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Original Article

Retrospective analysis of stereotactic body radiation therapy efficacy over radiofrequency ablation for hepatocellular carcinoma

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ABSTRACT

Background and purpose: To evaluate the efficacy of stereotactic body radiotherapy (SBRT) and radiofrequency ablation (RFA) for hepatocellular carcinoma (HCC).

Methods and materials: Patients treated for HCC between 2012 and 2016 were reviewed. Among these, 668 patients who underwent RFA of 736 tumors and 105 patients who underwent SBRT of 114 tumors were included. Using propensity score matching (PSM) to adjust for clinical factors, 95 tumors were selected from each treatment arm. Freedom from local progression (the primary endpoint, FFLP) was compared before and after adjustment with PSM.

Results: At baseline, SBRT-treated tumors were more advanced, larger (median, 2.4 *vs.* 1.6 cm), and more frequently located in the subphrenic region than RFA-treated tumors ($P < .001$). The median follow-up was 21.5 (interquartile range, 11.2–36.7) months. Before PSM, the 2-year FFLP rates were 76.3% for the SBRT group and 70.2% for the RFA groups, respectively. After PSM, the 2-year FFLP rates were 74.9% for the SBRT group and 64.9% for the RFA group, respectively. The local control rates were not significantly different. The Cox proportional hazards model revealed the treatment modality as an independent predictor of local recurrence favoring SBRT in the entire cohort and in the PSM model. Elevated tumor markers, tumor location (subphrenic region), and tumor size (>2.0 cm) were also independent predictors of local progression.

Conclusion: SBRT appears to be an effective alternative treatment for HCC when RFA is not feasible due to tumor location or size.

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In early-stage small hepatocellular carcinoma (HCC), a cure can be achieved with surgical resection; however, many patients are not appropriate candidates. Several non-surgical, locoregional curative treatments are available for localized HCC, including stereotactic body radiation therapy (SBRT), radiofrequency ablation (RFA), percutaneous ethanol injection, and transarterial chemoembolization (TACE).

According to the current guidelines of the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases (AASLD) [1,2], RFA is recommended as a first-line treatment for early-stage HCC. However, RFA has some limitations, including size discrepancies, tumor proximity to major vascular or biliary structures, and limited accessibility of ultrasonography (US) [3,4].

In recent decades, SBRT has increasingly been used to treat tumors not suited for surgery or RFA [5,6] and favorable outcomes have been noted with 1-year local control (LC) rates between 70 and 90% [7–9]. However, in the current guidelines, the effectiveness of SBRT is not well understood.

Until now, limited evidence has been available for determining the efficacy of SBRT in comparison to RFA. A recent study [10] has attracted widespread attention from physicians due to the potential applications of SBRT and RFA; however, much controversy exists, due to a lack of well-designed randomized trials [11–13]. There has only been one phase III randomized trial that tested the efficacy of SBRT and RFA in the treatment of colorectal carcinoma liver metastasis until now (NCT 01233544).

In this study, we investigated the role of SBRT in treating localized HCC. We retrospectively analyzed the therapeutic efficacy of SBRT compared with that of RFA using propensity score matching analysis (PSM) to overcome potential confounders.

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Methods and materials

Study population

Because SBRT for HCC has been introduced since 2012 in our institution as a phase I trial [14], the study period was set from 2012 to 2016. We retrospectively reviewed the institutional database for RFA and SBRT with curative intent and retrieved the following data during the study period. We included the patients regardless of prior liver-directed treatment; some had received treatment ("yes" for prior liver-directed treatment) while some had not ("no" for prior liver-directed treatment). We identified 719 patients who underwent RFA and 108 patients who underwent SBRT. Patient selection was based on the following exclusion criteria: previous RFA or SBRT to the treatment area, missing follow-up data (no follow-up within one month after each treatment), and RFA in combination with percutaneous ethanol injection. Tumor location was defined according to the Couinaud nomenclature using pretreatment imaging (liver dynamic computed tomography [CT], magnetic resonance imaging [MRI], and US). Lesions located in the liver dome or adjacent to the diaphragm (maximum distance of 0 mm between diaphragm and tumor) were classified as subphrenic tumors [15]. We defined tumor location based on both axial and coronal section of CT or MRI. The study was approved by the Institutional Review Board (no. 4-2017-0417) of Yonsei University Hospital (Seoul, Korea).

Treatment

The optimal treatment modality was discussed and determined by a multidisciplinary team. The team suggested local therapies even in selected patients with Barcelona Clinic Liver Cancer (BCLC) stage B or C after considering clinical situations. Operable patients underwent resection or liver transplantation. Inoperable patients were candidates for local therapies (external beam radiotherapy, RFA, or TACE).

Stereotactic body radiation therapy

The eligibility criteria, planning CT scan procedure, and immobilization techniques have been described previously [14]. Briefly, the eligibility criteria included primary HCCs not suited for surgery; recurrent HCCs after multiple liver-directed treatments; a maximum tumor diameter of $\leq$5.0 cm for a single tumor or the sum of the diameters being $\leq$6.0 cm for up to three tumors; a normal liver volume of >800 cc; and no prior radiotherapy to the targeted area. To minimize internal organ motion, Vac-Lok™ (CIVCO, Coralville, IA) and an abdominal compression device was used for immobilization and respiratory regulation.

The gross tumor volume (GTV) was defined as the gross disease, determined using liver dynamic CT and MRI. Internal target volume (ITV) included all respiratory movements of the GTV in 4-dimensional CT scans. A differential margin (radial 5.0 mm, cranio-caudal 7.0 mm) was added to the ITV to define the planning target volume (PTV). Median GTV and PTV were 24.1 (range, 2.3–140.0) cc and 65.0 (range, 8.2–239.2) cc, respectively. Sixty-five patients (61.9%) received a total of 60 Gy in 4 fractions (fx) (125.0 Gy of equivalent dose in 2.0 Gy fraction [EQD2]) and 22 patients (21.0%) received 52 Gy/4 fx (EQD2 100.0 Gy). Other dose-fractionation schedules (from the phase I dose-escalation cohort) included a total of 36 Gy/4 fx (n = 6; 5.7%), 45 Gy/3 fx (n = 6, 5.7%), 44 Gy/4 fx (n = 4; 3.9%), 40 Gy/4 fx (n = 1; 0.9%), and 40 Gy/5 fx (n = 1; 0.9%). SBRT was delivered using Tomotherapy (Hi-Art TomoTherapy; Accuray, Madison, WI) (n = 60; 57.1%), volumetric modulated arc therapy (Elekta VMAT™; Elekta, Stockholm, Sweden) (n = 33; 31.4%), CyberKnife (CyberKnife M6; Accuray, Sunnyvale, CA) (n = 6; 5.7%), and 3-dimensional conformal radiotherapy in (n = 6; 5.7%) with the goal of maximizing the dose to 95.0% of the PTV. The normal tissue constraints have been described previously [14]. Briefly, dose constraints included at least 700 cc of the uninvolved liver volume receiving less than 15 Gy, less than or equal to 2/3 of the right kidney receiving greater than 15 Gy, maximum spinal cord dose of 18 Gy, and a maximum dose of 24 Gy to the stomach or bowel. The median normal liver volume was 1,237 (range, 777–1,979) cc, with a mean liver dose of EQD2 11.0 (range, 2.0–24.0) Gy.

Image-guided radiation therapy was performed before each treatment session for verification and to reduce set-up uncertainties. Daily image guidance was achieved through megavoltage CT (Hi-Art TomoTherapy), kilovoltage cone-beam CT (Elekta VMAT™ or 3-dimensional conformal radiotherapy), or the implantation of three gold fiducials with two standard orthogonal x-rays (CyberKnife M6).

Radiofrequency ablation

RFA was performed percutaneously under US guidance. All procedures were performed using a 17-gauge cooled-tip needle (Cooltip RF ablation system, Valleylab, Boulder. Co, USA) and performed under real-time US guidance. Percutaneous RFA was performed under local anesthesia with conscious sedation. Two or three needles with optimal positioning permitted complete destruction of the tumor with at least a 1.0-cm margin surrounding the tumor. After an initial power application of 50.0 W, the power was increased in 10.0-W increments at 1, 2, 3, and 4 minutes to reach a maximum power of 90.0 W. The treatment was repeated with electrode repositioning until the tumor was visibly ablated. In all sessions, complete ablation was confirmed by CT immediately after the procedure. Without complete ablation, immediate additional RFA was performed.

Follow-Up

Patients were assessed during treatment and after the completion of treatment at first month, every 3 months for the first year, and every 6 months thereafter. At each follow-up, CT or MRI, liver function tests, and tumor markers (alpha-fetoprotein [AFP] and prothrombin induced by vitamin K absence-II [PIVKA-II]) were evaluated. Radiological responses were assessed using the modified Response Evaluation Criteria in Solid Tumors (mRECIST) [16] in each treated tumor. Local progression was defined as an in-field recurrence within or at the PTV for tumors receiving SBRT and recurrence within or adjacent to the ablation zone for tumors receiving RFA. Intrahepatic tumor progression outside of treated sites was defined as distant recurrence. Grading of treatment-related toxicity was performed at the time of follow-up, according to the CTCAE (version 4.03) [17]. In the SBRT group, radiation-induced liver disease (RILD) was defined as the presence of anicteric ascites with elevated alkaline phosphatase levels to at least twice the pretreatment levels in the absence of progression or elevated transaminase levels to at least five times above the normal upper limit or pretreatment level within 3 months of SBRT or a decline in liver function (measured by a worsening Child-Pugh score by 2 or more) [18].

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows (Version 23.0; IBM Corp., Armonk, NY) and SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). Mann–Whitney U (non-normally distributed data) and Student's t-tests (normally distributed data) were used to compare the continuous variables.

Pearson's Chi-square and Fisher's exact tests were employed to analyze the differences in categorical variables. The primary endpoint was freedom from local progression (FFLP). FFLP was defined as the duration from the first date of treatment with SBRT or RFA to the date of local progression at the level of the tumor or last follow-up. Progression-free (PFS) and overall survival (OS) were calculated from the date of treatment to the date of recurrence, death, or last follow-up. FFLP, PFS, and OS were analyzed using the Kaplan–Meier method. To minimize the effects of potential confounders and selection bias, PSM analysis was carried out. A multivariate logistic regression model, including age, sex, viral etiology, Child-Turcotte-Pugh class (C-P class), BCLC stage, platelet counts, serum AFP levels, PIVKA-II levels, treatment aim, tumor location, and tumor diameter was used to calculate the propensity scores. Following the estimation of propensity scores, the tumors were matched using 1:1 nearest neighbor matching with a caliper distance set at 0.15 standard deviations of the logit of the propensity score. PSM was performed without replacement. Non-matched results were discarded. The propensity score distribution was evaluated for sufficient overlap between the two groups to ensure comparability. Potential prognostic factors for FFLP, including all baseline covariates used in the PSM analysis and treatment modality, were assessed using Cox proportional hazards regression models in univariate and multivariate analyses for all tumors (not just the matched tumors) to determine adjusted hazard ratios (HRs) and 95.0% confidence intervals (CIs). We included all possible clinical candidates affecting prognosis in both univariate and multivariate analyses to minimize underestimation of each factor. PSM analysis was performed using the MatchIt package in R (The R Foundation for Statistical Computing, Vienna, Austria) [19]. Furthermore, inverse probability of treatment weighting (IPTW) was also used to adjust for covariable imbalance. Using the propensity score used in PSM, we fitted a weighted time-dependent Cox proportional hazards model to compare SBRT and RFA. For all statistical analyses, a $P < .05$ was considered statistically significant.

Results

Patient characteristics

In total, 773 patients with HCC were identified, including 668 patients who received RFA for 736 tumors and 105 patients who received SBRT for 114 tumors. The patient characteristics are summarized in Table 1. The etiology of HCC was related to chronic hepatitis B virus infection in 73.0% of patients, followed by chronic hepatitis C virus infection (14.0%), and alcoholic liver cirrhosis (13.1%). The majority of patients had BCLC stage 0 (46.2%) or A (34.7%) disease with pretreatment C-P class ranging from A5 to B9. One or more liver-directed treatments were administered before in 615 patients (79.6%). Median tumor size was 1.7 (range, 0.5–5.5) cm. SBRT-treated patients had more advanced-stage disease, larger tumors, higher pretreatment PIVKA-II levels, and a higher incidence of prior liver-directed treatments than RFA-treated patients ($P < .05$).

Distributions in the treated liver segments also differed significantly (Supplementary Table S1). In the SBRT group, the majority of tumors were located in segment 7 ($n = 31$; 27.2%), which differed from the RFA group ($n = 102$; 13.9%). SBRT-treated tumors were also more frequently located in the subphrenic region than those treated with RFA (50.0% vs. 31.2%, respectively; $P < .001$).

Treatment outcomes

The median follow-up period was 21.9 (interquartile range [IQR], 11.8–31.2) months for the SBRT group and 21.6 (IQR, 11.1–37.3) months for the RFA group ($P = .175$). The 1- and 2-year FFLP rates were 85.7% and 76.3% for tumors treated with SBRT and 82.3% and 70.2% for tumors treated with RFA groups, respectively ($P = .248$; Fig. 1A). The 1- and 2-year PFS rates were 37.8% and 35.6% for SBRT groups and 54.3% and 30.3% for RFA groups, respectively ($P = .838$). The 1- and 2-year OS rates were 88.5% and 74.8% for patients in SBRT group and 91.1% and 79.8% for patients in RFA group, respectively ($P = .504$).

Factors associated with freedom from local progression

In the univariate analysis, C-P class (B), serum AFP & PIVKA-II levels, tumor location (subphrenic region), and size (>2.0 cm) were attributed to local progression ($P < .05$). In the multivariate analysis, treatment modality was significantly associated with LC, favoring SBRT ($P = .004$). Other independent predictors included AFP & PIVKA-II levels, tumor location (subphrenic region), and size (>2.0 cm) (Table 2). There was no interaction between treatment modality and tumor size ($P = .630$). In the subgroup analysis based on tumor size, SBRT correlated with better local control in tumors larger than 2.0 cm ($P = .012$) but not in tumors $\leq$2.0 cm ($P = .061$) (Supplementary Table S2).

Freedom from local progression after propensity score matching

PSM was performed to minimize the discrepancies between the two treatment arms. Ninety-five matched pairs of tumors in individual patients were identified from each treatment arm and included in the following analysis. The two treatment groups had well matched baseline characteristics as shown in Table 1. The 1- and 2-year FFLP rates were 83.7% and 74.9% in the SBRT group, and 76.1% and 64.9% in the RFA group, respectively ($P = .243$, Fig. 1**B**). In the multivariate analysis, treatment modality showed a tendency to affect LC, favoring SBRT ($P = .060$) (Table 2). Additionally, tumor markers correlated with an increased rate of local progression. There was a trend of worse FFLP rates according to tumor sizes of >2.0 cm ($P = .058$). Furthermore, there was a significant difference in local control between RFA and SBRT in the IPTW analysis (Supplementary Table S3-4). Local control of RFA was inferior to SBRT ($P < .001$). After subgroup analysis based on tumor size in the matched cohort, SBRT was attributed to better local control only in tumors larger than 2.0 cm ($P = .036$) not in tumors $\leq$2.0 cm ($P = .635$) (Supplementary Table S2, Supplementary Fig. 1). Furthermore, there was no difference in OS rates between the two groups after PSM; 1- and 2-year OS rates were 87.1% and 71.8% for SBRT groups and 86.9% and 76.4% for RFA groups, respectively ($P = .667$) (Supplementary Fig. 2)

Prognostic factors for freedom from local progression in each treatment group

To determine prognostic factors in each treatment group, a subgroup analysis was performed based on treatment modality with respect to FFLP. A tumor size of >2.0 cm was identified as a prognostic factor for RFA ($P = .021$), but not for SBRT ($P = .167$) in the multivariate analysis. Increasing the GTV or PTV in the SBRT group was irrelevant to LC ($P = .376$ and $P = .382$, respectively) (data not shown). Tumor location in the subphrenic region also correlated with poorer LC in the RFA group ($P = .003$), but not in the SBRT group ($P = .996$). Furthermore, elevated tumor markers, (AFP and PIVKA-II) were significant prognostic factors for FFLP in the RFA group ($P < .05$) (Table 3).

Toxicity

Forty-three adverse events (6.5%) were observed in the RFA group. Complications included pleural effusion ($n = 18$), bile duct

Table 1
Baseline characteristics of the radiofrequency ablation (RFA)- and stereotactic body radiation therapy (SBRT)-treated groups before and after propensity score matching (PSM).

Patient characteristic	Before PSM			After PSM		
	RFA (n = 668)	SBRT (n = 105)	P	RFA (n = 95)	SBRT (n = 95)	P
Sex, n (%)			0.476			0.678
Male	523 (78.3)	86 (81.9)		83 (87.4)	80 (84.2)	
Female	145 (21.7)	19 (18.1)		12 (12.6)	15 (15.8)	
Median age (range), years	64 (26.0–86.0)	63.0 (35.0–86.0)	0.477	67.0 (40.0–86.0)	63.0 (35.0–85.0)	0.086
Etiology, n (%)			0.911			0.980
HBV	489 (73.2)	75 (71.5)		67 (70.5)	68 (71.6)	
HCV	92 (13.8)	16 (15.2)		16 (16.9)	15 (15.8)	
NBNC	87 (13.0)	14 (13.3)		12 (12.6)	12 (12.6)	
CTP class, n (%)			0.492			1.000
A	599 (89.7)	97 (92.4)		90 (94.7)	90 (94.7)	
B	69 (10.3)	8 (7.6)		5 (5.3)	5 (5.3)	
BCLC stage, n (%)			<0.001			1.000
0–A	585 (87.6)	40 (38.1)		29 (30.5)	29 (30.5)	
B–C	83 (12.4)	65 (61.9)		66 (69.5)	66 (69.5)	
Median platelets (IQR), 1,000/μL	111.0 (78.0–152.0)	119.0 (77.0–169.0)	0.119	105.0 (77.5–146.5)	116.0 (78.5–160.5)	0.183
Median AFP (IQR), ng/mL	8.4 (3.7–48.7)	13.4 (5.1–67.9)	0.068	7.3 (3.2–48.1)	12.8 (4.9–98.6)	0.137
Median PIVKA-II (IQR), mAU/mL	26.0 (18.0–49.5)	33.0 (20.0–103.0)	0.015	31.0 (19.0–91.0)	33.0 (20.5–103.0)	0.712
Prior liver-directed treatment, n (%)			0.001			0.333
No	150 (22.5)	8 (7.6)		12 (12.6)	7 (7.4)	
Yes	518 (77.5)	97 (92.4)		83 (87.4)	88 (92.6)	
Tumor characteristic	RFA (n = 736)	SBRT (n = 114)	P	RFA (n = 95)	SBRT (n = 95)	P
Tumor location, n (%)			<0.001			0.308
Subphrenic region	230 (31.2)	57 (50.0)		40 (42.1)	48 (50.5)	
Other	506 (68.8)	57 (50.0)		55 (57.9)	47 (49.5)	
Median diameter (range), cm	1.6 (0.5–4.6)	2.4 (0.7–5.5)	<0.001	2.1 (0.8–4.6)	2.4 (0.7–5.5)	0.551
Median diameter, n (%)						
≤2.0 cm	540 (73.4)	48 (42.1)	<0.001	43 (45.3)	37 (38.9)	0.463
>2.0 cm	196 (26.6)	66 (57.9)		52 (54.7)	58 (61.1)	

Abbreviations: AFP, alpha-fetoprotein; CTP, Child-Turcotte-Pugh; BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; NBNC, non-HBV/HCV; PIVKA-II, prothrombin induced by vitamin K absence-II.

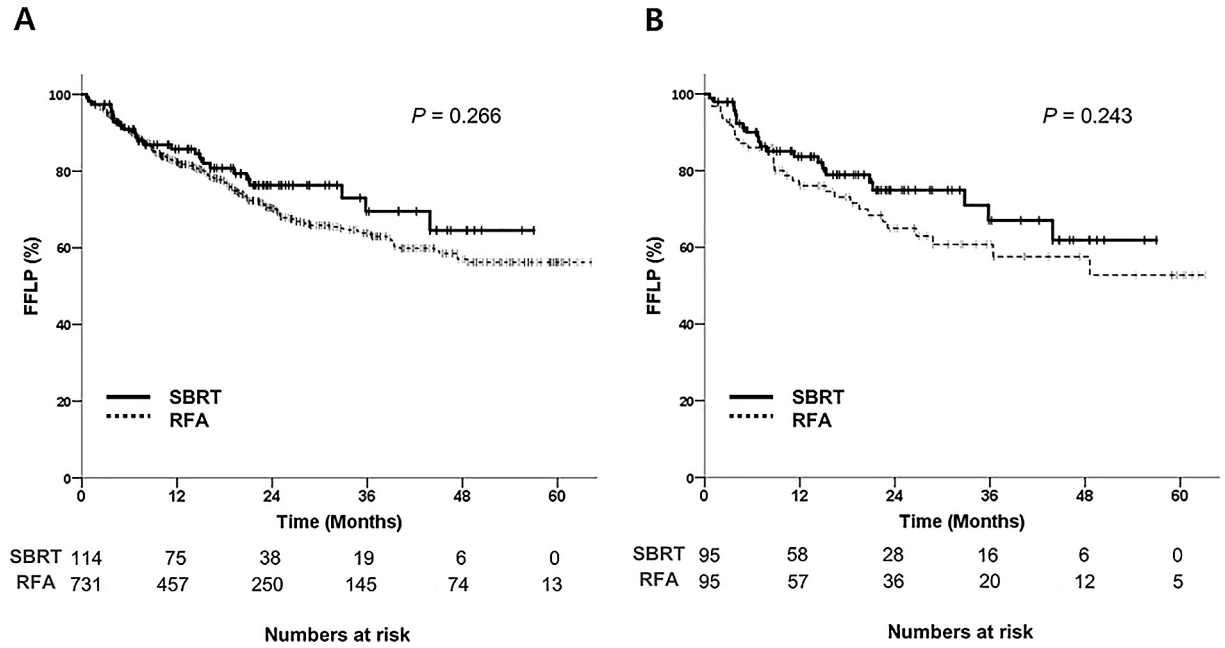

Fig. 1. Freedom from local progression (FFLP) after stereotactic body radiotherapy (SBRT) and radiofrequency ablation (RFA) for (A) all tumors and (B) tumors selected for propensity score matching.

injury (n = 10), burn injury (n = 6), abscess formation (n = 4), hemoperitoneum (n = 3), hemothorax (n = 1), and pneumothorax (n = 1). There were 25 patients (3.7%) in the RFA group presenting even grade 3 or 4 toxicities. All of the patients in the SBRT group completed the scheduled treatment without severe toxicity. However, seven patients (6.7%) developed RILD in the SBRT group. One patient had elevated transaminase levels at five times the normal upper limit, four patients had elevated alkaline phosphatase levels at twice the pretreatment levels, and two patients with a C-P class of A, experienced progression to a C-P class of B or C, respectively. The overall toxicity rate did not differ significantly between the two treatment arms (P = .850). No late adverse events of Grade 5

Table 2
Prognostic factors for freedom from local progression before and after propensity score matching (PSM).

Factor	Univariate analysis					Multivariate analysis				
	HR	95% CI			*P*	HR	95% CI			*P*
All Tumors (n = 850)										
Treatment (SBRT *vs.* RFA)	1.28	0.84	–	1.93	0.248	2.02	1.25	–	3.26	0.004
Age (<60.0 *vs.* ≥60.0 years)	1.08	0.82	–	1.42	0.577	1.10	0.83	–	1.45	0.516
Etiology (HBV/HCV *vs.* NBNC)	1.35	0.87	–	2.07	0.177	1.31	0.85	–	2.04	0.221
CTP class (A *vs.* B)	1.51	0.99	–	2.29	0.053	1.24	0.81	–	1.92	0.321
BCLC stage (0–A *vs.* B–C)	1.35	1.00	–	1.82	0.047	1.25	0.86	–	1.79	0.240
AFP	1.07	1.02	–	1.12	0.004	1.07	1.02	–	1.12	0.004
PIVKA-II	1.13	1.07	–	1.20	<0.001	1.12	1.05	–	1.20	0.001
Tumor location (other *vs.* subphrenic region)	1.44	1.11	–	1.87	0.007	1.44	1.10	–	1.89	0.007
Tumor diameter (≤2.0 *vs.* >2.0 cm)	1.50	1.15	–	1.96	0.003	1.47	1.11	–	1.96	0.008
Prior liver-directed treatment (no *vs.* yes)	1.29	0.92	–	1.82	0.143	1.33	0.94	–	1.88	0.108
Tumors Selected for PSM (n = 190)										
Treatment (SBRT *vs.* RFA)	1.38	0.80	–	2.38	0.243	1.73	0.98	–	3.05	0.060
Age (<60.0 *vs.* ≥60.0 years)	0.79	0.46	–	1.38	0.416	0.86	0.48	–	1.52	0.595
Etiology (HBV/HCV *vs.* NBNC)	2.06	0.74	–	5.70	0.166	1.70	0.60	–	4.86	0.322
CTP class (A *vs.* B)	0.86	0.21	–	3.52	0.829	0.46	0.11	–	1.97	0.294
BCLC stage (0–A *vs.* B–C)	1.86	0.96	–	3.61	0.066	1.30	0.65	–	2.64	0.459
AFP	1.09	1.00	–	1.18	0.049	1.09	1.01	–	1.19	0.038
PIVKA-II	1.19	1.07	–	1.33	0.001	1.19	1.06	–	1.34	0.004
Tumor location (other *vs.* subphrenic region)	1.45	0.85	–	2.49	0.174	1.55	0.86	–	2.77	0.142
Tumor diameter (≤2.0 *vs.* >2.0 cm)	1.77	1.00	–	3.14	0.052	1.80	0.98	–	3.31	0.058
Prior liver-directed treatment (no *vs.* yes)	1.37	0.55	–	3.46	0.499	1.74	0.67	–	4.50	0.257

AFP and PIVKA-II (per doubling) were treated as continuous variables. The foreparts of the parentheses were set as the reference groups in the multivariate analysis.
Abbreviations: AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CTP, Child-Turcotte-Pugh; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; NBNC, non-HBV/HCV; PIVKA-II, prothrombin induced by vitamin K absence-II; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy.

Table 3
Prognostic factors for freedom from local progression in each treatment group.

Factor	Univariate Analysis					Multivariate Analysis				
	HR	95% CI			*P*	HR	95% CI			*P*
RFA (n = 736 tumors)										
Age (<60.0 *vs.* ≥60.0 years)	1.09	0.82	–	1.45	0.566	1.10	0.82	–	1.47	0.539
Etiology (HBV/HCV *vs.* NBNC)	1.5	0.92	–	2.43	0.102	1.50	0.92	–	2.46	0.107
CTP class (A *vs.* B)	1.48	0.97	–	2.27	0.071	1.24	0.80	–	1.92	0.345
BCLC stage (0–A *vs.* B–C)	1.77	1.24	–	2.53	0.002	1.24	0.83	–	1.83	0.292
AFP	1.07	1.02	–	1.12	0.008	1.06	1.01	–	1.11	0.013
PIVKA-II	1.13	1.06	–	1.22	<0.001	1.12	1.04	–	1.21	0.002
Tumor location (other *vs.* subphrenic region)	1.56	1.18	–	2.06	0.002	1.53	1.15	–	2.03	0.003
Tumor diameter (≤2.0 *vs.* >2.0 cm)	1.53	1.14	–	2.04	0.004	1.44	1.06	–	1.95	0.021
Prior liver-directed treatment (no *vs.* yes)	1.31	0.92	–	1.86	0.138	1.32	0.92	–	1.88	0.134
SBRT (n = 114 tumors)										
Age (<60.0 *vs.* ≥60.0 years)	1.15	0.48	–	2.75	0.761	1.28	0.48	–	3.38	0.621
Etiology (HBV/HCV *vs.* NBNC)	0.75	0.28	–	2.00	0.567	1.38	0.48	–	3.98	0.552
CTP class (A *vs.* B)	1.68	0.22	–	12.55	0.615	1.53	0.18	–	12.90	0.694
BCLC stage (0–A *vs.* B–C)	1.69	0.58	–	4.96	0.338	1.50	0.48	–	4.69	0.489
AFP	1.08	0.94	–	1.24	0.266	1.09	0.94	–	1.26	0.247
PIVKA-II	1.18	1.02	–	1.37	0.025	1.14	0.98	–	1.34	0.098
Tumor location (other *vs.* subphrenic region)	1.01	0.46	–	2.21	0.985	1.00	0.42	–	2.42	0.996
Tumor diameter (≤2.0 *vs.* >2.0 cm)	2.22	0.92	–	5.32	0.075	1.94	0.76	–	4.97	0.167
Prior liver-directed treatment (no *vs.* yes)	1.49	0.35	–	6.37	0.590	1.27	0.27	–	6.04	0.767
PTV	0.96	0.88	–	1.05	0.382	–		–		–
Fraction dose	1.05	0.83	–	1.32	0.705	–		–		–
Total dose*	0.99	0.82	–	1.20	0.919	–		–		–
Total dose* (<125.0 *vs.* ≥ 125.0 Gy)	0.90	0.39	–	2.06	0.796	0.91	0.38	–	2.20	0.841

AFP, PIVKA-II (per doubling), PTV (per 10.0 cm^3), fraction dose (per Gy), and total dose (per 10.0 Gy) were treated as continuous variables.
Abbreviations: AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CTP, Child-Turcotte-Pugh; EQD2, equivalent dose in 2.0 Gy per day fractions; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; NBNC, non-HBV/HCV; PIVKA-II, prothrombin induced by vitamin K absence-II; PTV, planning target volume; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy.
* EQD2 was calculated for all dosimetric data using an alpha/beta value of 10.0 Gy for tumor effect on PTV.

were observed. The toxicities reported in this study are shown in Supplementary Table S5.

Discussion

In this single-institutional cohort study, we retrospectively reviewed 850 HCC tumors in 773 patients treated with SBRT or RFA. Although SBRT-treated tumors were more advanced, recurrent, and larger at baseline, SBRT provided comparable LC to RFA. Overall, SBRT was associated with a better LC rate than RFA in the entire cohort and in the matched cohort. Notably, tumor location in the subphrenic region and a tumor size of >2.0 cm were negative predictors of FFLP in the RFA group, but not in the SBRT group.

Since RFA is based on the principle of frictional heat production by frequency waves, heat conduction rates decrease with increasing tumor size, resulting in inadequate tumor control [4,20]. To achieve complete ablation, an adequate ablative margin of ≥5.0 mm is required. Therefore, a single session of ablation for large tumors may be insufficient to provide overlapping composite thermal injury, resulting in the size discrepancies of RFA [21]. Consequently, the AASLD guidelines recommend RFA as the first choice for tumors <2.5 or 3.0 cm [2]. We found that both a tumor size of >2.0 cm and size increments as a continuous variable (HR: 1.26 per cm^3, 95.0% CI: 1.05–1.52; $P = .014$) (data not shown) were associated with an increased risk of local progression in the RFA group. However, neither a tumor size of >2.0 cm nor increments of the PTV were associated with local progression in the SBRT group. Furthermore, we also revealed the same results favoring SBRT for larger tumors (>2.0 cm) after subgroup analysis. Therefore, we postulate that SBRT could be an effective treatment modality for larger tumors.

In general, it is well accepted that RFA of tumors in the liver dome is limited due to the invisibility under US guidance. Several reports have described that either a subphrenic location or a short distance from the diaphragm is associated with higher local recurrence after RFA [22,23]. It has also been reported that approximately half of tumors located in the liver dome recur within 3 years after RFA because of inadequate ablation due to difficulties in visualizing the tumor [24]. The subphrenic region is a well-known determinant of US invisibility that constitutes a blind spot because this segment of the liver is surrounded by the lung situated deep within the liver on subcostal and intercostal US scanning [25]. The implementation of daily image-guided radiation therapy in SBRT, however, allows no limitation of the therapeutic approach depending on tumor location [6]. As expected, the distribution of tumor locations differed significantly with a higher frequency of subphrenic tumors in the SBRT group than in the RFA group. Furthermore, the subphrenic location was a poor prognostic factor in the RFA group, but not in the SBRT group.

In our study, RFA-treated tumors exhibited a lower FFLP rate than previous reports [20,23]. The largest retrospective experience of RFA in a hepatitis B endemic area reported 1- and 2-year LC rates of 90.3% and 78.6%, respectively, for 1502 primary HCC tumors in 1305 patients [23]. Our reduced results might be explained by a greater proportion of patients treated with salvage intent consistent with other reports of repeated RFA for recurrent HCC (1-year PFS: 30.0–70.0%) [26,27]. In our series, 1- and 2-year FFLP was 87.2% and 76.4% for treatment naïve tumors and 80.9% and 68.5% for prior liver-directed treatment tumors, respectively.

The LC rates of SBRT-treated tumors in the present study are comparable to those of previous reports [7–9,28]. In a recent meta-analysis, SBRT exhibited a LC rate of 87% with tolerable acute toxicities of grade >3 (4.9%) [29]. As several clinical trials have demonstrated the efficacy and safety of SBRT, modern SBRT could provide an ablative dose to a tumor while sparing the remaining liver parenchyma [8,9,28,30]. In the present study, there was no dose–response relationship. We adopted biologically equivalent doses of 150.0 Gy (60 Gy/4 fx) or 120.0 Gy (52 Gy/4 fx) most frequently, which is higher than that of other reports. Recently, evidence shows that local control is not correlated with intense dosing regimens in HCC [31]. Further investigation with patient-level data is required to explore the association between higher dose and local control.

The better LC achieved by SBRT in our study is in accordance with the observation from a recent study by Wahl et al. that compared FFLP rates between SBRT and RFA [10]. Our study period was relatively recent and short (2012–2016) compared to the study by Wahl et al. [10] (2004–2012), which could assure both up-to-date techniques and the homogeneity of RFA in the present study. To compensate for the discrepancies in clinical factors between the two groups, which were noted in the previous study [10], we performed a PSM analysis to minimize potential bias. In the propensity model, we could cautiously assume that treatment modality has a tendency to affect LC that favors SBRT. The previous [10] study supports a preference of SBRT for large tumors. Our findings are in agreement, demonstrating that increases in tumor size are associated with decreased LC after RFA compared to SBRT. Our findings also demonstrate that SBRT may be a better treatment option for tumors in the subphrenic region.

Both AFP and PIVKA-II levels were significantly correlated with local progression in the current cohort, and both serum markers were independent factors, even in the matched cohort. These findings are consistent with reports that both AFP [32,33] and PIVKA-II [34,35] are indicative of tumor activity and biological aggressiveness, resulting in a poor prognosis. Moreover, it has been reported that elevated tumor markers may be useful for predicting tumor response irrespective of treatment modalities [36].

Our study has several limitations. First and foremost, this is a retrospective analysis and the results should be reviewed with caution. Even after PSM analysis to reduce the vulnerability of potential biases, confounders may still exist. For example, the median AFP was higher in the SBRT group than the RFA group. Because we conducted PSM as 1:1 matching, the higher tendency cannot be suppressed. Further well-controlled randomized trials are still in need. Second, this is a single-center study with its related bias. Third, the sample size of the SBRT group was relatively small, which increases the risk of a beta error. Therefore, external validation studies are needed to draw definitive conclusions [5].

Both SBRT and RFA could achieve tolerable LC for localized HCC. However, SBRT achieves better LC than RFA for tumors located in the subphrenic region and larger tumors of >2.0 cm. Our findings suggest that SBRT could be an effective alternative treatment modality when RFA is not feasible due to tumor location or size.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2018.12.013.

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