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Long-Term Outcome of a Multicenter Prospective Study on Efficacy and Safety of High-Dose Stereotactic Body Radiation Therapy ≥48-h Interfraction Interval for ≤5 cm Hepatocellular Carcinoma

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Keywords
Hepatocellular carcinoma · High-dose stereotactic radiotherapy · Fractionated interval radiotherapy · Gastrointestinal toxicity

Abstract

Introduction: The goal of this study was to evaluate the efficacy and safety of high-dose stereotactic body radiation therapy (SBRT) with an extended (48 h or more) interfraction interval for hepatocellular carcinoma (HCC) ≤5 cm in size after incomplete response to transarterial chemoembolization (TACE). ***Methods:*** This multicenter prospective study included 54 patients with inoperable HCC of ≤5 cm size between July 2012 and June 2015. A total SBRT dose of 60 Gy in 3 fractions was administered within 14 days with ≥48-h interfraction interval to patients who showed an incomplete response after 1–5 sessions of TACE. Treatment responses were defined according to the modified Response Evaluation Criteria for Solid Tumors. Toxicities were evaluated using the Common Terminology Criteria for Adverse Events

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version 4.0. ***Results:*** Forty-eight patients were evaluated with a median follow-up period of 66 months (range, 2–126 months). The median tumor size was 2.0 cm (range, 1.0–4.5 cm), and most patients (87.5%) had a single lesion. The 1-, 2-, and 5-year local control (LC) rates were 100%, 94.8%, and 90.7%, respectively. The 1-, 2-, and 5-year progression-free survival (PFS) rates were 63.4%, 56.9%, and 24.9%, respectively. The 1-, 2-, and 5-year overall survival (OS) rates were 95.6%, 90.9%, and 76.5%, respectively. None of the patients experienced grade 3+ gastrointestinal toxicity, while 1 patient developed non-classic radiation-induced liver disease 2 months after SBRT. ***Conclusion:*** High-dose SBRT with a ≥48-h interfraction interval after incomplete response to TACE is effective for HCC ≤5 cm in size as evidenced by the high rates of LC and OS and acceptable treatment-related toxicity.

Introduction

Classically, external beam radiation therapy (RT) is used as a palliative rather than a curative treatment for hepatocellular carcinoma (HCC) given the difficulty of administering high doses of radiation owing to technical limitations. However, with the advancement of radiation technologies, including particle beam therapy (PBT) and stereotactic body radiation therapy (SBRT), which deliver tumoricidal doses to tumors while minimizing radiation exposure to healthy surrounding tissues, EBRT has emerged as an alternative curative option for inoperable HCC. A recent randomized clinical trial revealed that PBT was not inferior to radiofrequency ablation (RFA) and could be safely performed for patients with small HCC [1]. Several recent prospective studies on HCC have reported that SBRT is effective and provides durable tumor control with acceptable risks of toxicity [2–14]. In this context, these results have led to the increased use of SBRT as a noninvasive ablative treatment option for inoperable HCC at various stages.

Despite these encouraging findings, challenges persist, particularly concerning the optimal delivery protocol, such as duration of interfraction interval, i.e., the duration of SBRT, and dose of SBRT for HCC to maximize efficacy while minimizing toxicity. Because the combination of transarterial chemoembolization (TACE) and SBRT in HCC has several technical advantages – such as tumor shrinkage after TACE facilitating the delivery of a high radiation dose, and the remaining lipiodol inside tumors simplifying tumor volume determination and providing a target for image-guided RT using cone-beam CT – our previous study showed promising efficacy for salvage SBRT in patients with HCC who showed an incomplete response to TACE. However, this study faced the challenge of reducing gastrointestinal (GI) toxicity associated with SBRT [4]. In particular, the importance of setting a constraint dose for the GI tract and the extended interfraction interval to at least 48 h to mitigate severe GI toxicity associated with SBRT was confirmed [4, 15, 16]. To address this concern, efforts have been made to refine SBRT protocols at our institution, including setting dose constraints for the GI tract and optimizing interfraction interval of SBRT. In this study, we aimed to evaluate the efficacy and safety of high-dose SBRT with an extended (≥48 h) interfraction interval for HCC ≤5 cm in size at a distance of ≥3 cm from the GI tract after incomplete response to TACE.

Materials and Methods

Study Design and Patient Eligibility

In this single-arm, multicenter, open-label, phase 2 study, patients were prospectively enrolled in a single cohort. This study was approved by Institutional Review Boards of all participating institutions. All patients provided written informed consent before participating in the study. During the study design stage, we presumed that the response rate (1-year LC rate) would improve from 75% to 90%. Using Simon's two-stage approach, the sample size was calculated based on a significance level of 0.05 and a power of 80%. The target number of patients was 48, and the final sample size required was 54 participants after considering the potential ineligibility. The detailed trial protocol is presented in the Supporting Information and is available online (https://clinicaltrials.gov/ct2/show/NCT01825824).

The study included patients who met the following inclusion criteria: age ≥20 years; with Eastern Cooperative Oncology Group performance status of 0 or 1; having newly diagnosed HCC (diagnosed at the time of enrollment in this study) or recurrently diagnosed HCC (previously diagnosed lesions in a control state with a new intrahepatic lesion confirmed at the time of enrollment in this study); with unresectable HCC who were not indicated for local ablative treatment (including RFA or percutaneous ethanol injection) as judged by surgeons and interventional radiologists at the institutional liver

conference; with a Child-Pugh (CP) class A or B7 without ascites and hepatic encephalopathy; with single or multiple tumors having a diameter of ≤5 cm; with tumors at least 3 cm from the luminal GI normal tissues; with a normal liver volume (NLV) (total liver volume minus cumulative gross tumor volumes [GTVs]) of at least 700 mL; with an incomplete response to TACE (contrast enhancement in the tumor remained in arterial phase CT images, aside from dense lipiodol uptake after TACE) after 1–5 sessions; and with no evidence of an uncontrolled lesion in other sites, uncontrolled complications of cirrhosis, and uncontrolled intercurrent illness. In contrast, patients with a history of abdominal RT, direct invasion of the GI tract by the tumors, or tumors located less than 3 cm from the luminal GI normal tissue on the SBRT plan CT or on the last CT image at the time of enrollment in this study were excluded.

SBRT Simulation

All patients underwent TACE, which could be repeated up to five times at the discretion of the interventional physician, and multiphase liver computed tomography (CT) was performed 3–4 weeks after TACE. If viable tumors were noted in the liver, defined as an incomplete tumor filling by the lipiodol-doxorubicin mixture used in CT or magnetic resonance imaging studies (which was regarded as an incomplete response to TACE), patients were considered for SBRT and evaluated for their eligibility for this trial. Planning CT (slow CT) was performed with patients in the supine position and immobilized by abdominal compression to minimize tumor motion.

GTV was defined as enhancing lesions, including lipiodol-laden areas and necrotic areas, noted on planning CT or MR images. Based on the condition of the tumors on slow CT, internal target volumes (ITVs) were noted on images involving scanning using a slow gantry rotation speed to capture tumor motion during each slice acquisition that could include the respiratory movement of the target GTVs. The planning target volume (PTV) was defined as an ITV of +4 mm in the longitudinal direction and an ITV of +2 mm in all other directions.

SBRT Planning and Treatment

The prescribed dose delivered to tumors was 60 Gy in 3 fractions, which covered at least 90% of the PTV. For a normal liver volume of 700 mL, the total dose should not exceed 17 Gy in 3 fractions for patients with a CP score A5 and 15 Gy in 3 fractions for those with CP scores of A6 and B7. For the spinal cord, the maximum dose should not exceed 22 Gy in 3 fractions and 18 Gy in 3 fractions for 0.25 mL or less of irradiated volume. For the gastroduodenum, based on our previous findings of a preexisting gastroduodenal ulcer (GDU) as a significant risk factor for GI toxicity, the maximum dose should not exceed 28 Gy in 3 fractions if the patient has a GDU and 35 Gy in 3 fractions if the patient has no GDU, as evaluated by esophagogastroduodenoscopy (EGD) within 6 months before SBRT [4, 15]. The maximum point dose to the other GI tract was 30 Gy delivered in 3 fractions (online suppl. Table S1; for all online suppl. material, see https://doi.org/10.1159/000541685). For SBRT planning, dosimetric parameters showed acceptable compliance with the study protocol based on the results of the dummy run procedure [15]. In addition, regular protocol review workshops were held four times a year during the study, and clinical data were independently verified by cross-checking patients' files and RT charts, including Digital Imaging and Communications in Medicine RT format files, after the study.

High-energy X-rays with voltages of at least 6 MV were used. Cone-beam CT was used as an image-guided RT tool to verify and correct target positions before the delivery of each fraction. If the treatment machine is equipped with a fluoroscope, the verification can be performed using fluoroscopy instead of cone-beam CT. The treatment interval for each fraction (interfraction interval) was at least 48 h, and the total treatment time was limited to 14 days.

Response and Toxicity Evaluations

Treatment responses were defined as the best response observed on multiphase liver CT performed 2 and 6 months after SBRT by measuring the longest diameter (LD). For multiple tumors, treatment responses were defined as the sum of each LD. After 6 months, tumor evaluation was continued by performing dynamic liver CT every 4–6 months until disease recurrence or death. Complete response (CR) was defined as the disappearance of contrast enhancement in tumors during the arterial phase according to the modified Response Evaluation Criteria for Solid Tumors. Partial response (PR) was defined as a decrease in the volume of the enhanced area by >30% of the initial tumor size. Stable disease (SD) was defined as decreases in the initial tumor volume of <30%, while progressive disease (PD) was defined as increases in the tumor volume of ≥20%. Toxicities were evaluated using the Common Terminology Criteria for Adverse Events version 4.0. The patients were evaluated for GI toxicity using EGD at 2 months after SBRT. However,

Table 1. Patients' and treatment characteristics (n = 48)

Characteristics	Patients, n (%)
Age, median (range), years	61 (44–84)
Sex	
Female	12 (25.0)
Male	36 (75.0)
ECOG performance status	
0	28 (58.3)
1	20 (41.7)
Hepatitis etiology	
HBV	31 (64.6)
HCV	9 (18.7)
NBNC	8 (16.7)
Diagnosis history	
Newly (de novo)	25 (52.1)
Recurrently	23 (47.9)
Cirrhosis	
Absence	11 (22.9)
Presence	37 (77.1)
BCLC stage	
0	23 (47.9)
A	10 (20.8)
B	15 (31.3)
UICC stage	
I	27 (56.3)
II	15 (31.3)
III	6 (12.4)
Initial CP score (pre-SBRT)	
5	34 (70.8)
6	12 (25.0)
7	2 (4.2)
Pre-SBRT albumin, g/dL (range)	4.1 (1.9–4.8)
Total bilirubin, mg/dL (range)	0.8 (0.2–2.9)
Pre-SBRT GDU	
Absence	39 (81.2)
Presence / unknown	8 (16.7) / 1 (2.1)
Pre-SBRT treatment	
Resection	6 (12.5)
RFA	11 (22.9)
Resection and RFA	3 (6.25)
Resection and RFA and chemotherapy	1 (2.1)
Number of TACE before SBRT	
1	25 (52.1)
2	11 (22.9)
3	8 (16.7)
4–5	4 (8.3)
Pre-SBRT tumor marker	
AFP, median (range), ng/mL	8.9 (0.5–3,921)
PIVKA-II, median (range), mAU/mL	20 (7.11–20,973)
Number of tumors	
1	42 (87.5)
2	6 (12.5)

Table 1 (continued)

Characteristics	Patients, *n* (%)
Tumor thrombus	
Absence	48 (100)
Presence	0 (0)
LD sum, median (range), cm	2.0 (1.0–4.5)
1.0–2.0 cm	28 (58.3)
2.1–3.0 cm	7 (14.6)
3.1–4.0 cm	8 (16.7)
4.1–5.0 cm	5 (10.4)
GTV, mL (range)	7.8 (1.0–63.5)
PTV, mL (range)	14.8 (3.3–92.9)
Normal liver volume, median (range), mL	1,146 (736–2114)
Overall treatment time, median (range), days	7 (4–14)

ECOG, European Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-B, non-C hepatitis; BCLC, Barcelona Clinic Liver Cancer; UICC, Union for International Cancer Control; CP, Child-Pugh score; SBRT, stereotactic body radiation therapy; GDU, gastroduodenal ulcer; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; AFP, alpha-fetoprotein; PIVKA, protein induced by vitamin K antagonist; LD, longest diameter; GTV, gross tumor volume; PTV, planning target volume.

EGD could be omitted if an asymptomatic patient refused EGD or if the patient had high risk of bleeding, owing to underlying cirrhosis.

Endpoints and Statistical Analysis

The primary endpoint of this trial was the 1-year LC rate, which was defined as the sum of CR, PR, and SD rates divided by the total number of patients 1 year after SBRT. The secondary endpoints included 2-year OS rate, progression-free survival (PFS) rate, and treatment-related toxicity. LC, OS, and PFS were measured from the date of SBRT initiation using the Kaplan-Meier method. Data were analyzed with a closeout (study censor) date of April 3, 2023. The last follow-up date was defined as the date of the latest hospital visit for OS, and the date of the latest image follow-up (such as CT or magnetic resonance imaging) for PFS and LC. Intergroup comparisons for all factors described in Table 1 were performed using log-rank tests. All factors influencing prognosis in the univariate analysis were included in the multivariate analysis using a Cox proportional hazards regression model with a backward, conditional, stepwise procedure to determine whether the factors acted independently. All calculations were performed using the SPSS statistical software (version 25.0; SPSS, Inc., Chicago, IL, USA), and p values <0.05 were considered significant.

Results

Study Population

Between July 2012 and June 2015, 54 patients from the six participating institutions were enrolled in this study. Among them, four were excluded from this study: 2 patients were found ineligible before SBRT as their LD sum was >5 cm (6.6 cm [1 patient] and 6.9 cm [1 patient]), while 2 patients were treated with 57 Gy in 3 fractions. Additionally, 2 patients withdrew their consent after enrollment in the trial. Hence, only 48 patients were analyzed and followed up (shown in Fig. 1). Some patients enrolled in this study were also included in another phase 2 study [10].

Table 1 summarizes patients' characteristics. The participants were predominantly men (75%), with a median age of 61 years (range, 44–84 years). Hepatitis B virus infection (64%) was the frequent cause of background liver disease. Overall, 25 (52%) patients were initially diagnosed with HCC, while 23 (48%) were diagnosed with recurrent HCC. CP scores were 5, 6, and 7 in 34, 12, and 2 patients, respectively. The median AFP and PIVKA-II levels at baseline were 7.8 ng/mL (range, 0.5–3,921 ng/mL) and 20 mAU/mL (range, 7.11–20,973 mAU/mL), respectively. The median tumor size was 2.0 cm (range, 1.0–4.5 cm), and most patients (87.5%) had a single lesion. Online supplementary Table

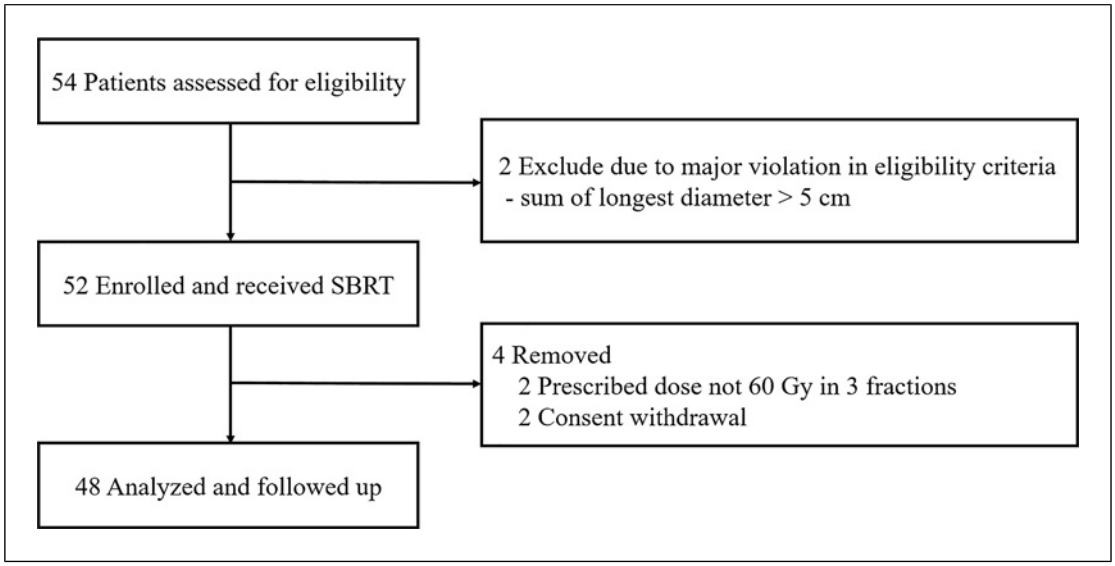

Fig. 1. Study flowchart. SBRT, stereotactic body radiation therapy.

S3 presents the dosimetric parameters for tumors, including the GTV and PTV, as well as for organs at risk (GI normal tissue and normal liver).

Efficacy

The median follow-up duration at evaluation was 66 months (range, 2–126 months). Among the study participants, 10 (21.3%), 17 (36.2%), 20 (42.5%), and 0 (0%) showed CR, PR, SD, and PD, respectively, at 2 months after SBRT, while 25 (56.8%), 13 (29.5%), 6 (13.6%), and 0 (0%) showed CR, PR, SD, and PD, respectively, at 6 months after SBRT. One and four patients were not evaluated for treatment response, respectively, due to death or loss to follow-up.

Primary tumor failure occurred in 4 patients. The 1-, 2-, and 5-year LC rates were 100%, 94.8%, and 90.7%, respectively (shown in Fig. 2). Intrahepatic failure, distant metastases, and both intrahepatic failure and distant metastases occurred in 31, 2, and 2 patients, respectively. The 6-month and 1-, 2-, and 5-year intrahepatic failure-free survival rates were 78.8%, 63.4%, 52.5%, and 27.3%, respectively. The 6-month and 1-, 2-, and 5-year distant metastasis-free survival rates were 100%, 97.6%, 97.6%, and 94.7%, respectively. The 1-, 2-, and 5-year PFS rates were 63.4%, 50.3%, and 24.9%, respectively. Among the 35 patients who relapsed after SBRT, 31 received salvage treatment, and the modalities of the salvage treatments are shown in online supplementary Table S4. During the follow-up period, 16 of the 48 patients died. The 1-, 2-, and 5-year OS rates were 95.6%, 90.9%, and 76.5%, respectively. Among the 16 patients who died, 11 succumbed to HCC, 4 to other diseases, and 1 to an unknown cause. The 1-, 2-, and 5-year cause-specific survival rates were 95.6%, 93.2%, and 88.4%, respectively. Online supplementary Figure S1 illustrates Kaplan-Meier survival outcomes from the date of initial TACE. Only preexisting cirrhosis was a significant prognostic factor for intrahepatic recurrence-free survival in the univariate ($p = 0.044$) and multivariate analyses ($p = 0.048$) (online suppl. Table S2).

Toxicity

The adverse events associated with TACE before SBRT were generally mild, with grade 2 abdominal pain occurring in 3 patients and no grade 3 or higher toxicity observed. During SBRT, no patient experienced grade 3 or higher adverse events (Table 2). Only 2 patients experienced grade 2 nausea and abdominal pain. One patient experienced grade 3 hepatic toxicity within 3 months of SBRT and had elevated alanine aminotransferase levels and increased CP score from 6 to 10, indicating non-classic radiation-induced liver disease. However, because this patient showed intrahepatic progression immediately after SBRT and died 4 months after SBRT, whether the cause of hepatic toxicity was SBRT itself or HCC progression remained unclear. Except for this patient, the remaining patients did not develop grade 3 hepatic toxicity, 38 showed consistent CP scores, 6 showed a 1-point increase in the CP score, and 3 showed a 1-point decrease in the CP score within 3 months after completion of SBRT. Only 1 patient experienced grade 2 GI toxicity, while none of them

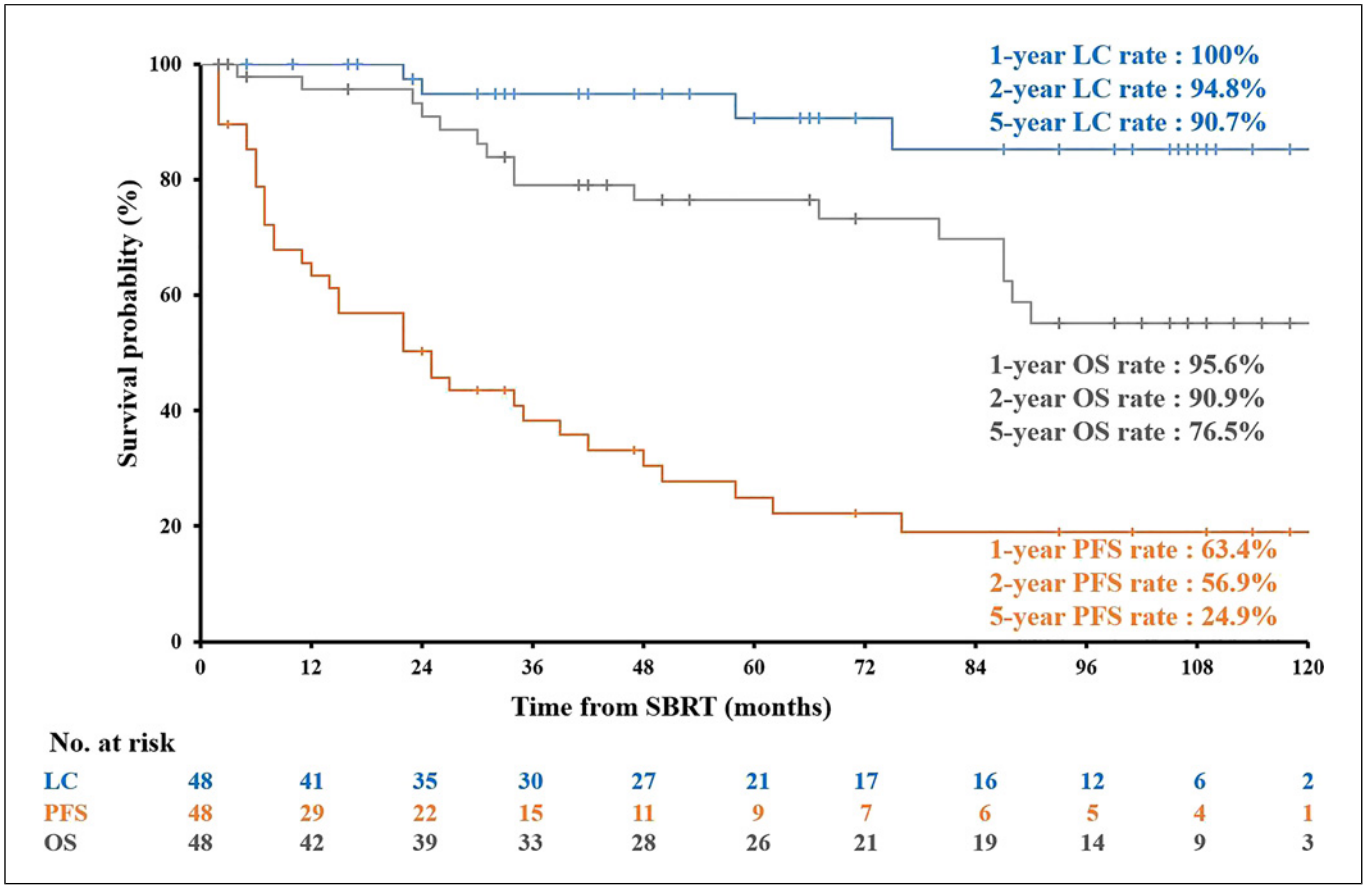

Fig. 2. Kaplan-Meier survival outcomes after SBRT. SBRT, stereotactic body radiation therapy; LC, local control; OS, overall survival; PFS, progression-free survival.

developed grade 3 or higher GI toxicity. Two patients experienced grade 2 chronic hepatic toxicity, while 3 patients experienced grade 3 chronic hepatic toxicity; however, whether these toxicities were due to SBRT itself or disease progression remained unclear. Severe chronic toxicities caused by SBRT were not reported.

Discussion

We evaluated the efficacy and safety of high-dose SBRT in patients with ≤5 cm HCC within ≥3 cm from the GI tract who showed an incomplete response to TACE. Several previously published prospective studies on SBRT for HCC reported favorable 2-year LC and OS rates of 81–100% and 34–96%, respectively [2–14]. In the current study, the 2-year LC and OS rates were 97.4% and 90.9%, respectively; with a long-term follow-up, the 5-year LC rate and the OS rate were 90.7% and 76.5%, respectively, which were highly comparable to or even better than those reported previously [4]. These promising results are probably due to rigorous patient selection as enrolled patients with relatively small tumor sizes and good baseline liver function were selected.

Although RFA is the accepted first-line treatment for patients with inoperable early-stage HCC according to current guidelines, there is a lack of high-level evidence demonstrating the durable long-term LC and OS of retreated patients, and current guidelines do not clearly describe the role of SBRT despite high LC rates [16–19]. Although no significant difference was found between RFA and SBRT in terms of LC rates for tumors <2 cm in size, Wahl et al. [20] reported that SBRT showed significant superiority in terms of LC for tumors ≥2 cm in size ($p = 0.025$) without significant difference in OS and treatment-related toxicities. They concluded that SBRT was a reasonable first-line treatment for inoperable large HCC. In the multinational study that compared the effectiveness of RFA and SBRT in patients with inoperable HCC, the 2-year cumulative local recurrence

Table 2. Toxicities according to the common toxicity criteria for adverse events version 4.0 grading scale

Adverse event	Patients, *n*	Grade 1	Grade 2	Grade 3+
Acute toxicities				
During SBRT				
Fatigue		1	0	0
Anorexia		3	0	0
Nausea/vomiting		3	2	0
Abdominal pain		2	2	0
Constipation		0	0	0
Diarrhea		0	0	0
General weakness		3	0	0
Elevation of liver enzyme				
AST		4	1	1
ALT		5	0	0
ALP		5	1	0
Bilirubin		2	4	0
Albumin		3	2	0
PT/INR		3	0	0
Ascites		2	0	0
Gastrointestinal toxicity				
Esophagitis		0	0	0
Gastritis		0	0	0
Epigastric discomfort		0	1	0
Abdominal distension		1	0	0
Gastric bleeding		0	0	0
Gastric ulcer		1	0	0
Duodenal ulcer		1	0	0
Late toxicities				
Elevation of liver enzyme				
AST		10	0	1
ALT		7	0	0
ALP		3	0	0
Bilirubin		4	3	0
Albumin		2	0	0
PT/INR		1	0	0
Ascites		0	1	0
Gastrointestinal toxicity				
Esophagitis		0	0	0
Gastritis		0	1	0
Epigastric discomfort		0	0	0
Abdominal distension		0	0	0
Gastric bleeding		0	0	0
Gastric ulcer		1	0	0
Duodenal ulcer		2	0	0
Changes of CP score (2 months after SBRT)				
−1	3			
No change	38			
+1	6			
+2 or more	1			

SBRT, stereotactic body radiation therapy; AST, alanine aminotransferase; ALT, aspartate aminotransferase; ALP, alkaline phosphatase; PT/INR, prothrombin time/international normalized ratio; CP, Child-Pugh score.

rates were 16.4% and 31.1% in the SBRT and RFA groups, respectively, favoring SBRT ($p < 0.001$) without significant difference in OS and treatment-related toxicities. In the subgroup analysis, SBRT was associated with superior LC in small tumors (≤3 cm) irrespective of the location, large tumors located in the

subphrenic region, and tumors progressing after TACE [21]. A recent meta-analysis including 17 studies with 22,180 patients found that although RFA showed better 1-year and 2-year OS rates, no significant differences were observed for long-term survival; additionally, SBRT resulted in better LC, especially for tumors ≥2 cm in size (p = 0.001). The overall treatment-related complication rate did not differ significantly between the two arms [22]. In the current study, the LC rates were 100% in 12 patients with tumors ≥3 cm. These results suggest that SBRT can be used as an excellent alternative treatment for HCC, especially for tumors ≥2–3 cm in size, regardless of the location.

In our previous study, 5 of 47 patients experienced grade 3 or higher GI toxicity; the D_{max} (the maximum dose at which bowel toxicity occurred) was 42–60 Gy in 3 fractions, while the D_{2cc} (the minimum dose up to 2 mL at which bowel toxicity occurred) was 28–56 Gy in 3 fractions. Moreover, a preexisting GDU was a significant risk factor for GI toxicity, and SBRT duration was an accurate clinical predictor of severe GI toxicity [4, 15]. Based on these results, several strategies have been adopted to reduce the incidence of treatment-related toxicity in the current study. Tumors at least 3 cm away from the GI tract were selected, and the maximum dose constraints for the GI were set to 28 Gy in 3 fractions if the patient had GDU and 35 Gy in three fractions, which has a 5% probability of developing severe GI toxicity, for patients without GDU; the interfraction interval was at least 48 h. Accordingly, owing to the use of high-dose SBRT (60 Gy in 3 fractions), only 1 patient experienced grade 2 GI toxicity, while none experienced grade 3 or higher GI toxicity.

Although our current single-arm study was unable to directly analyze whether SBRT with an extended interfraction interval could reduce treatment toxicity or improve treatment efficacy, there might be some potential advantages. Particularly in the case of SBRT, which administers large dose fractions, giving sufficient time to repair sublethal damage can be effective in reducing the toxicity of late-responding tissues [23]. In addition to our previous study mentioned above, a study by King et al. showed a reduced rate of severe rectal toxicities with an every-other-day treatment regimen versus a 5-consecutive-day treatment regimen (0% vs. 38%, p = 0.0035) for SBRT in prostate cancer [24]. From the perspective of efficacy, using a murine tumor model, Song et al. [25] suggested that the efficacy of SBRT may be significantly improved by allowing an interfraction time of 2–5 days than by administering a 10–30 Gy dose of irradiation on consecutive days, which enables the re-oxygenation of surviving hypoxic cells, thus increasing radiosensitivity. A recent preclinical study also reported that extended interval RT (5 or 7 days) was more effective than 1-day interval RT through tumor growth delay and abscopal effect [26]. From a clinical perspective, Shibamoto and Iwata [27] reported that interfraction intervals of 48–72 h may be better than a 24-h interval, and an interval of >24 h is recommended to enable reoxygenation and redistribution of SBRT in non-small-cell lung cancer. Taken together, additional studies on the potential efficacy of extended interfraction intervals of SBRT for HCC appear to be necessary.

To our knowledge, the 60-Gy dose delivered in 3 fractions is the highest biologically equivalent dose (BED_{10} using the linear-quadratic model, assuming an α/β of 10 Gy) in SBRT for HCC. In a previous study, the 2-year LC rate in patients who received ≤54 Gy in 3 fractions was 81.7%, while that in patients who received >54 Gy in 3 fractions was 100% (p = 0.029 in the univariate analysis) [4]. Another study also revealed that >54 Gy in 3 fractions for HCC could improve LC (p = 0.009) and OS rates (p < 0.001), and confirmed a positive linear relationship between SBRT dose and LC (p = 0.006) and OS (p = 0.002) [28]. Thus, higher-intensity SBRT doses may be warranted in patients with inoperable HCC to achieve high LC rates. However, patients with tumors of ≤5 cm generally showed higher LC rates (>90%) despite the relatively lower BED_{10} compared with that reported in the current study (Table 3). In a previous retrospective study comparing the efficacy of 45 Gy in 3 fractions and 60 Gy in 3 fractions, no statistical differences were found in oncological outcomes and treatment-related toxicities after SBRT for HCCs <3 cm in size [29]. In that study, the LC rate was >90% using a BED_{10} >100 Gy, but no linear associations were observed when using a BED_{10} >100 Gy. Several studies reported that a BED_{10} ≥100 Gy has a positive effect on LC and OS rates of HCC patients treated with SBRT; however, evidence for prescribing a higher dose, including 60 Gy in 3 fractions, for small HCCs remains lacking. Since a sufficient LC rate could be obtained even with just a BED_{10} of 100 Gy, the additional therapeutic effect would not be so significant even if the BED_{10} is >100 Gy [11, 30–32]. In addition, when intrahepatic recurrence occurs after SBRT, high-dose radiation exposure to the entire liver (mean liver dose) due to previous high-dose SBRT may act as an obstacle when considering the need for a repeat SBRT.

In conclusion, high-dose SBRT with a ≥48-h interval between each fraction for ≤5 cm HCC after incomplete response to TACE is safe and effective as evidenced by the

Table 3. Comparison between the current study and published studies on the efficacy of external beam radiation therapy, including stereotactic body radiation therapy, proton beam therapy, and carbon ion therapy, for small (≤50 mm) HCC

Reference	RT dose/fx	Patients, *n* (number of lesion)	BED_{10}	Tumor size, mm (median)	FU duration (median)	LC rate, %	OS rate, %	Toxicity (Gr 3+)
Komatsu et al. [30] (2011)	PBT or CIT: 52.8–76 GyE/ 4–38 fx	74	87.65–122.50	≤50	NA	95.5 (PBT 5Y) 94.5 (CIT 5Y) All 95.3 (5Y)	37.8 (PBT) 53.5 (CIT) 39.2 (5Y)	NA for ≤50, all 10.9%, RILD 3.6%
Shibuya et al. [31] (2018)	CIT: 48–60 GyE/2–4 fx	84	150–163.2	<30	NA	94.0 (2Y)	95.7 (2Y)	NA
Kim et al. [1] (2021)	PBT: 66 GyE/ 10 fx	80 (85)	109.6	<30 10–29 (12)	(51.6)	94.8 (2Y) 85.8 (4Y)	88.8 (2Y) 74.0 (4Y)	0%
Lee et al. [29] (2018)	45 Gy/3 fx	10	112.5	≤30	10–42 (24)	100 (3Y)	67.5 (3Y)	RILD 12%
	60 Gy/3 fx	34	180			93.7 (3Y)	80.3 (3Y)	
Kubo et al. [32] (2018)	48 Gy/4 fx	65 (74)	105.6	≤50 5–47 (16)	3–79 (41)	100 (5Y)	41.4 (5Y)	Hepatic toxicity 23.1%
Yeung et al. [33] (2019)	40–55 Gy/ 3–5 fx	31 (34)	72–155.8	≤50 13–50 (33)	18.3	94 (2Y)	74 (2Y)	Increased CP 19%
Kim et al. [8] (2019)	36–44 Gy/4 fx	32 (35)	68.4–92.4	≤45	12–55 (27)	25–67 (2Y)	70 (2Y)	Hematologic 28.1%
	52–60 Gy/4 fx		119.6–150.0	10–45 (21)		88–94 (2Y)	100 (2Y)	Hepatic toxicity 0%
Yoon et al. [12] (2020)	45 Gy/3 fx	50 (53)	112.5	≤50 7–31 (13)	2.9–70.6 (47.8)	100 (2Y) 97.1 (5Y)	96 (2Y) 77.6 (5Y)	Increased CP 4%
Kimura et al. [13] (2021)	40 Gy/5 fx	36 (36)	72	≤50 10–50 (23)	4–57 (20.8)	90 (3Y)	77.5 (3Y)	11.4%
Current study	60 Gy/3 fx	48 (54)	180	≤50 10–45(20)	2–126 (66)	90.7 (5Y) 85.3 (10Y)	76.5 (5Y) 55.1 (10Y)	Increased CP 4%

RT, radiation therapy; BED, biologically equivalent dose; FU, follow-up; LC, local control; OS, overall survival; Gr, grade; PBT, proton beam therapy; CIT, carbon ion therapy; GyE, Gray equivalent; fx, fraction; NA, not available; RILD, radiation-induced liver disease; Gy, Gray; GI, gastrointestinal; CP, Child-Pugh score.

long-term high rates of LC and OS with acceptable treatment-related toxicities. However, further studies are required to determine the optimal radiation dose and fractionation schedules for SBRT in HCC patients to maximize its efficacy while reducing the incidence of treatment-related toxicities.

Statement of Ethics

This study protocol was reviewed and approved by the Institutional Review Board of the Korea Institute of Radiological and Medical Sciences (KIRAMS) (K-1205-001-005). Written informed consent was obtained from all participants of this study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Dr. Jin-Kyu Kang and Won-Il Jang had full access to all of the data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Mi-Sook Kim, Won Il Jang, Chul Won Choi, Ah Ram Chang, Hae Jin Park, Younghee Park, Eun Seog Kim, Sunmi Jo, and Woo Chul Kim. Acquisition, analysis, or interpretation of data: Jin-Kyu Kang, Mi-Sook Kim, Won Il Jang, Chul Ju Han, Jin Kim, Su Cheol Park, Young-Joo Shin, Chul Won Choi, Wan Jeon, Tosol Yu, Ah Ram Chang, Hae Jin Park, Younghee Park, Eun Seog Kim, Sunmi Jo, Woo Chul Kim, Hun Jung Kim, Sun Hyun Bae, and Eunji Kim. Drafting of manuscript and statistical analysis: Jin-Kyu Kang, Mi-Sook Kim, and Won-Il Jang. Critical revision of the manuscript for important intellectual content: Jin-Kyu Kang, Mi-Sook Kim, Won-Il Jang, Chul Ju Han, Chul Won Choi, Ah Ram Chang, Hae Jin Park, Younghee Park, Eun Seog Kim, Sunmi Jo, Woo Chul Kim, Sun Hyun Bae, and Eunji Kim. Administrative, technical, or material support; and supervision: Mi-Sook Kim and Won-Il Jang.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants, but are available from the corresponding authors (Dr. Mi-Sook Kim and Dr. Won-Il Jang) upon reasonable request.

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