Stereotactic Body Radiotherapy Versus Intensity-Modulated Radiotherapy For Hepatocellular Carcinoma With Portal Vein Tumor Thrombosis

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Abstract

Background: It is unclear whether robotic stereotactic body radiotherapy (SBRT) is superior to intensity-modulated radiotherapy (IMRT) in advanced hepatocellular carcinoma (HCC). This study aimed to compare the long-term outcomes of SBRT with those of IMRT in HCCs with portal vein tumor thrombosis (PVTT).

Methods: We retrospectively evaluated 287 HCC patients with PVTT who underwent radiotherapy between January 2000 and January 2017. Of them, 154 and 133 patients were treated with IMRT and SBRT, respectively. Overall survival (OS), progression-free survival (PFS), intrahepatic control (IC), and local control (LC) were evaluated in univariable and propensity-score matched analyses.

Results: After matching, 102 well-paired patients were selected. There was no significant difference in the 6-, 12-, 24-, and 60-month cumulative OS (73.5, 42.9, 23.6, 7.6% vs. 72.4, 45.1, 29.8, 13.2%, $P=0.151$), PFS (53.9, 29.3, 21.8, 7.5% vs. 54.5, 19.3, 12.0, 9.6%, $P=0.744$), IC (61.4, 45.7, 39.0, 26.8% vs. 75.1, 45.8, 35.9, 28.7%, $P=0.144$), and LC (85.2, 56.5, 52.1, 47.4% vs. 87.4, 65.2, 62.1, 62.1%, $P=0.191$) between the IMRT and SBRT groups. A biologically effective dose assumed at an a/b ratio of 10 (BED_{10}) of ≥ 100 Gy was the optimal cutoff for predicting the OS, PFS, IC, and LC in the patients who received SBRT.

Conclusions: When high-precision tracking technology is available, SBRT appears to be a safe and more time-efficient treatment, achieving comparable OS, PFS, IC and LC to IMRT for local advanced HCC with PVTT. A $BED_{10} \geq 100$ Gy is recommended if tolerated by normal tissue.

Introduction

Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer-related death worldwide [1]. Approximately 10–40% of patients with HCC have portal vein tumor thrombosis (PVTT) at diagnosis, classified as Barcelona Clinic Liver Cancer (BCLC)-C stage). If left untreated, the median survival time of HCC patients with PVTT is only 2.7–4.0 months [2]. Over the past decade, sorafenib has been the recommended first-line treatment for advanced HCC patients with BCLC-C stage [3]. However, the outcomes of these patients treated with sorafenib remains poor, with an extended survival of only 1.5–4.0 months [4, 5]. Radiotherapy, such as three-dimensional radiotherapy and intensity-modulated radiotherapy (IMRT), has been increasingly applied in advanced HCC management. A randomized clinical trial by Yoon *et al.* [6] showed superior efficacy of trans-arterial chemoembolization (TACE) plus RT to sorafenib in HCC patients with PVTT, with significantly extended overall survival (OS). Treatment guidelines in the Asian region, such as in Korea and China, recommend radiotherapy as treatment for PVTT [7, 8].

Stereotactic body radiation therapy (SBRT) achieves encouraging outcomes comparable to those of liver resection, radiofrequency ablation, and TACE in early stage HCC [9–11]. For advanced HCC, Bettinger *et al.* [12] reported a considerable survival benefit of SBRT compared to sorafenib, extending OS to a median of 9.3 months. However, it is unclear whether SBRT is also superior to IMRT in advanced HCC. Thus, this study aimed to compare the long-term outcomes of SBRT with those of IMRT in advanced HCC with PVTT.

Materials And Methods

Study design and patients

This was a retrospective study of advanced HCC patients with PVTT who underwent external radiation therapy in China. The patients who underwent IMRT in Cancer Hospital during January 2000–January 2017 and the patients who underwent SBRT in Rui Kang Hospital during January 2009–January 2017 were included. The eligibility criteria were as follows: (1) advanced HCC with PVTT diagnosed via histopathology or according to the clinical criteria for HCC diagnosis [8]; (2) Eastern Cooperative Oncology Group score 0–2; (3) Child-Pugh class A (CP-A) or B (CP-B), (4) no concurrent systemic treatments, and (5) Patients with TACE-refractory disease were included.

Radiotherapy protocol

Hypofractionated intensity-modulated radiation therapy

All patients underwent plain and contrast-enhanced computed tomography (CT) scans in the supine position with both arms raised above the head for RT planning. Vacuum molds were used for patient immobilization. The CT images were acquired at 3-mm slice thickness in free quiet breathing mode. All target areas were sketched in the MIM 6.8 system (MIM, USA), and IMRT plans were generated using Pinnacle 3 system (Philips, Netherlands). The patients underwent hypofractionated IMRT using a linear accelerator with 6 MV X-rays (ELEKTA Synergy, Sweden).

Computerized tomography-magnetic resonance imaging (CT-MRI) fusion was performed to clearly show the intrahepatic lesion. The gross tumor volume (GTV) was defined by the hyperdense area of the intrahepatic primary tumor during the arterial phase and the hypodense filling defect area of the venous thrombus including PVTT during the venous phase. The clinical target volume (CTV) was 4–5 mm larger than the diameter of the tumor area and the distal end of the venous thrombus.

The planning target volume (PTV) was defined as the CTV plus an asymmetric 1-cm expansion in the cranial caudal direction and 5-mm axially for setup uncertainty and respiratory motion. For both IMRT and SBRT, the PVTT was treated with same dose as the primary tumor in the same patient. Hypofractionation was performed every other day (3 fractions a week). The final median radiation dose delivered to the isocenter was 51 Gy (range, 30–60 Gy), with a median per dose of 4 Gy (range, 2.5–7 Gy) and a median fraction of 12 (range, 7–20). The median total irradiation time was 25 days (range, 15–50 days).

The fraction doses were determined according to the following principles: 3 to 5 Gy/fraction for tumors larger than 5 cm in diameter and/or CP-B and more than 5 to 6 Gy/fraction for tumors less than 5 cm in diameter and/or CP-A. The dose is usually limited to 30–45 Gy for CP-B patients.

Stereotactic body radiation therapy

SBRT was delivered using the CyberKnife system (Accuray Inc., Sunnyvale, CA, USA) with tracking of liver motion using implanted fiducials. The simulation CT scan process and motion management were the same as those for IMRT. Seven days prior to the CT scan or MRI (slice thickness, 3 mm), 3 to 4 fiducials (diameter, 0.8 mm) were inserted into tumor tissue or into the surrounding area of the tumor under B-ultrasound or CT guidance. The definition of GTV was similar as that for the IMRT technique, and the CTV was equivalent to the gross tumor volume. GTV was expanded by 3–5 mm to establish the planning target volume (PTV), and this was usually decreased manually when the dose-limiting organs overlapped.

SBRT was performed on consecutive days. The final median radiation dose delivered was 42 Gy (range, 30–50 Gy), with a median per dose of 11 Gy (range, 7–15 Gy) and a median fraction of 4 (range, 3–5) with the median 66% (range, 60–80%) isodose line, which covered >97% PTV. The dose is usually limited to less than 30–40 Gy for CP-B patients. For all cases in both groups, the total dose was determined by the volume of the normal liver, CP-class, and the maximum dose to the stomach or duodenum. Treatment delivery and dose-volume constraints for organs at risk are shown in **Table S1**.

Response evaluation and follow-up

Patients were re-evaluated 1 month after treatment and subsequently every 3 or 6 months. Follow-up laboratory examinations included levels of alanine transaminase, aspartate transaminase, prothrombin time (PT), total bilirubin, albumin, and alpha-fetoprotein (AFP). Follow-up assessments also included CT or MRI at 1 month after the procedure and every 3 to 6 months thereafter.

Classic radiation-induced liver disease (c-RILD) was defined as an anicteric elevation in alkaline phosphatase levels of at least twofold the upper normal level and/or anicteric hepatomegaly and/or ascites within 2 weeks to 3 months after RT. Non-classic radiation-induced liver disease (nc-RILD) was defined as an elevation of liver transaminases more than 5 times the upper limit of normal or changes in CP class of ≥ 2 points within 3 months after RT. Patients with toxicity due to liver tumor progression were excluded.

Statistical analysis

Cumulative OS, progression-free survival (PFS), intrahepatic control (IC), and local control (LC) were calculated using the Kaplan-Meier method and compared using the log-rank test. OS was evaluated from the date of the first radiotherapy treatment to the date of any-cause death or the last follow up. PFS was evaluated from the date of the first treatment to the date of any tumor recurrence, progression, or death or the date of censoring. IC was evaluated from the date of the first treatment to the date of intrahepatic failure (defined as the reappearance of radiologic hallmarks of HCC in the whole parenchyma of the liver including in- and out-field-treated lesions) or the date of censoring. LC was evaluated from the date of the first treatment to the date of infield recurrence. Categorical variables were compared using the Pearson's chi-squared test, while continuous variables were compared using the Wilcoxon rank-sum test. Univariate and multivariate analyses were performed with the Cox proportional hazards model. The receiver operating characteristic (ROC) curve analysis was performed to determine the best cutoff value of BED₁₀ for the prediction of OS, PFS, LC, and IC.

To reduce potential selection bias and confounding effects of treatment, propensity score matching analysis (PSM) was applied. Patients in the SBRT and IMRT groups were matched in a 1:1 ratio using the nearest neighbor matching algorithm with a caliper of 0.2 without replacement. The propensity scores were calculated using logistic regression model including the following variables: age, sex, bilirubin-albumin (ALBI) score, TACE, PT, alpha fetoprotein level, and tumor size.

All statistical analyses were performed using R version 4.0.2 (2020-06-22) software. $P < .05$ was considered statistically significant.

Results

Patient characteristics

Overall, 287 patients were evaluated. Of them, 214 (74.6%) patients died, and 73 patients were right-censored. **Table 1** shows the baseline characteristics of the SBRT group (n=133) and the IMRT group (n=154). Before propensity score matching, the proportion of patients with unfavorable baseline characteristics was higher in the SBRT group than that in the IMRT group, including TACE refractory disease, older age, PT, albumin, ALBI score, and ALBI grade (all $P < .05$). After matching, 102 paired patients from the SBRT and IMRT groups were selected. The patient characteristics were well balanced between the two groups in the matched cohort.

Overall survival, progression-free survival, intrahepatic control, and local control

The median follow-up time was 31 months (range, 3–84 months). Before propensity score matching, the median OS in the IMRT and SBRT groups was 10.0 vs. 10.0 (HR=0.893; 95% CI: 0.677–1.178; $P = 0.422$) months; PFS, 6.0 vs. 6.0 (HR=1.103; 95% CI: 0.855–1.422; $P = 0.450$) months; IC, 9.0 vs. 11.0 (HR=1.269; 95% CI: 0.792–2.035; $P = 0.322$) months. There was no significant difference between the IMRT group and the SBRT group with respect to the 6-, 12-, 24-, and 60-month cumulative OS (73.2, 48.1, 25.1, 10.7% vs. 70.3, 46.5, 29.3, 11.3%, $P = 0.407$; **Figure 1a**), PFS (52.3, 30.6, 20.7, 8.7% vs. 51.3, 21.6, 10.0, 8.3%, $P = 0.424$; **Figure 1b**), IC (61.8, 44.3, 35.6, 26.0% vs. 75.4, 46.3, 33.0, 26.4%, $P = 0.094$; **Figure 1c**), and LC (84.5, 62.6, 58.1, 52.7% vs. 87.0, 64.8, 54.6, 54.6%, $P = 0.498$; **Figure 1d**).

Consistent results of no statistically significant difference in OS, PFS, IC, and LC were obtained after propensity score matching (**Figure 2a, 2b, 2c, 2d**). The median OS, PFS, and IC was 8 vs. 10 (HR=0.795; CI: 0.574–1.099; P=0.165), 6 vs. 6 (HR=1.048; CI: 0.776–1.415; P=0.758), and 8 vs. 11 (HR=0.756; CI: 0.512–1.116; P=0.159) months in the IMRT and SBRT groups. The 6-, 12-, 24-, and 60-month cumulative OS (73.5, 42.9, 23.6, 7.6% vs. 72.4, 45.1, 29.8, 13.2%, P=0.151; **Figure 2a**), PFS (53.9, 29.3, 21.8, 7.5% vs. 54.5, 19.3, 12.0, 9.6%, P=0.744; **Figure 2b**), IC (61.4, 45.7, 39.0, 26.8% vs. 75.1, 45.8, 35.9, 28.7%, P=0.144; **Figure 2c**), and LC (85.2, 56.5, 52.1, 47.4% vs. 87.4, 65.2, 62.1, 62.1%, P=0.191; **Figure 2d**) rates of the IMRT group were similar to those of the SBRT group.

Multivariate survival analysis in the matched cohort (**Online Resource: Table S2**) showed that the AFP level (HR=1.433; 95% CI: 0.928–2.214; P=0.023) and ALBI score (HR=1.860; 95% CI: 1.298–2.665; P=0.004) were independent predictors of OS. Further, ALBI score (HR, 1.609; 95% CI, 1.154–2.244; P= 0.005) was an independent predictor of PFS.

Subgroup analysis by biologically effective dose

Univariable survival analysis showed that BED₁₀ was a prognostic factor for OS, PFS, IC, and LC. BED₁₀ was excluded from multivariate analysis to avoid collinearity). Therefore, we further performed subgroup analyses by BED₁₀. No optimal cutoff value was found in ROC analyses for the IMRT group. In ROC analyses of the matched cohort, the optimal cutoff for predicting OS, PFS, IC and LC of the SBRT group was 100 Gy (AUC=0.601, **Online Resource: Figure S1a**), 100 Gy (AUC=0.670; **Online Resource: Figure S1b**), 100 Gy (AUC=0.601; **Online Resource: Figure S1c**), and 100 Gy (AUC=0.598; **Online Resource: Figure S1d**), respectively. Therefore, the prognostic effect of BED₁₀ ≥100 Gy for the OS, PFS, IC, and LC in the SBRT group was further investigated.

In Kaplan-Meier analyses of the unmatched cohort, the 6-, 12-, 24-, and 60-month OS (87.5%, 61.5%, 46.2%, and 46.2% vs. 63%, 36.5%, 22.6%, and 8.5%; P=0.0078; **Figure 3a**), PFS (66.9%, 46%, 30.7%, and 30.7% vs. 38.8%, 15.6%, 5.4%, and 3.6%; P=0.0011; **Figure 3b**), IC (90.9%, 69.2%, 60.6%, and 60.6% vs. 62.8%, 40.1%, 25.5%, and 17%; P=0.0059; **Figure 3c**), and LC (95.5%, 86.8%, 77.1%, 77.1% vs. 84.7%, 58.0%, 47.0%, 47.0%, 17%; P=0.04; **Figure 3d**) were significantly better in patients treated with a high BED₁₀ level (BED₁₀ ≥100 Gy) than in patients with a low BED₁₀ level (BED₁₀ <100 Gy). The results of ROC analyses and Kaplan-Meier analyses with a BED₁₀ cutoff value of 100 Gy are shown in **Online Resource: Table S3**.

Toxicity

In the matched IMRT group, 15 (14.7%) patients experienced RILD (c-RILD, n=2; nc-RILD with elevation of CP-score ≥ 2, n=13). Of them, 6 (6/89 with CP-A, 6.7%) and 9 (9/13 with CP-B, 69.2%) had CP-A and CP-B disease, respectively. Five patients died within 2 months and 2 died within 5-6 months due to RILD after IMRT. There were 4 patients (3.9%) with tumor adjacent to the gastrointestinal tract (<1 cm) who experienced radiation-induced gastrointestinal (GI) bleeding within 5–6 months.

In the matched SBRT group, 12 (11.8%) patients developed RILD (c-RILD, n=2; nc-RILD with elevation of CP-score ≥2, n=10). Of them, 5 (5/91 with CP-A, 5.4%) and 7 (7/11 with CP-B, 63.6%) had CP-A and CP-B disease, respectively. Among the patients who received BED₁₀ ≥100 Gy, 4 patients (1 with CP-A5, 3 with CP-A6) treated with 42–45 Gy in 3 fractions experienced nc-RILD with elevation of CP-score ≥2 after SBRT. Among the patients who received BED₁₀ <100 Gy group, 2 patients with CP-B7 died within 3 and 5 months due to c-RILD after SBRT, and 3 patients (2.9%) with tumors adjacent to the gastrointestinal tract (<1 cm) experienced radiation-induced GI bleeding within 4–7 months.

Discussion

With the improvement of precision radiotherapy techniques, robotic SBRT was widely used in the treatment of HCC. In the current study, SBRT achieved higher BED within fewer fractions and a shorter duration of treatment than IMRT but obtained comparable OS, PFS, IC, and LC. To our best knowledge, this is the first study to directly compare the efficacy of SBRT with that of hypofractionated IMRT in the treatment of HCC.

Our results in both groups compared favorably to the published literatures [12-21] (**Table 2**). The comparability of PFS and OS in our study may be because the therapeutic effect is actually the same, and not the artificial result of particularly poor or excellent IMRT and SBRT procedures. Similarly, Rim et al. [22] reported a comparable 1-year OS between 3-dimensional conformal RT and SBRT (48.5% vs 46.5%). Yang *et al* [18] also showed a considerable survival benefit in SBRT compared to RT (1- and 2-year OS: 33.1% and 16.5% vs. 17.3% and 5.2%) in 140 patients with advanced HCC with PVTT. Consequently, it is plausible that SBRT is feasible for patients with PVTT, with acceptable toxicity and survival outcomes.

In the current study, the SBRT group received significantly higher BED₁₀ than did the IMRT group (median: 89.7 Gy vs. 72.8 Gy after matching, P<0.001). Further, BED₁₀ ≥100 Gy was a favorable predictor of OS, PFS, IC, and LC for patients who underwent SBRT, while no optimal BED cutoff was identified for the IMRT group. After propensity score matching, 41 (40.2%) patients in the SBRT group experienced intrahepatic progression. The patients receiving BED₁₀ ≥100 Gy achieved better intrahepatic control and local control, along with better OS, PFS in the SBRT group, while the incidence of RILD in the BED₁₀ ≥100 Gy group had no significant difference from that in the BED<100 Gy group (4/25 vs. 8/108, P=0.228). BED₁₀ ≥100 Gy was used to be considered as radiation “ablation” and associated with improved outcomes in multiple prior studies of HCC <5 cm [23]. Our previous results also showed that an escalated dose (BED₁₀ ≥100 Gy) was a significant prognostic factor for HCC >5 cm [24]. Scorsetti et al. [25] also reported that the 2-year in-field local control (100% vs 87%) and PFS (52.5% vs 17.3%) was higher for BED ≥100 Gy than for <100 Gy. In a large-scale study of 456 patients by Robbins et al. [26], the median and 1-year OS were 15.3 months and 56.6% for BED ≤75 Gy, 18.3 months and 67.5% for BED >75 Gy and ≤100 Gy, and 37.2 months and 81.4% for BED >100 Gy. In summary, our results may provide the rationale for using high BED (BED₁₀ ≥100 Gy) SBRT to treat HCC patients with PVTT if tolerated by normal tissue.

The toxicities were tolerable in both groups, and there was no difference in the rate of RILD (15/102 [14.7%] vs. 12/102 [11.8%], Chi-square P=0.5). Our previous studies shown V15 ≤21.5% and/or the absolute liver volume spared from at less 10 Gy (V10) ≥621.8 mL could improve the safety of SBRT in the treatment of HCC [27]. For hypofractionated treatment, mean normal liver doses of <23 Gy and/or V20 <48.5% were crucial for reducing the risk of RILD [28,

29]. According to our previous experience, patients with CP-B class are at higher risk of RILD than those with CP-A; consistent findings were obtained in this study (16/24 [66.6%] vs. 11/180 [6.1%], Chi-square $P = 0.000$). Xu et al. [30] also reported a lower hepatic tolerable dose (TD5) from a mean normal liver dose of 6 Gy for Child–Pugh B compared to 21 Gy for Child–Pugh A patients.

We have to acknowledge some limitations of our study. First, this was a retrospective and non-randomized study. Second, selection bias may have increased given the long study duration of 17 years (2000–2017). Third, we cannot account for the unknown differences between the two groups, such as the institutional experience, and the patient's financial capacity. Further randomized prospective clinical trials are warranted to provide robust conclusions.

Conclusions

When high-precision tracking technology is available, SBRT appears to be a safe and more time-efficient treatment, achieving comparable OS, PFS, IC and LC to IMRT for local advanced HCC with PVTT. A BED₁₀ ≥ 100 Gy is recommended if tolerated by normal tissue.

Declarations

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Conflicts of Interest: The authors declare no conflict of interest.

Ethics approval and consent to participate: The study design was approved by the ethics review board of Guangxi Medical University Cancer Hospital (LW2020036). The requirement of written informed consent for participation was waived owing to the retrospective nature of the study.

Consent for publication: Not applicable.

Availability of data and codes: The statistical datasets and codes used and/or analyzed in the current study are available from the corresponding author (sutingshi@163.com) on reasonable request.

Author Contributions: Data curation, Ying Zhou, Yong Huang, Ping Liang, and Ting-Shi Su; Formal analysis, Li-Qing Li, Shi-Xiong Liang, and Ting-Shi Su; Funding acquisition, Ting-Shi Su; Writing – original draft, Li-Qing Li and Ting-Shi Su; Writing – review & editing, Shi-Xiong Liang and Ting-Shi Su.

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Tables

Table 1. Patient characteristics and treatment results of different treatment groups.

Factor	Level	Befor PSM			After PSM		
		IMRT	SBRT	<i>P</i>	IMRT	SBRT	<i>P</i>
N		154	133		102	102	
Sex	male	135 (87.7%)	120 (90.2%)	0.49	92 (90.2%)	92 (90.2%)	1.00
	femal	19 (12.3%)	13 (9.8%)		10 (9.8%)	10 (9.8%)	
age, median (IQR)		47 (40, 55)	51 (41, 58)	0.034	49 (43, 58)	48 (40, 57)	0.47
HBV	negative	23 (14.9%)	23 (17.3%)	0.59	17 (16.7%)	18 (17.6%)	0.85
	positive	131 (85.1%)	110 (82.7%)		85 (83.3%)	84 (82.4%)	
AFP	0-8	26 (16.9%)	27 (20.3%)	0.47	17 (16.7%)	20 (19.6%)	0.53
	8-100	30 (19.5%)	22 (16.5%)		19 (18.6%)	17 (16.7%)	
	100-200	13 (8.4%)	5 (3.8%)		10 (9.8%)	4 (3.9%)	
	200-400	7 (4.5%)	7 (5.3%)		5 (4.9%)	6 (5.9%)	
	>400	78 (50.6%)	72 (54.1%)		51 (50.0%)	55 (53.9%)	
CP-class	A	139 (89.6%)	115 (86.4%)	0.80	89 (87.3%)	91 (89.2%)	0.60
	B	15 (10.4%)	18 (13.5%)		13 (12.7%)	11 (10.8%)	
ALBI grade	1	61 (39.6%)	38 (28.6%)	0.002	39 (38.2%)	35 (34.3%)	0.12
	2	93 (60.4%)	87 (65.4%)		63 (61.8%)	63 (61.8%)	
	3	0 (0.0%)	8 (6.0%)		0 (0.0%)	4 (3.9%)	
PVTT type*	□	20 (12.9%)	19□14.8%□	0.093	13 (12.7%)	13 (12.7%)	0.536
	□	86 (55.8%)	74 (55.6%)		58 (56.9%)	56 (54.9%)	
	□	43 (27.9%)	40 (30.1%)		29(28.4%)	32 (31.3%)	
	□	5 (3.2%)	0 (0%)		2 (2.0%)	0 (0%)	
TACE refractory disease	No	98 (63.6%)	62 (46.6%)	0.004	59 (57.8%)	55 (53.9%)	0.57
	Yes	56 (36.4%)	71 (53.4%)		43 (42.2%)	47 (46.1%)	
PT, median (IQR)		12.8 (12, 14)	13.3 (12.6, 14.3)	<0.001	13 (12, 14.1)	13.15 (12.4, 14.2)	0.29
Tbil, median (IQR)		16.1 (11.2, 23.5)	15.2 (10.9, 20.6)	0.18	15.35 (11.1, 24)	15.2 (10.4, 20.6)	0.36
albumin, median (IQR)		38.85 (36, 42)	36.3 (32.6, 40.1)	<0.001	38.2 (34.4, 41.2)	37 (33.4, 40.9)	0.18
ALP, median (IQR)		131 (96, 182)	124 (97, 172)	0.54	123 (91, 167)	122 (94, 172)	0.96
BUN, median (IQR)		4.72 (3.9, 5.53)	4.36 (3.65, 5.24)	0.032	4.645 (3.86, 5.7)	4.415 (3.65, 5.31)	0.14
ALBI score, median (IQR)		-2.540 (-2.728, -2.203)	-2.292 (-2.649, -2.013)	0.001	-2.532 (-2.729, -2.128)	-2.40717 (-2.693, -2.113)	0.40
ALP, median (IQR)		131 (96, 182)	124 (97, 172)	0.54	123 (91, 167)	122 (94, 172)	0.96
size, median (IQR)		9 (6.3, 11.2)	8.1 (5.4, 11)	0.11	9.35 (6.5, 11.2)	8.3 (5.5, 11)	0.16
Total dose, median (IQR)		50.6 (46, 54)	42 (39, 45)	<0.001	50.5 (45, 55)	42 (39, 45)	<0.001
Fractions, median (IQR)		12 (10, 15)	4 (3, 4)	<0.001	12 (10, 15)	4 (3, 4)	<0.001
Per dose, median (IQR)		4 (4, 5)	11.25 (10.5, 13)	<0.001	4 (3, 4.6)	11.25 (10.5, 13)	<0.001
BED10 , median (IQR)		73.1 (67.2, 79.0)	89.7 (86.1, 95.7)	<0.001	72.8 (61.6, 79.0)	89.7 (86.1, 95.7)	<0.001
BED3 to nomal liver, median (IQR)		27.6 (19.2, 35.6)	35.0 (25.9□43.2)	<0.001	28.3 (19.2-37.5)	35.0 (23.4-43.2)	<0.001
Effective PGTV volume, median (IQR)		535 (209-959)	498 (232-927)	0.26	535(209-959)	504 (303-927)	0.87
OS	median	10 (CI,7.918-12.082)	10 (CI,7.754-12.246)	0.407	8 (CI,6.274-9.726)	10 (CI,7.793-12.207)	0.151
(%)	6ms	73.2	70.3		73.5	72.4	
	12ms	48.1	46.5		42.9	45.1	

	24ms	25.1	29.3		23.6	29.8	
	60ms	10.7	11.3		7.6	13.2	
PFS	median	6(CI,3.868-8.132)	6(CI,5.161-6.839)	0.424	6(CI,3.723-8.277)	6(CI,4.939-7.061)	0.744
(%)	6ms	52.3	51.3		53.9	54.5	
	12ms	30.6	21.6		29.3	19.3	
	24ms	20.7	10.0		21.8	12.0	
	60 ms	8.7	8.3		7.5	9.6	
LC	6ms	84.5	87.0	0.498	85.2	87.4	0.191
(%)	12ms	62.6	64.8		56.5	65.2	
	24ms	58.1	54.6		52.1	62.1	
	60 ms	52.7	54.6		47.4	62.1	
IC	median	9(CI,7.112-12.888)	11(CI,7.797-14.203)	0.094	8(CI,4.462-11.538)	11(CI,7.827-14.173)	0.144
(%)	6ms	61.8	75.4		61.4	75.1	
	12ms	44.3	46.3		45.7	45.8	
	24ms	35.6	33.0		39.0	35.9	
	60ms	26.0	26.4		26.8	28.7	

Table 2. Treatment outcomes of radiation therapy for hepatocellular carcinoma with PVTT.

Authors	Study design	Technique	Number of cases	BCLC stage	Median per dose (range)	Fraction	Median total dose (range)	Median BED ₁₀ (range)	combined/previous treatment	OS	
										1y	2
Kim, 2013	retrospective	IMRT	35	C	NA*	10F, 5F/ per week	50 (45-60)	75 (65.3-96)	Chemotherapy with capecitabine	51.4	2
Chen, 2014	prospective	IMRT	24	C	2-2.5	5 F/ per week	50 (40-60)	NA	Sorafenib	NA	3
Hou, 2016	retrospective	IMRT	54	C	2.5-4	average 19.4F	60 (40-66)	72.35	NA	59.3	N
Im, 2017	retrospective	3D-CRT/IMRT	985	C	2.5 (1.8-17)	NA	45 (12-66)	48.75 (13.0–114.75)	TACE/TACI /HAIC(66.7)	43.3	2
Xi, 2013	retrospective	SBRT	41	C	6 (5-8)	6F/2 weeks	36 (30–48)	NA	sorafenib(34.1)	50.3	N
Bettinger, 2019	retrospective	SBRT	22	C	NA	median 7 (3-12)	44 (21–66)	84.4 (36–124)	NA	NA	N
Yang, 2019	retrospective	SBRT	54	C	6-12.5	4-5	45–40-48	< 65:25.9%;≥65:74.0%	sorafenib	34.9	1
Chopra, 2019	retrospective	SBRT	21	B (57.1%)/ C (42.9%)	NA	6 (5-6)	42 (25-54)	59.5 (23.4-100)	TACE(66.7)	51	1
Liu,, 2020	retrospective	SBRT	37	B (32.4%)/ C (70.2%)	NA	5 (3-5)	35	60 (45-100)	TACE (40.5%)	71%	N
Yadav, 2020	retrospective	SBRT	30	C	NA	6 (5-6)	48 (32-50)	NA	NA	60	N
Present study	retrospective	IMRT	154	C	4 (2-7)	median 12 (7-25),5 F/ per week	51 (24-64)	73 (31-95)	TACE (36.4%)	48.1	2
		SBRT	133	C	11.3 (7-15)	3-5	42 (30-50)	90 (36-116)	TACE(53.4%)	46.5	2
*Abbreviation–NA=not available											

Figures

Figure 1
Before propensity matching, Kaplan-Meier curve of SBRT versus IMRT. (a) overall survival; (b) progression-free survival; (c) intrahepatic failure; (d) local control

Figure 2
After propensity matching, Kaplan-Meier curve of SBRT versus IMRT. (a) overall survival; (b) progression-free survival; (c) intrahepatic failure; (d) local control

Figure 3
Kaplan-Meier curve with a BED cutoff value of 100Gy in unmatched SBRT group. (a) overall survival; (b) progression-free survival; (c) intrahepatic failure; (d) local control

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