



Stereotactic body radiation therapy versus radiofrequency ablation for single small hepatocellular carcinoma: a propensity-score matching analysis of their impact on liver function and clinical outcomes

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Background: Stereotactic body radiation therapy (SBRT) has high efficacy for early-stage hepatocellular carcinoma (HCC) and is an accepted alternative to radiofrequency ablation (RFA). However, SBRT for HCC may cause subacute liver injury leading to negative clinical outcomes. In this study, we compared changes of liver function and prognosis after SBRT or RFA in patients with single, small HCC by using a propensity-score matching analysis.

Methods: We reviewed medical records of 140 patients with single ≤ 3 cm HCC treated with SBRT or RFA at Kurashiki Central Hospital between January 2014 and February 2019. Changes of albumin-bilirubin (ALBI) score, local recurrence, and overall survival were compared between the propensity-score matched groups (31 patients treated with SBRT and 62 treated with RFA).

Results: The ALBI score increased modestly but significantly after SBRT, while it was unchanged in the RFA group; the intergroup difference was statistically significant ($P=0.004$). No local recurrence was identified in the SBRT group, whereas the cumulative recurrence incidence was 9.7% in the RFA group ($P=0.023$). Overall survival was not significantly different between the two groups (hazard ratio: 1.32, 95% confidence interval: 0.60–2.89, $P=0.401$).

Conclusions: SBRT had modestly negative impact on liver function but with appraisable local control of HCC. Our findings should contribute to the selection of this modality for treatment of single, small HCC.

Keywords: Hepatocellular carcinoma (HCC); stereotactic body radiation therapy (SBRT); radiofrequency ablation (RFA); liver function; propensity-scores

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Introduction

Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer-related death worldwide (1). Curative treatment at an early stage is a cornerstone for improving the outcome of HCC (2). According to current guidelines, surgical resection, radiofrequency ablation (RFA), or liver transplantation is recommended for treatment of early-stage HCC (3). However, each treatment has drawbacks: surgical resection is invasive and may cause postoperative morbidity and liver failure (4); the therapeutic efficacy with RFA may be limited by tumor size and its location (5,6); and, because of the scarcity of donor organs, liver transplantation is rarely performed in Asian countries (7).

Remarkable technological advances in radiotherapy for HCC have been made in recent years (8). Stereotactic body radiation therapy (SBRT) uses hypo-fractionated irradiation with a very high dose per fraction, which enables satisfactory therapeutic effects with lower toxicity (8). The local control rate of SBRT for early-stage HCC has been reported to be 87–100% (9–11). SBRT is expected to overcome the drawbacks of surgical resection and RFA because it is less invasive than resection, and it is less influenced by tumor size and location than is RFA (6).

However, important issues with SBRT remain to be clarified. First, SBRT can cause radiation-induced liver disease (RILD) (12,13). Thanks to modern radiotherapy techniques, classic RILD (i.e., hepatomegaly, ascites, and elevated liver enzymes) is rare in the current era (14). Nonetheless, non-classic RILD, which also is associated with worse prognosis, sometimes occurs (13), and the long-term impact of SBRT on liver function is uncertain. Second, survival outcomes with SBRT are variable; a multi-center study reported better overall survival with SBRT than with RFA (6,15), whereas an analysis using the National Cancer Database reported an opposite result (16,17). In this study, using a propensity-score matching analysis, we compared the long-term impact on liver function and clinical outcomes of patients with single, small HCC treated with SBRT or RFA. We present the following article in accordance with the STROBE reporting checklist (available at <https://dx.doi.org/10.21037/jgo-21-356>).

Methods

Patients

We conducted a retrospective study by reviewing medical records of 641 patients with HCC treated at Kurashiki

Central Hospital between January 2014 and February 2019. The inclusion criteria for this study were (I) a single HCC of 3 cm or smaller; (II) diagnosis established by histology or contrast-enhanced imaging, according to the Liver Imaging Reporting and Data System (18); (III) treatment with SBRT or RFA; and (IV) patients age 20 years old or older. The exclusion criteria were (I) macrovascular invasion or extrahepatic metastasis; (II) Child-Pugh score 10 or higher; and (III) refusal to join in the study. One hundred and forty patients were included in this study; 44 were treated with SBRT and 96 with RFA. In our institution, RFA was the first-choice therapy for single, small HCC, and SBRT was chosen when RFA was considered inappropriate (e.g., local recurrence after RFA and tumors adjacent to the vessels or liver surface). All procedures were performed in accordance with the Helsinki Declaration (as revised in 2013). This study was approved by the Medical Ethics Committee of Kurashiki Central Hospital (No. 2948). Informed consent was obtained from all patients included in the study in an opt-out protocol.

SBRT procedure

Patients were immobilized with use of an individually shaped vacuum pillow and underwent a four-dimensional (4D) computed tomography (CT) scan. The gross tumor volume was delineated with the assistance of contrast-enhanced CT scans and magnetic resonance imaging (MRI). The 4D CT was used to help create an internal target volume to compensate for respiratory motion. The planning target volume (PTV) included the internal target volume plus a 3- to 5-mm expansion. A stereotactic, multiarc, dynamic, conformal radiation procedure or volumetric modulated arc therapy was performed by use of TrueBeam or Clinac IX (Varian Medical Systems, Palo Alto, CA, USA), with respiratory gating or breath hold. Target alignment and setup accuracy were ensured through use of implanted fiducial markers [Gold AnchorTM (Naslund Medical AB, Huddinge, Sweden) or VISICOILTM (IZI Medical Products, Baltimore, MD, USA)]. A total dose of 40 Gy was delivered in five fractions over 5–9 days on either an inpatient or outpatient basis.

RFA procedure

RFA was performed with real-time ultrasonographic guidance on an inpatient basis. We used Cool-tipTM RF Ablation System E Series (Covidien, Mansfield, TX,

USA) and tried to create an ablative margin of at least 5 mm surrounding the tumor; the margin setting was modified appropriately based on tumor location and its aggressiveness. Switching RFA with multiple electrodes was not conducted. Contrast-enhanced CT or nonenhanced MRI was performed on the day after RFA; if ablation was incomplete, an additional session was conducted during the same hospital stay.

Follow-up

After treatment, patients were assessed every 3 months with laboratory and radiological examination. Contrast-enhanced CT or MRI was performed at least every 6 months unless patients had contraindications to contrast administration. Post-treatment response was assessed according to the Response Evaluation Criteria in Cancer of the Liver (19). If HCC recurred, appropriate treatment was provided based on the clinical guideline (3).

Statistical analysis

Categorical variables were expressed as numbers (percentages) and continuous variables were expressed as median [interquartile range] or mean \pm standard deviation. To compare differences in patients' characteristics between the two groups, Fisher's exact test and the Mann-Whitney U test were used for categorical values and continuous values, respectively. Longitudinal changes of albumin-bilirubin (ALBI) score, local recurrence, and overall survival were compared between the propensity-score matched groups. Patients in the SBRT group were matched at a 1:2 ratio with patients treated with RFA. Propensity-score matching was performed without replacement and with a caliper of 0.2. The variables included in the propensity-score model were age, tumor size, performance status, baseline ALBI score, baseline Child-Pugh score, and the number of previous treatments for HCC. To achieve good matching of baseline liver function, minor characteristics such as sex and etiology were not included in the propensity-score model. Tumor location was excluded from the model because the intergroup difference was too large to be matched. Barcelona Clinic Liver Cancer (BCLC) staging was also not included because the stage was determined by other variables (tumor size, performance status, and Child-Pugh score).

Time to local recurrence was defined as the time from SBRT or RFA to radiologic diagnosis of local recurrence.

Overall survival was defined as the time from SBRT or RFA to all-cause death, with living patients censored on the date of last follow-up. In each treatment group, ALBI scores at 12 months after treatment were compared with the baseline values by using the Wilcoxon rank sum test. To analyze the intergroup difference of the longitudinal change of ALBI scores, repeated measures analysis of variance was employed. Some values were missing because of death or loss to follow-up; thus, we used complete-case analysis. In the SBRT group, the relationship between PTV and absolute difference of ALBI scores (baseline *vs.* 12 months after treatment) was studied by using Pearson's product-moment correlation coefficient. Kaplan-Meier analysis, the log-rank test, and the Cox proportional hazards models were used for analysis of local recurrence and overall survival. A two-tailed P value of <0.05 was considered statistically significant. All statistical analyses were performed with R (version 3.5.1, R Foundation) and JMP (version 12.2, SAS Institute, Japan).

Results

Baseline characteristics

Among the 140 patients, 101 (72.1%) were male, and the median age was 75 [67.3–81] years. Most patients (80.7%) had well-compensated liver function (Child-Pugh class A). Median tumor size was 13 [10–20] mm. Before propensity-score matching (*Table 1*), patients in the SBRT group had significantly higher age, worse performance status, higher proportion of stage A tumors, and more patients having had previous treatment than did those in the RFA group. In addition, tumor location was significantly different and SBRT was more frequently performed as salvage therapy for recurrence after RFA or transcatheter arterial chemoembolization (TACE). SBRT was implemented in several circumstances: when tumors were adjacent to vessels ($n=25$), adjacent to the liver surface or the diaphragm ($n=6$), adjacent to the biliary tracts ($n=3$), or near the heart ($n=3$); local recurrence after RFA ($n=3$); tumor undetectable with ultrasonography ($n=1$); no safe ablation route ($n=1$); the presence of a pacemaker ($n=1$); and patient's choice ($n=1$). After the matching (*Table 2*, *Table S1*), 31 patients treated with SBRT were compared with 62 patients treated with RFA. ALBI scores and other baseline characteristics were well balanced between the two groups, but patients with hepatitis C virus (HCV) infection were more numerous in the RFA group (41/62, 66.1% *vs.* 13/62, 41.9%; $P=0.044$), and the frequency of salvage therapy was significantly

Table 1 Patients' baseline characteristics before propensity-score matching

Characteristics	SBRT group (n=44)	RFA group (n=96)	P value
Age (years)	78 [70–82]	73 [67–79]	0.020
Sex (male/female)	32/12	69/27	1.000
Etiology, n (%)			0.170
HBV	8 (18.2)	12 (12.5)	
HCV	22 (50.0)	64 (66.7)	
Others	14 (31.8)	20 (20.8)	
Tumor size (mm)	14 [10–23]	13 [10–17]	0.189
Tumor location, segment			0.222
1/2/3/4	0/1/2/7	1/3/6/16	
5/6/7/8	4/7/10/13	17/16/6/31	
Tumor location, n (%)			
Periportal	25 (56.8)	15 (15.6)	<0.001
Perivenous	17 (38.6)	9 (9.4)	<0.001
Subphrenic	20 (45.5)	19 (19.8)	0.002
BCLC staging (0/A)	27/17	76/20	0.044
AFP (ng/mL)	6 [3–15]	8 [4–20]	0.575
PIVKA-II (mAU/mL)	31 [18–72]	26 [18–40]	0.134
Total bilirubin (mg/dL)	0.6 [0.4–0.9]	0.6 [0.5–0.9]	0.637
Albumin (g/dL)	3.5 [3.2–3.8]	3.5 [3.1–3.9]	0.597
ALBI score	−2.40 [−2.51 to −1.93]	−2.33 [−2.65 to −1.97]	0.760
Child-Pugh score (5/6/7/8/9)	19/18/6/1/0	43/33/12/5/3	0.666
Performance status (0/1)	32/12	85/11	0.036
Prior treatment, n (%)			
Surgery	21 (47.7)	37 (38.5)	0.401
RFA	28 (63.6)	55 (57.3)	0.600
TACE	32 (72.7)	44 (45.8)	0.005
Others	10 (22.7)	3 (3.1)	<0.001
Number of prior treatments	3.5 [2–6]	2 [0–4]	0.006
Disease-free interval (months)	8 [5–26]	10 [5–20]	0.635
Treatment setting (salvage*/not salvage)	11/33	1/95	<0.001

*, recurrence after RFA or TACE. SBRT, stereotactic body radiation therapy; RFA, radiofrequency ablation; HBV, hepatitis B virus; HCV, hepatitis C virus; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; PIVKA, protein induced by vitamin K absence or antagonists; ALBI, albumin-bilirubin; TACE, transcatheter arterial chemoembolization.

higher in the SBRT group (8/23, 25.8% vs. 1/16, 1.6%, $P<0.001$). Perivascular and subphrenic tumors were more common in the SBRT group. In HCV-infected patients,

antiviral therapy would have influenced the longitudinal change of liver function, but only a small number of patients received antiviral therapy within 1 year after SBRT or RFA

Table 2 Patients' baseline characteristics after propensity-score matching

Characteristics	SBRT group (n=31)	RFA group (n=62)	SMD	P value
Age* (years)	75.2±9.1	75.0±7.5	0.025	0.907
Sex (male/female)	24/7	43/19	0.183	0.471
Etiology				
HBV	8/23	7/55	0.380	0.132
HCV	13/18	41/21	0.500	0.044
Tumor size* (mm)	14.7±6.4	15.0±5.5	0.043	0.842
Tumor location				
Right lobe/left lobe	25/6	48/14	0.079	0.795
Periportal, n (%)	32 (51.6)	9 (14.5)	0.858	<0.001
Perivenous, n (%)	22 (35.5)	6 (9.7)	0.649	0.001
Subphrenic, n (%)	30 (48.4)	13 (21.0)	0.602	0.002
BCLC staging (0/A)	22/9	46/16	0.072	0.806
AFP (ng/mL)	5 [3–15]	8 [4–21]	0.135	0.037
PIVKA-II (mAU/mL)	31 [18–62]	26 [19–45]	0.011	0.565
ALBI score*	-2.32±0.45	-2.28±0.46	0.088	0.692
Child-Pugh score*	5.74±0.81	5.82±1.05	0.086	0.709
Performance status* (0/1)	26/5	51/11	0.043	1.000
Number of prior treatments*	3.9±3.1	3.7±3.4	0.065	0.774
Surgery	0.52±0.63	0.55±0.69	0.049	0.828
RFA	1.39±1.63	1.55±1.60	0.100	0.649
TACE	1.68±1.47	1.40±1.58	0.180	0.422
Disease-free interval (months)	8 [5–18]	10 [5–20]	0.135	0.582
Treatment setting (salvage/not salvage)	8/23	1/61	0.751	<0.001

*, variables included in the propensity score model. SBRT, stereotactic body radiation therapy; RFA, radiofrequency ablation; SMD, standardized mean difference; HBV, hepatitis B virus; HCV, hepatitis C virus; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; PIVKA, protein induced by vitamin K absence or antagonists; ALBI, albumin-bilirubin; TACE, transcatheter arterial chemoembolization.

treatment (Table S2).

Longitudinal changes of ALBI score

Figure 1 illustrates the longitudinal ALBI scores in the two treatment groups. In the SBRT group, the ALBI score gradually increased (i.e., liver function got worse) between the baseline and 12 months after treatment (-2.32 ± 0.45 vs. -2.17 ± 0.61 , $P<0.001$) (Figure 1A). In contrast, the ALBI score was unchanged in the RFA group (-2.28 ± 0.46 at the baseline vs. -2.30 ± 0.55 at 12 months after treatment, $P=0.839$) (Figure 1B). Table 3 presents the numerical

values for the longitudinal changes in ALBI values for the SBRT and RFA groups; the intergroup difference of the longitudinal changes of ALBI scores was statistically significant in the propensity-score matched cohort ($P=0.004$) and in the whole cohort ($P=0.034$). No significant difference was observed when we excluded the patients with disease-free interval of less than 24 months ($P=0.531$). Figure 2 illustrates the subgroup analysis stratified by baseline modified ALBI (mALBI) grade (20); whereas ALBI scores increased after SBRT in patients who had reduced liver function (mALBI grade 2a, $P=0.007$; and 2b, $P=0.041$) at baseline, scores did not increase in the patients who had

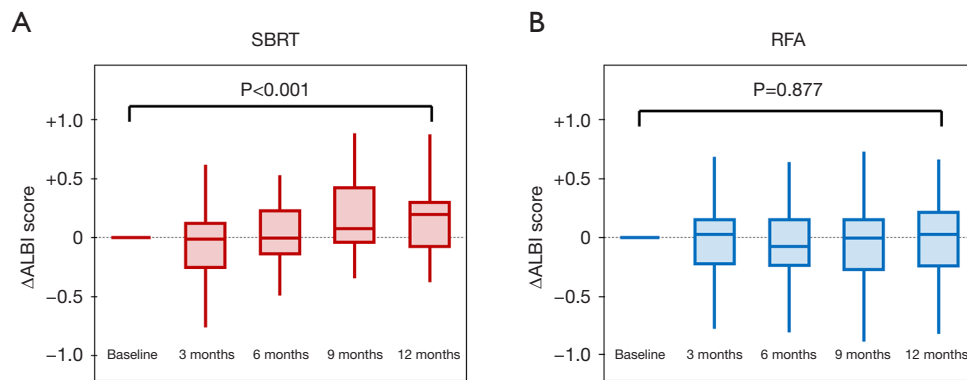


Figure 1 Longitudinal changes of ALBI score in (A) SBRT group and (B) RFA group. Differences of ALBI scores from baseline (Δ ALBI scores) are shown in the figure. Vertical lines represent the ranges and box contains values between 25th and 75th percentiles (central line, median). ALBI scores at 12 months in the SBRT group were significantly increased from baseline, whereas scores were unchanged in the RFA group. ALBI, albumin-bilirubin; SBRT, stereotactic body radiation therapy; RFA, radiofrequency ablation.

Table 3 Longitudinal change of ALBI score after treatment

Types of cohorts	SBRT group	RFA group	P _{interaction} *
Matched cohort (n=93)			0.004
Baseline	-2.32±0.45	-2.28±0.46	
3 months	-2.33±0.48	-2.29±0.43	
6 months	-2.28±0.47	-2.31±0.57	
9 months	-2.15±0.56	-2.36±0.48	
12 months	-2.17±0.61	-2.30±0.55	
Cohort before the matching (n=140)			0.034
Baseline	-2.26±0.52	-2.29±0.49	
3 months	-2.28±0.55	-2.30±0.47	
6 months	-2.17±0.65	-2.32±0.57	
9 months	-2.13±0.65	-2.34±0.54	
12 months	-2.16±0.68	-2.30±0.56	
Cohort excluding patients with disease-free interval of <24 months (n=57)			0.531
Baseline	-2.35±0.61	-2.41±0.48	
3 months	-2.44±0.68	-2.43±0.47	
6 months	-2.42±0.68	-2.49±0.55	
9 months	-2.33±0.76	-2.59±0.45	
12 months	-2.39±0.69	-2.52±0.44	

*, repeated measures analysis of variance. ALBI, albumin-bilirubin; SBRT, stereotactic body radiation therapy; RFA, radiofrequency ablation.

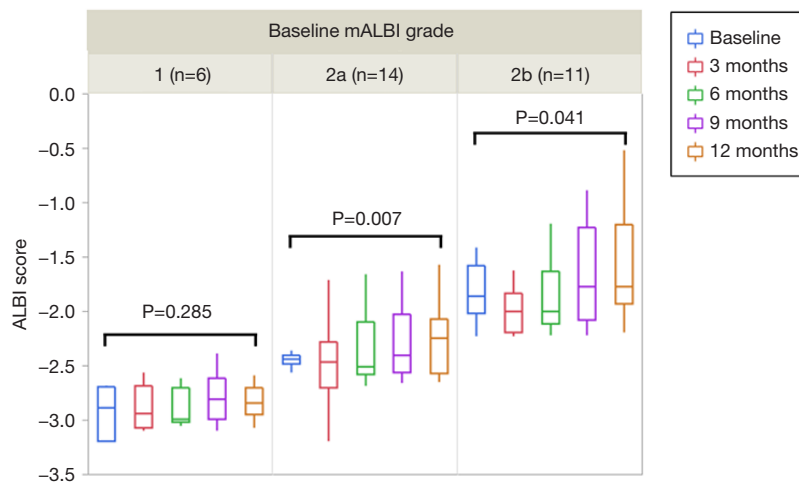


Figure 2 Subgroup analysis of the longitudinal changes of ALBI score after SBRT. The whole cohort was divided into three subgroups according to the baseline mALBI grade. ALBI, albumin-bilirubin; SBRT, stereotactic body radiation therapy; mALBI, modified ALBI.

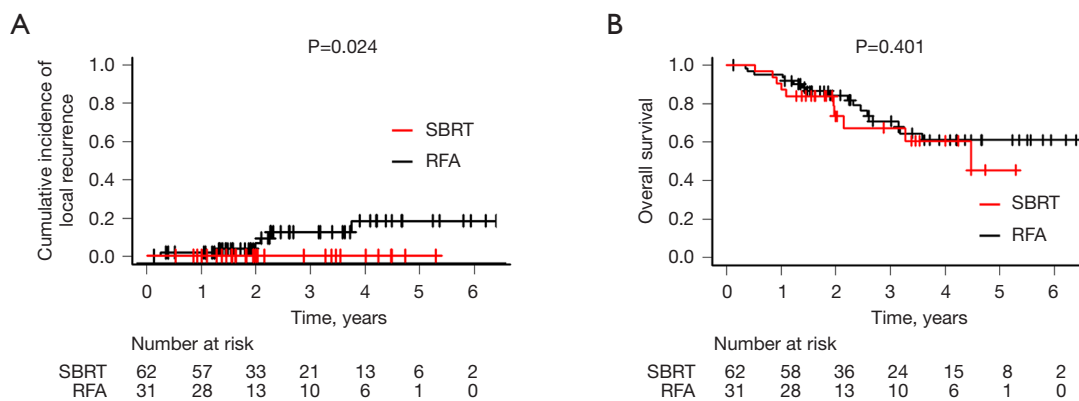


Figure 3 Kaplan-Meier analysis of cumulative incidence of local recurrence (A) and overall survival (B). SBRT, stereotactic body radiation therapy; RFA, radiofrequency ablation.

good ALBI score (mALBI grade 1, $P=0.285$) at baseline. During the 12 months after therapy, intrahepatic recurrence of HCC including local recurrence was identified in 9 patients in the SBRT group (29.0%) and 19 patients in the RFA group (30.6%), a statistically insignificant difference ($P=1.000$). This result is evident that recurrence of HCC was not responsible for differences in longitudinal changes of ALBI scores in the two groups. In the SBRT group, medians of gross tumor volume and PTV were 3.4 (range, 0.5–32.0) mm^3 and 27 (range, 5–104) mm^3 , respectively. PTV was not significantly associated with absolute difference of ALBI scores (baseline *vs.* 12 months after SBRT); the correlation coefficient = -0.22 and $P=0.191$ (Figure S1). Besides worsening of liver function, no specific

treatment-related toxicity was detected, except one case with acute cholecystitis after SBRT.

Local recurrence and overall survival

Figure 3A illustrates that during the follow-up periods of up to 63.3 (median, 23.4) months in the SBRT group and up to 76.6 (median, 27.1) months in the RFA group, no local recurrence of HCC was identified in the SBRT group, whereas 6 cases were identified in the RFA group, a cumulative incidence of 9.7% ($P=0.024$). Figure 3B illustrates that during the follow-up periods, 10 (32.3%) patients in the SBRT group and 17 (27.4%) patients in the RFA group died, a statistically insignificant difference

(hazard ratio: 1.32, 95% confidence interval: 0.60–2.89, $P=0.401$). The cumulative incidence of all-cause mortality at 5 years was 32.3% in the SBRT group and 43.5% in the RFA group. When we excluded patients with disease-free intervals less than 24 months instead of propensity-score matching, no significant intergroup difference was observed in the local recurrence (6.3% in the SBRT group and 14.6% in the RFA group, $P=0.660$) or overall survival (hazard ratio: 1.84, 95% confidence interval: 0.33–10.35, $P=0.484$).

Impact of increased ALBI score on survival outcomes

In the SBRT group, ALBI score increased by 0.15 on average during 12 months follow-up. To investigate the clinical impact of the increase, we compared survival outcomes between patients with and without worsening of ALBI score. Increase of ALBI score (absolute difference ≥ 0.15) was seen in 15 patients (48.4%) in the SBRT group and 21 (33.9%) patients in the RFA group. The increase of ALBI score was significantly associated with worse overall survival ($P=0.024$), whereas there was no significant association with local-recurrence free survival ($P=0.628$) (Figure S2).

Discussion

In this study of therapy for single, small HCC, SBRT had significantly worse impact on liver function, assessed by ALBI score, but achieved better local control than did RFA. Despite these differences, overall survival was similar between patients treated with the two procedures. To our best knowledge, this is the first study that compared, with propensity-score matching analysis, the long-term effects of SBRT and RFA on liver function.

In studies that have used Child-Pugh score for assessment of liver toxicity, the changes of liver function after treatment were not significantly different between SBRT- and RFA-treated patients (15,21). We used ALBI score for assessment of liver function—which is reportedly a better predictor of the prognosis of HCC than Child-Pugh score (22)—to analyze the liver function as a continuous variable. Thus, we could analyze the delicate changes of liver function, which disclosed the differences between SBRT and RFA treatment.

The increases in ALBI score became noticeable more than 6 months after SBRT. This long interlude can be explained by the fact that, after SBRT, blood flow decreases and the necrotic parenchyma expands over several months (23,24). We also found that increase of ALBI scores was associated

with abnormal liver function (mALBI grade 2a and 2b) at baseline. This observation is in accordance with reports that worse liver function at baseline was associated with higher risk of RILD (25–27). Thus, careful follow-up of liver function should be continued for at least 1 year after SBRT, especially in patients with known impaired liver function.

Although liver toxicity, defined by increased ALBI score, was associated with SBRT more than with RFA, the degree was mild and not critical. Moreover, it should be appreciated that the excellent local control rate and the similar overall survival with SBRT was achieved despite the procedure being mostly performed for tumors that were difficult to completely ablate with RFA. Other studies also have found better local control of HCC with SBRT than with RFA, especially for perivascular tumors (6,15,21). Since complete ablation is associated with better prognosis (28), the excellent local control with SBRT may also be beneficial. In contrast to our findings, an analysis of the National Cancer Database in the United State found SBRT inferior to RFA in survival benefit (14). However, that study did not include important variables, such as liver function, performance status, and treatment history for HCC, as matching factors. Other studies that balanced baseline liver function and previous treatment history found that survival outcomes with SBRT were similar to (15,29) or even superior to outcomes with RFA (6). We also included the numbers of previous treatment and liver function in the propensity-score model and found that overall survival with SBRT was like that with RFA. Taken together, our findings suggest that SBRT is a promising treatment for early-stage HCC, especially for HCCs that are difficult to treat with RFA, despite its modest adverse effect on liver function.

The adverse effect on liver function in our patients treated with SBRT occurred despite our cautious use of that modality. Patients were treated with a total dose of 40 Gy, TACE was not combined, and fiducial gold marker was used to compensate for respiratory liver motion. In other institutions, doses higher than 40 Gy together with TACE have been used (30,31). The results of our subgroup analysis stratified by baseline liver function suggest that lower radiation dose (35 Gy) may be appropriate for patients with impaired liver function (15).

Limitations of our study are these: (I) it is a retrospective study, thus inherently flawed by selection and indication bias; though we performed propensity-score matching, unidentified confounding factors could have existed. (II) The sample size was relatively small; thus, some baseline characteristics including tumor location

and treatment setting (salvage/not salvage) were not fully balanced even after matching. (III) The follow-up period was insufficient in some patients, which might have skewed the interpretation of survival outcomes. (IV) Most patients in this study had previously been treated for HCCs. When we excluded patients with disease-free intervals less than 24 months, no significant intergroup difference was observed in local recurrence or the longitudinal change of ALBI scores. Thus, our results cannot be simply applied to patients for treatment-naïve HCCs. To overcome these limitations, a prospective study (UMIN000036081) is ongoing in our institution to reassess the present results. (V) Dose and fractions of radiation used for HCC may not have been optimal. Although giving 40 Gy in five fractions is a commonly accepted protocol for treating HCC (15,31), the issue needs further study. (VI) Details of the RFA protocol differ among institutions or countries. Although we adopted the standard protocol in Japan (32), other procedures such as switching RFA using multiple electrode or CT-guided RFA are common in other countries. Switching RFA may provide better local tumor control than conventional RFA; however, the local recurrence rate in our study was not inferior to the results of previous studies with switching RFA (12.4–20.5% at 36 months) (33,34). Other studies have also shown that local control and survival outcomes did not differ between ultrasound-guided and CT-guided RFA (35,36).

Conclusions

SBRT had modestly negative impact on liver function but with appraisable local control of HCC in the real-world practice for single, small HCC. These advantage and disadvantage of SBRT should be considered in selecting the treatment modality, and long-term monitoring of liver function is advised after SBRT, especially in patients with pretreatment impaired liver function.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of Kurashiki Central Hospital (No. 2948). Informed consent was obtained from all patients included in the study in an opt-out protocol.

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Table S1 Details of previous treatments before SBRT and RFA after propensity-score matching

Variables	SBRT group (n=31)	RFA group (n=62)	P value
Any prior treatment (present/absent)	28/3	49/13	0.247
Surgery (present/absent)	14/17	27/35	1.000
Surgery, times	0 [0–1]	0 [0–1]	0.956
RFA (present/absent)	19/12	42/20	0.644
RFA, times	1 [0–3]	1 [0–2]	0.505
SBRT (present/absent)	3/28	4/58	0.682
SBRT, times	0 [0–0]	0 [0–0]	0.630
TACE (present/absent)	22/9	36/26	0.262
TACE, times	2 [0–3]	1 [0–2]	0.291

SBRT, stereotactic body radiation therapy; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization.

Table S2 Antiviral therapy for chronic hepatitis C infection

Timing of treatment	SBRT group (n=13)	RFA group (n=41)	P value
No treatment, n (%)	6 (46.2)	18 (43.9)	1.000
Treated before SBRT/RFA, n (%)	6 (46.2)	10 (24.4)	0.170
Treated within 1 year after SBRT/RFA, n (%)	1 (7.7)	6 (14.6)	1.000
Treated more than 1 year after SBRT/RFA, n (%)	0 (0.0)	7 (17.1)	0.176

SBRT, stereotactic body radiation therapy; RFA, radiofrequency ablation.

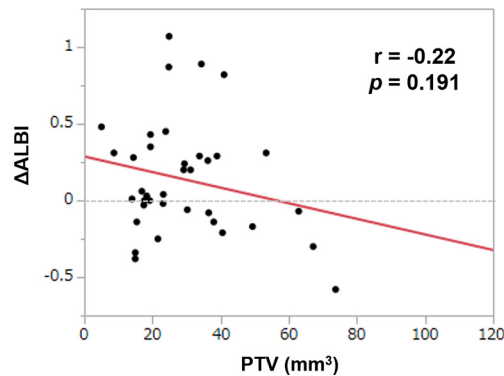


Figure S1 Correlation between PTV and absolute difference of ALBI scores (Δ ALBI, baseline vs. 12 months after SBRT). PTV, planning target volume; ALBI, albumin-bilirubin; SBRT, stereotactic body radiation therapy.

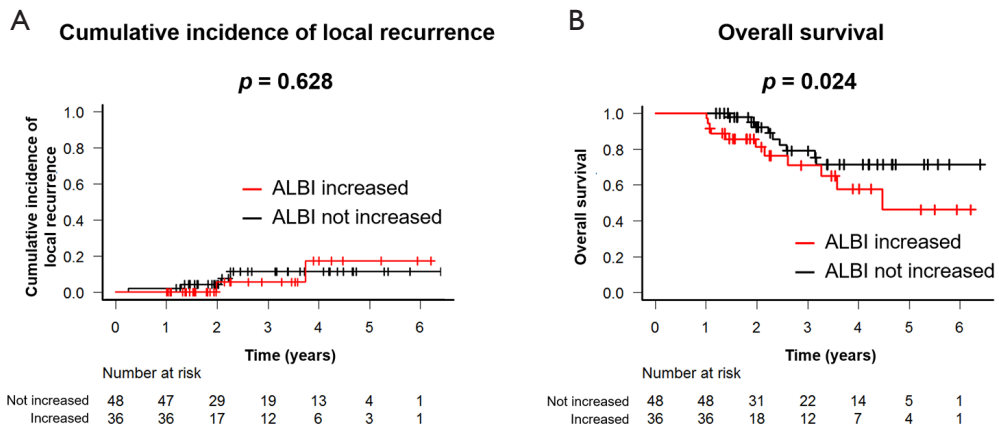


Figure S2 Comparison of cumulative incidence of local recurrence (A) and overall survival (B) between patients with and without ALBI score increase. ALBI, albumin-bilirubin.