Clinical and Translational Radiation Oncology 46 (2024) 100767

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

Stereotactic body radiation therapy in patients with centrally located hepatocellular carcinoma: A retrospective, single-arm, multi-center study

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ARTICLE INFO

Keywords:
Centrally located hepatocellular carcinoma
Stereotactic body radiation therapy
Overall survival
Progression free survival
Toxicity

ABSTRACT

Centrally located hepatocellular carcinoma (HCC) is difficult to be radically resected due to its special location close to major hepatic vessels. Thus, we aimed to assess whether stereotactic body radiation therapy (SBRT) can be an effective and safe approach for centrally located HCC. This retrospective study included 172 patients with centrally located HCC who were treated with SBRT. Overall survival (OS) was analyzed as the primary endpoint. Rates of progression-free survival (PFS), local control, intrahepatic relapse, extrahepatic metastasis and toxicities were analyzed as secondary endpoints. The OS rates of 1-, 3-, and 5-year were 97.7%, 86.7%, and 76.3%, respectively. The PFS/local control rates of 1-, 3-, and 5-year were 94.1%/98.2%, 76.8%/94.9%, and 59.3%/92.3%, respectively. The cumulative incidence of intrahepatic relapse/extrahepatic metastases of 1-, 3-, and 5-year were 3.7%/2.9%, 25.0%/7.4%, and 33.3%/9.8%, respectively. Both univariate and multivariate analyses revealed that patients received BED_{10} at 100 Gy or more had better OS. Radiation-related adverse events were mild to moderate according to Common Terminology Criteria for Adverse Events, and no toxicities over grade 3 were observed. Patients with centrally located HCC in our cohort who received SBRT had similar OS and PFS rates compared to those reported in literatures who received surgery with neoadjuvant or adjuvant intensity-modulated radiation therapy. These results indicate that SBRT is an effective and well-tolerated method for patients with centrally located HCC, suggesting that it may serve as a reasonable alternative treatment for these kind of patients.

1. Introduction

Primary liver cancer is one of the most common and deadly malignant neoplasms in the world, and hepatocellular carcinoma (HCC) is the dominant histological subtype. According to global cancer statistics, about 600,000 new cases of primary liver cancer occur worldwide per year, and China alone accounts for more than half of the global incidence, with approximately 410,000 new cases reported in 2020. Due to the malignancy of HCC, liver cancer-related death is the third-leading cause of cancer mortality worldwide and the second-most common cause of cancer-related death in China [1].

Centrally located HCC, a special type of lesion which is located beside major vessels, is defined as "carcinoma adjoined hepatic portals, less than 1 cm from major vascular structures (including the main trunks of the hepatic veins, main portal branches as well as the inferior vena cava) which are usually located in Couinaud segments I, IV, V, VIII, or at the junction of the central segments" [2]. Surgical resections of centrally located HCC are difficult, and patients face the risk of incomplete

Abbreviations: HCC, hepatocellular carcinoma; OS, overall survival; PFS, progression-free survival; BED_{10}, biologically effective dose; GTV, gross tumor volume; PTV, planning target volume; ITV, internal target volume; RFA, radiofrequency ablation; RILD, radiation-induced liver disease; SBRT, stereotactic body radiation therapy.

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https://doi.org/10.1016/j.ctro.2024.100767
Received 13 August 2023; Received in revised form 17 February 2024; Accepted 23 March 2024
Available online 27 March 2024

resection and narrow surgical margins due to the close relationship between cancer and major vessels, which may lead to operative hemorrhage and result in high recurrence and low survival rates [3]. It is reported that the 5-year overall survival (OS) rate of patients with centrally located HCC who underwent surgery alone only reached 40.2% [4]. Therefore, it is necessary to develop new treatment strategies to improve the survival rates of these patients.

According to current guidelines [5–7], surgical resection, liver transplantation and radio frequency ablation (RFA) are considered as first-line treatments for patients with early-stage HCC. Although these therapeutic models have the potential to provide radical cures, they have drawbacks and contraindications, and thus, for those patients who are not suitable for surgical approaches, they can only receive palliative interventions [8,9]. Therefore, it is necessary to find a new curative strategy for these patients, especially those with centrally located HCC. Previous studies have shown that the combination of radiotherapy with clinical surgery may provide a safe and curative choice for HCC patients. Addition of adjuvant radiotherapy after hepatectomy with narrow margins increases both the OS and progression-free survival (PFS) of patients with centrally located HCC [10]. It was also reported that intensity-modulated radiation therapy (IMRT) following hepatectomy may lead to survival benefit for patients with HCC close to major vessels [11]. Moreover, neoadjuvant radiotherapy conducted before surgery can decrease tumor burden, and improve PFS and OS [12]. These studies suggest that radiation may serve as an option for patients who have complicated conditions or are unsuitable for clinical surgery.

Stereotactic body radiation therapy (SBRT), a non-invasive radiation treatment, has been developed rapidly and is expected to be an alternative option for HCC patients [13]. It uses highly conformal beams for the precise delivery of high doses per fraction to target tumors [14]. When compared with other radiation therapy, SBRT requires fewer fractions and sharp dose gradients are spared for normal tissues [15]. Recent study showed that patients with HCC who received SBRT achieved competitive rates of local control and OS with tolerable toxicities [16]. Compared with RFA, SBRT provided similar local control rates [17]. In the past decade, many patients with centrally located HCC underwent SBRT in our hospital and achieved considerable results. However, the effects of SBRT for patients with centrally located HCC, especially for treatment-naïve lesions, have not been analyzed and reported. To address this gap in knowledge, we assess the outcomes and toxicities of SBRT for patients with centrally located HCC and discuss the potential for our findings to serve as higher-level clinical evidence in supporting the use of SBRT for this group of patients.

2. Materials and methods

2.1. Patients

This retrospective study was conducted at Zhongshan Hospital and The Fifth Medical Center of PLA General Hospital. The study included 172 patients with HCC who received SBRT from January 2011 to December 2022 and was approved by the institutional review board of the Ethics Committee of Zhongshan Hospital. Informed consent was obtained from all patients. All the patients are eligible candidates for surgery and ablation/ TACE and underwent MDT (Multi-Disciplinary Treatment). They made their final decision after knowing all the pros and cons of different treatments. Patients who met all of the following inclusion criteria were eligible for this study: (1) a diagnosis of HCC with pathological confirmation or typical HCC characteristics based on ultrasound combined with computed tomography (CT) or magnetic resonance imaging (MRI) [18], according to the guidelines proposed by the Chinese Liver Cancer Association [19]; (2) carcinoma adjoining the hepatic portals <1 cm from major vascular structures (including the main portal branches, the main trunks of the hepatic veins, and the inferior vena cava); (3) total tumor number ≤ 3 and tumors ≥ 1 cm from the luminal gastrointestinal (GI) tract, with at least one measurable centrally located lesion; (4) primary HCC without previous treatment or treated with TACE at the same tumor site before SBRT; (5) age 18–90 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, and Child–Pugh class A; and (6) absence of extrahepatic metastases. Patients with tumor thrombi, lymph node metastasis, distant metastasis, double primary malignancy, and previous anti-tumor treatment for HCC other than TACE were excluded from the study.

2.2. SBRT treatment

SBRT were conducted using Cyber-Knife or TOMO therapy. Patients who received Cyber-Knife were implanted with four to six fiducial markers 1 week prior to CT simulation. The distance between each marker and the lesion was <6 cm. Patients were asked to hold their breath and to maintain smooth breathing during the CT simulation imaging. Contrast-enhanced CT was performed, with MRI used to produce auxiliary images for fusion when the tumors were not clearly shown on CT. For each patient, an oncologist contoured the gross tumor volume (GTV), the planning target volume (PTV), and the organs at risk. The arterial phase were selected for delineation of GTV in most cases, while venous phase and portal phase were also used as reference. The PTV was defined as a 3–5 mm expansion of the GTV, avoiding the organs at risk. All plans were calculated by G4 CyberKnife MultiPlan, version 4.0.2, or VSI CyberKnife MultiPlan, version 4.6.1 (Accuracy, USA). The plans enclosed PTV with 75–90% isodose line of maximum dose equated to the prescribed dose. Normal tissue tolerance doses were determined according to the AAPM TG-101 report [20]. Doses of 49 to 56 Gy in 5–7 fractions were delivered to the PTV everyday in weekdays for most patients. During CK-SBRT treatment, the CK tracks the tumor by tracking fiducials to confirm the relative position of the fiducial marker and the tumor in the synchrony system.

Patients who received TOMO therapy were trained to maintain shallow breathing with respiratory exercise prior to treatment. The patients were immobilized in the supine position using a customized vacuum body mold, while the abdomen was compressed using the Body Pro-Loksystem. Abdominal compression techniques (using the Body Pro-Loksystem) were employed as part of a fixed position to minimize liver movement. Patients underwent four-dimensional CT (4D-CT) scans with a slice thickness of 3 mm (Siemens Somatom Sensation; Siemens Healthineers Corporation), and MRI was used for fusion when tumors were not clearly shown by CT. The primary tumor in the arterial phase in enhanced CT scan was defined as the GTV, while venous phase and portal phase were used as reference as well. The internal target volume (ITV) was generated after including the extension of the GTV on the 4D-CT scan. The PTV was defined as the ITV plus a radial margin of 3 mm. The tolerance dose of normal tissue was determined according to the AAPM TG-101 report regardless of different fractions. Dose of 48 to 54 Gy in six fraction were delivered to the PTV everyday in weekdays for most patients. SBRT was administered using a Helical TomoTherapy Hi-Art Treatment System (Accuray).

2.3. Follow-up

All patients were re-evaluated 6–8 weeks after SBRT treatment and every 3–6 months thereafter. Evaluations included imaging with CT or MRI and laboratory tests, including routine blood, liver function, and alpha-fetoprotein (AFP). Tumor response was assessed using mRECIST version1.1. The primary end point was OS, defined as the time from the date of SBRT until the date of death or February 28, 2023, the date of our final follow-up. PFS, local control, intrahepatic relapse, and extrahepatic metastasis rates were calculated from the date of SBRT until the dates of progression (including local recurrence, intrahepatic relapse and extrahepatic metastasis), local recurrence in PTV according to mRECIST, intrahepatic relapse out of PTV, and extrahepatic metastasis or death. SBRT-related toxicities were evaluated weekly during SBRT and monthly after SBRT and were graded according to the Common

Terminology Criteria for Adverse Events (version 4.03, National Cancer Institute). Radiation induced liver disease (RILD) is defined as anicteric ascites and elevation of alkaline phosphatase levels to at least two-fold of the pretreatment values in the absence of progression (classic), or elevation of transaminases to at least 5 times above the upper normal limit or pretreatment level within 3 months after SBRT (nonclassic). Patients who experienced progression after SBRT were free to receive salvage therapy following the guidelines.

2.4. Statistical analysis

Kaplan–Meier curves were used to calculate rates of OS, PFS, local control, intrahepatic relapse, and extrahepatic metastases. Variables that were significant in univariate analyses were further analyzed in multivariate analyses using the Cox regression model with hazard ratios (HRs) and 95% confidence intervals (CIs) to determine whether they show independent prognostic significance. All statistical analyses were performed using R (version 4.1.0, R Foundation for Statistical Computing), with *P*-values <0.05 considered as significant.

3. Results

3.1. Patient characteristics

Between January 2011 and December 2022, a total of 172 patients with centrally located HCC (Fig. 1A and B) underwent SBRT in two centers, including 153 patients treated with Cyber-Knife in the Fifth Medical Center of PLA General Hospital and 19 patients treated with TOMO Therapy in Zhongshan Hospital. Total doses ranging from 39 to 70 Gy in 3 to 10 fractions were administered to patients without any interruptions. When converted into the biologically effective dose (BED_{10}), the median dose was 97.2 Gy and ranged from 72 to 132 Gy. Variations in dose and fraction resulted from the distance between the tumor and the GI tract, the liver function of the patient, and the different types of radiation therapy employed.

Clinical characteristics of patients are summarized in Table 1. Most of the patientswere infected with hepatitis B virus (164 [95.3%]) and had ECOG grade of 0 (165 [95.9%]). All patients were Child–Pugh class A and most patients (106 [61.6%]) had HCC with Barcelona Clinic Liver Cancer (BCLC) stage A. One hundred and fifty-seven patients (91.3%) were treatment-naïve before SBRT, the remaining 15 patients (8.7%) were treated with TACE at the same tumor site before SBRT. The final decision to combine TACE with SBRT were made during MDT in order to possibly get better control rate of the disease for patients and all these patients underwent SBRT within one month after TACE. Patients didn't receive any other treatment during or after SBRT until progression.

Table 1
Patient characteristics.

Characteristic	Patients, No. (%)
Age, mean ± SD (range), y	55.8 ± 10.0 (30–86)
Male sex	113 (65.7%)
Female sex	59 (34.3%)
Underlying hepatitis B	164 (95.3%)
No underlying hepatitis	8 (4.7%)
ECOG	
0	165 (95.9%)
1	7 (4.1%)
Treatment before SBRT	
TACE	15 (8.7%)
Naïve	157 (91.3%)
Child-Pugh score	
5	155 (90.1%)
6	17 (91.3%)
Baseline AFP, ng/mL	
<20	77 (44.8%)
20–200	45 (26.2%)
>200	50 (29.1%)
BCLC stage	
0	66 (38.4%)
A	106 (61.6%)
Maximal size of tumor, mean ± SD (range), cm	2.5 ± 1.12 (0.6–6.1)
<2	58 (33.7%)
2–5	112 (65.1%)
≥5	2 (1.2%)
BED_{10}, mean ± SD (range), Gy	97.2 ± 10.4 (72–132)
<80	8 (4.6%)
80 ≤ X < 100	44 (25.6%)
≥100	120 (69.8%)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; TACE, transcatheter arterial chemoembolization; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; BED_{10}, biologically effective dose; SD, standard deviation.

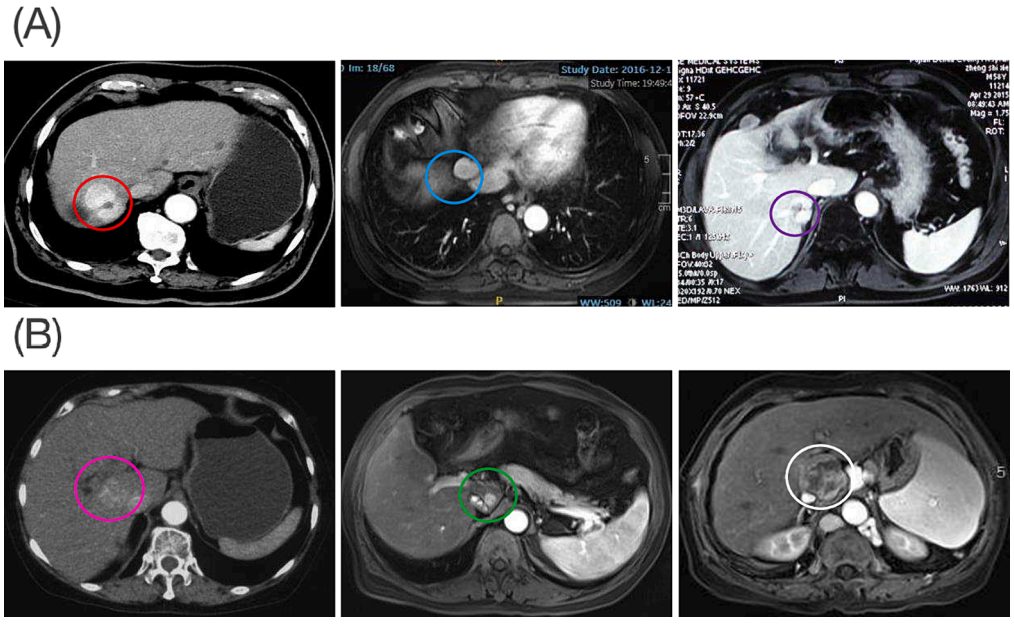

Fig. 1. Representative MRI images of centrally located HCC (A). HCC located beside inferior vena cava. (B). HCC located beside main trunks of hepatic veins.

3.2. Overall survival rates and progression-free survival rates

Among all 172 patients with centrally located HCC treated with SBRT, median follow-up time was 45 months, and the median OS was not reached at the end of this study, whereas the median PFS was 69 months. The 1-, 3-, and 5-year OS rates were 97.7%, 86.7%, and 76.3%, respectively (Fig. 2A). And the PFS rates of 1-, 3-, and 5-year were 94.1%, 76.8%, and 59.3%, respectively (Fig. 2B).

3.3. Local, intrahepatic, and extrahepatic recurrence

Among all 172 patients, only 10 patients (5.8%) experienced local progression of in-field-treated lesions. The local control rates of 1-, 3-, and 5-year were 98.2%, 94.9%, and 92.3%, respectively (Fig. 3A). Intrahepatic relapse occurred in 56 patients (32.6%), with 1-, 3-, and 5-year cumulative incidence of intrahepatic relapse rates of 3.7%, 25.0%, and 33.3%, respectively (Fig. 3B). Thirteen patients experienced extrahepatic metastases, with rates of 2.9%, 7.4%, and 9.8% at 1-, 3-, and 5-year after SBRT, respectively (Fig. 3C).

3.4. Adverse events

Radiation-related toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03) and summarized in Table 2. The main adverse events were gastrointestinal reactions of grade 1–2, including nausea, vomiting, anorexia, abdominal pain and diarrhea, which occurred in 18% (31/172) patients. Fourteen (8.1%) patients experienced fatigue during SBRT treatment, and hematologic toxicities of grade 1–2 occurred in 9 (5.2%) patients. No toxicities over grade 3 were observed. Among all 172 patients, only eleven (6.4%) had Child–Pugh scores increased by two or three points after SBRT.

All patients completed the planned SBRT. Within three months after SBRT, radiation-induced liver disease occurred in a total of 18 (10.5%) patients, including 10 (5.8%) cases with classic RILD, defined as ascending ALP or transaminases with anicteric ascites, and eight (4.7%) cases with non-classic RILD, defined as abnormal liver function, manifesting as increases in aspartate transaminase, alanine transaminase and bilirubin levels.

3.5. Prognostic analysis

Univariate analyses revealed that patients with tumor size >2 cm had increased death risk compared to those with tumor size ≤2 cm (HR 2.5, $P = 0.047$), and BED_{10} value ≥100 Gy provided patients better survival benefits (HR 0.45, $P = 0.026$). In contrast, age, sex, AFP level, Child–Pugh score, ECOG score, and BCLC stage were not correlated with OS in this cohort (Table 3), possibly due to the similar disease stage (i.e., early stage) of these patients. Multivariate analyses (Table 3) further confirmed BED_{10} values >100 Gy were significantly associated with better OS, whereas tumor size was marginally significant.

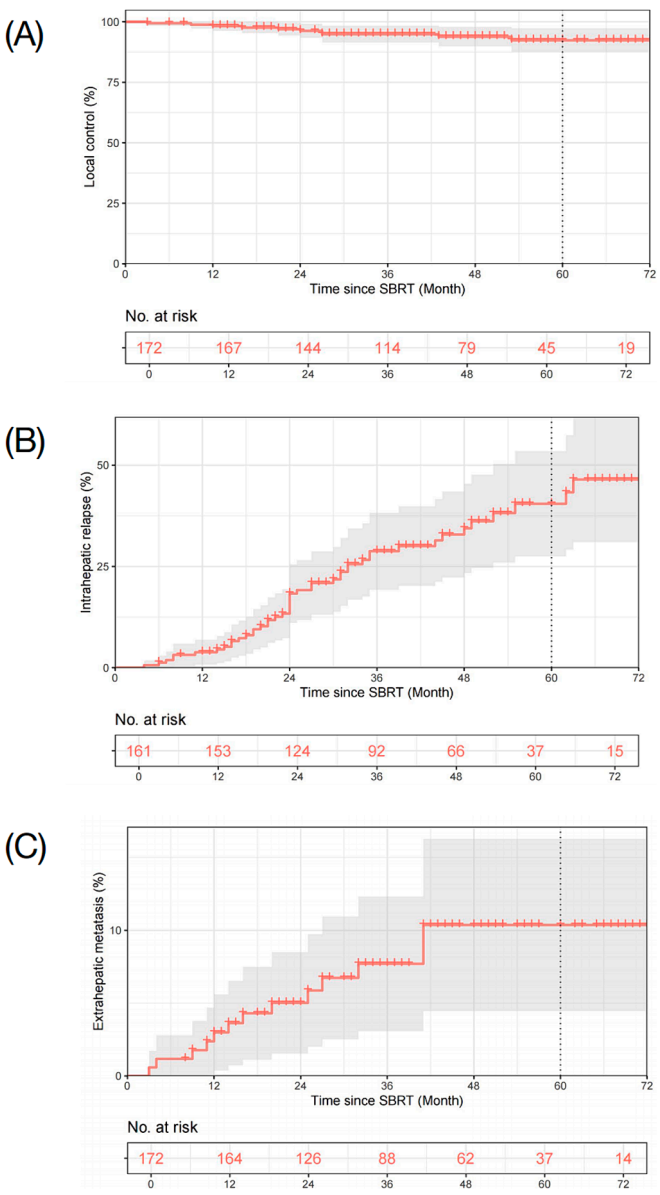

Fig. 3. Kaplan–Meier plots used to calculate local control rate (A), cumulative incidences of intrahepatic relapse (B) and extrahepatic metastasis (C) for 172 patients.

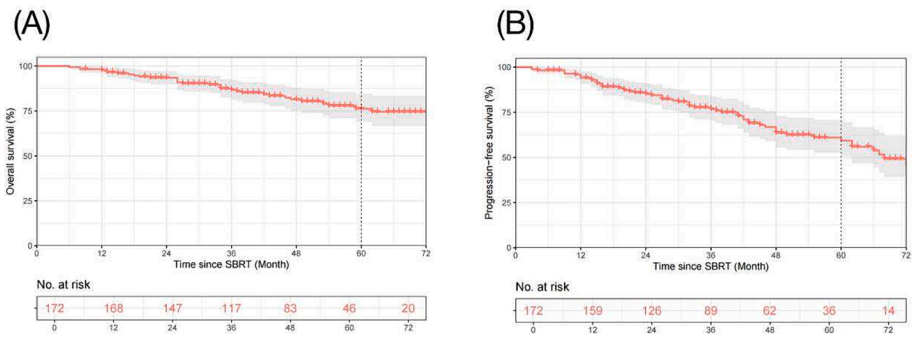

Fig. 2. Kaplan–Meier plot used to calculate rates of overall survival (A) and progression-free survival (B) for 172 patients.

Table 2
Radiation-related toxicities after SBRT treatment.

Adverse reaction	Case no.	Percentage
Fatigue (Grades 1–2)*	14	8.1%
Gastrointestinal toxicity (Grades 1–2)*	31	18.0%
Nausea/vomiting	21	12.2%
Anorexia	11	6.4%
Abdominal pain	0	0
Diarrhea	3	1.7%
Hematologic toxicity*(Grades 1–2)	9	5.2%
Increase in Child–Pugh score**	11	6.4%
2 points	6	3.5%
3 points	5	2.9%
RILD	18	10.5%
Classic	10	5.8%
Non-classic	8	4.7%

Abbreviations: SBRT, stereotactic body radiation therapy; RILD, radiation-induced liver disease.
* Common Terminology Criteria for Adverse Events, version 4.03.
** Changes in Child–Pugh scores after SBRT treatment.

Table 3
Univariate and multivariate analyses of overall survival.

	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Age	1.7 (0.83–3.4)	0.15		
Sex	0.78 (0.36–1.7)	0.54		
ECOG	1.4 (0.34–6)	0.63		
HBV status	0	1		
Child–Pugh score	1.7 (0.7–4.2)	0.24		
TACE	1.1 (0.33–3.6)	0.88		
AFP	0.85 (0.56–1.3)	0.46		
Tumor size (2 cm)	2.5 (1–6)	0.047	2.4 (0.97–5.8)	0.059
BED_{10} (100 Gy)	0.45 (0.22–0.91)	0.026	0.47 (0.23–0.94)	0.033

Abbreviations: AFP, alpha-fetoprotein; BED_{10}, biologically effective dose; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; TACE, transcatheter arterial chemoembolization.

4. Discussion

Hepatectomy is considered as a first-line treatment for early-stage HCC patients [21]. However, this approach sacrifices a large volume of functional liver and leads to high complication and surgical mortality rates [22]. Furthermore, patients with centrally located HCC suffers from incomplete resection or narrow surgical margins of hepatectomy, which leads to high recurrence and low survival rates. Meanwhile, these patients have a higher risk of operative hemorrhage.

SBRT is an emerging radiation treatment modality based on CT imaging that enables the delivery of ablative doses to tumors while sparing a sufficient portion of the normal tissue [23]. RTOG 1112 have shown that SBRT followed by sorafenib could improve overall survival rates of patients, indicating SBRT as a potential method for HCC patients. Patients with centrally located HCC who underwent SBRT previously have shown considerable good local control rates and overall survival rates. It is reported that the treatment efficacy of SBRT is comparable to that of RFA or surgery due to its high local control rate [24]. Recent studies have shown long-term survival for early-stage HCC patients treated with SBRT. Fifty patients with small HCC (tumor size $\leq$ 5 cm) who received SBRT had a 5-year OS of 77.6% [25], and 28 patients with early-stage HCC who were initially treated with SBRT achieved a 5-year OS rate of 82% in our previous study [26]. These data suggest that SBRT may serve as an alternative treatment for patients with small HCC. To date, no reports have assessed the effects of SBRT for treatment-naïve centrally located HCC [27], since these patients face more risk of surgery due to its close relationship with major vessels.

In the current retrospective study, SBRT was performed in 172 patients with centrally located HCC. The 1-, 3- and 5-year OS rates of these patients were 97.7%, 86.7% and 76.3%, respectively, which were higher than those of centrally located HCC patients who underwent surgery alone [28]. In order to get a better understanding of current literature about HCC patients, we summarize different papers regarding various treatments (Table 4). It has been reported that the 5-year OS rate of patients with early-stage HCC who received adjuvant radiotherapy after hepatectomy with narrow margins was 72.2% [29]. Another study showed that the 5-year OS rates of patients with centrally located HCC who received neoadjuvant IMRT after surgery or adjuvant radiation before surgery were 69.1% and 48.4%, respectively [12]. Taken together, the survival benefit of SBRT treatment alone in our study might be similar to the reported strategy.

The observed survival benefit of SBRT may be explained based on several factors. First, SBRT is a radical treatment technique that can administer significantly higher radiation doses to tumors than other radiotherapies, which may improve the local control rate of HCC. Indeed only 10 patients (5.4%) experienced local progression of in-field-treated lesions in our study. Improved local control may lead to better PFS rates, therefore resulting in better OS rates. Second, the radiation dose employed in SBRT focuses on the tumor without an apparent increase in the dose to organs at risk, patients seldom experience complications or other severe toxicities. Third, SBRT can reach precise GTVs and requires fewer fractions, which may be able to protect lymphocytes relative to conventional radiation therapy [30]. Moreover, compared with surgery, SBRT is more convenient for patients and is a non-invasive treatment which avoids trauma and complication. These results indicate that SBRT can function as a curative method and it may be a feasible choice for patients with centrally located HCC.

In the current study, treatment-related toxicities were mild and tolerable. Only 10.5% of patients experienced RILD. Grades 1/2 radiation-related toxicities only occurred in a small proportion of patients, and no grade 3+ toxicities were observed. The low rates of adverse events observed in our study may be explained by the fact that 1) patients who are treatment-naïve have better liver function; 2) centrally located HCCs are usually localized far from the GI tract; 3) the modified fractionation regimens and the non-invasive nature of SBRT; 4) compared with those who received perioperative radiotherapy, patients who received SBRT alone experienced lower complication rates, as they did not suffer from complications due to hepatectomies [29].

This study has several limitations. First, this was a single-arm, retrospective study. The retrospective nature of our study limited the accuracy of the toxicity evaluation. However, the baseline clinical characteristics of patients in our study are similar to those reported, making our results comparable. Though several randomized trials aimed to address the use of surgery versus SBRT for patients, including RTOG 1021 (NCT01336894), ROSEL, STARS and SABRTooth (NCT02629458), they had not been able to complete due to physician and patients' biases to favour surgery [31]. Although further research involving multi-institutional prospective studies is needed to confirm the true effects of SBRT, it is almost impossible to conduct randomized prospective multicenter clinical studies on early stage primary liver cancer with stereotactic radiotherapy. Second, the risk factors associated with OS did not show significance mainly because of the small patient sample size for this special type of lesion. Thus, additional studies with larger cohorts are needed to investigate the subgroup characteristics that would be more likely to benefit from SBRT. Third, it is hard to distinguish another original HCC from recurrence due to the diagnose standard of HCC and ethical reasons. In the present study, we define all the new lesion as recurrence, and the actual PFS may be longer. Last, most cases of HCC in this study are related to HBV infection. The etiology differs from HCC in other countries. It will be interesting to validate our findings in non-HBV-associated HCC and in other ethnicities or countries.

Our findings showed that treatment-naïve patients with centrally located HCC who received SBRT achieved competitive OS and PFS rates and low toxicity rates, indicating SBRT as an alternative treatment for

Table 4
Teatment for hepatocellular carcinoma patients.

Author	Year	Patients' number	Type of tumors	Approaches	Outcomes
ChenXP et al	2007	256	Centrally located HCC	Mesohepatectomy	5-year OS rate: 31.7%
Yu W et al	2014	119	Centrally located HCC	Hepatectomy	5-year OS rate: 48.3%
Qiu J et al	2016	353	Centrally located liver tumors	Mesohepatectomy	5-year OS rate: 40.2%
Daniel et al	2016	161	Nonmetastasis HCC	Radiofrequency ablation	2-year OS rate: 52.9%
Wang WH et al	2015	33	Centrally located HCC	Adjuvant IMRT + surgery	5-year OS rate: 62.4%
Wu F et al	2022	38	Centrally located HCC	Neoadjuvant IMRT + surgery	5-year OS rate: 69.1%
Zheng D et al	2023	172	Centrally located HCC	SBRT	5-year OS rate: 76.3%

Abbreviations: OS, overall survival; IMRT, intensity-modulated radiation therapy; SBRT, stereotactic body radiation therapy.

patients with these types of lesions. A multi-institutional prospective randomized clinical trial is needed to investigate the exact effects of SBRT.

Funding information

This study was supported by the Ministry of Science and Technology of the People's Republic of China (2022YFC2503704).

Ethic statements

Approval of the research protocol by an Institutional Reviewer Board: This study was approved by the institutional review board of the Ethics Committee of Zhongshan Hospital (approval numbers B2023-081).

Credit authorship contribution statement

Dan-Xue Zheng: Writing – original draft, Investigation, Methodology, Formal analysis, Data curation. **Yi-Xing Chen:** Resources, Writing – review & editing, Methodology. **Jing Sun:** Resources, Investigation. **Yong Hu:** Resources, Methodology, Software. **Ping Yang:** Resources. **Yang Zhang:** Formal analysis, Methodology. **Xue-Zhang Duan:** Resources. **Zhao-Chong Zeng:** Conceptualization, Supervision, Resources, Visualization, Funding acquisition, Writing – review & editing, Validation, Project administration.

Declaration of Competing Interest

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

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