grade A cirrhosis. Radiother Oncol. 2011;98:265–9. https://doi.org/10.1016/j.radonc.2010.10.014.
26. Tao Z-W, Cheng B-Q, Zhou T, Gao Y-J. Management of hepatocellular carcinoma patients with portal vein tumor thrombosis: a narrative review.

Hepatobiliary Pancreat Dis Int. 2022;21:134–44. https://doi.org/10.1016/j.hbpd.2021.12.004.
27. Llovet JM, Hilgard P, de Oliveira AC, Forner A, Zeuzem S, Galle PR, et al. Sorafenib in Advanced Hepatocellular Carcinoma. N Engl j Med. 2008. https://doi.org/10.1056/NEJMoa0708857.
28. Cheng A-L, Kang Y-K, Chen Z, Tsao C-J, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2009;10:25–34. https://doi.org/10.1016/S1470-2045(08)70285-7.
29. Nakazawa T, Hidaka H, Shibuya A, Okuwaki Y, Tanaka Y, Takada J, et al. Overall survival in response to sorafenib versus radiotherapy in unresectable hepatocellular carcinoma with major portal vein tumor thrombosis: propensity score analysis. BMC Gastroenterol. 2014;14:84. https://doi.org/10.1186/1471-230X-14-84.
30. Kim J, Byun HK, Kim TH, Kim SI, Kim BK, Kim SU, et al. Liver-Directed Concurrent Chemoradiotherapy versus Sorafenib in Hepatocellular Carcinoma with Portal Vein Tumor thrombosis. Cancers. 2022;14:2396. https://doi.org/10.3390/cancers14102396.
31. Cheng S, Chen M, Cai J, Sun J, Guo R, Bi X, et al. Chinese Expert Consensus on Multidisciplinary diagnosis and Treatment of Hepatocellular Carcinoma with Portal Vein Tumor Thrombus (2018 Edition). Liver Cancer. 2020;9:28–40. https://doi.org/10.1159/000503685.
32. Yu JI, Kang W, Yoo GS, Goh MJ, Sinn DH, Gwak G-Y, et al. Safety and Efficacy of Liver-Directed Radiotherapy in Combination with Lenvatinib for Hepatocelluar Carcinoma with macroscopic tumor thrombosis. Front Oncol. 2022;12:888755. https://doi.org/10.3389/fonc.2022.888755.
33. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim T-Y, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020;382:1894–905. https://doi.org/10.1056/NEJMoa1915745.
34. Shui Y, Yu W, Ren X, Guo Y, Xu J, Ma T, et al. Stereotactic body radiotherapy based treatment for hepatocellular carcinoma with extensive portal vein tumor thrombosis. Radiat Oncol. 2018;13:188. https://doi.org/10.1186/s13014-018-1136-5.
35. Li X, Ye Z, Lin S, Pang H. Predictive factors for survival following stereotactic body radiotherapy for hepatocellular carcinoma with portal vein tumour thrombosis and construction of a nomogram. BMC Cancer. 2021;21:701. https://doi.org/10.1186/s12885-021-08469-1.
36. Zhang S, He L, Bo C, Yang S, An Y, Li N, et al. Comparison of stereotactic body radiation therapy versus fractionated radiation therapy for primary liver cancer with portal vein tumor thrombus. Radiat Oncol. 2021;16:149. https://doi.org/10.1186/s13014-021-01874-7.
37. Liu M, Shi J, Mou T, Wang Y, Wu Z, Shen A. Systematic review of hepatic arterial infusion chemotherapy *versus* sorafenib in patients with hepatocellular carcinoma with portal vein tumor thrombosis. J Gastroenterol Hepatol. 2020;35:1277–87. https://doi.org/10.1111/jgh.15010.
38. Im JH, Yoon SM, Park HC, Kim JH, Yu JI, Kim TH, et al. Radiotherapeutic strategies for hepatocellular carcinoma with portal vein tumour thrombosis in a hepatitis B endemic area. Liver Int. 2017;37:90–100. https://doi.org/10.1111/liv.13191.
39. Amioka K, Kawaoka T, Kosaka M, Johira Y, Shirane Y, Miura R, et al. Analysis of survival and response to Lenvatinib in Unresectable Hepatocellular Carcinoma. Cancers. 2022;14:320. https://doi.org/10.3390/cancers14020320.
40. DeMets DL, Psaty BM, Fleming TR. When can Intermediate outcomes be used as surrogate. Outcomes? JAMA. 2020;323:1184. https://doi.org/10.1001/jama.2020.1176.

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