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ORIGINAL REPORT

Outcomes After Stereotactic Body Radiotherapy or Radiofrequency Ablation for Hepatocellular Carcinoma

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ABSTRACT

Purpose

Data guiding selection of nonsurgical treatment of hepatocellular carcinoma (HCC) are lacking. We therefore compared outcomes between stereotactic body radiotherapy (SBRT) and radiofrequency ablation (RFA) for HCC.

Patients and Methods

From 2004 to 2012, 224 patients with inoperable, nonmetastatic HCC underwent RFA (n = 161) to 249 tumors or image-guided SBRT (n = 63) to 83 tumors. We applied inverse probability of treatment weighting to adjust for imbalances in treatment assignment. Freedom from local progression (FFLP) and toxicity were retrospectively analyzed.

Results

RFA and SBRT groups were similar with respect to number of lesions treated per patient, type of underlying liver disease, and tumor size (median, 1.8 *v* 2.2 cm in maximum diameter; $P = .14$). However, the SBRT group had lower pretreatment Child-Pugh scores ($P = .003$), higher pretreatment alpha-fetoprotein levels ($P = .04$), and a greater number of prior liver-directed treatments ($P < .001$). One- and 2-year FFLP for tumors treated with RFA were 83.6% and 80.2% *v* 97.4% and 83.8% for SBRT. Increasing tumor size predicted for FFLP in patients treated with RFA (hazard ratio [HR], 1.54 per cm; $P = .006$), but not with SBRT (HR, 1.21 per cm; $P = .617$). For tumors ≥ 2 cm, there was decreased FFLP for RFA compared with SBRT (HR, 3.35; $P = .025$). Acute grade 3+ complications occurred after 11% and 5% of RFA and SBRT treatments, respectively ($P = .31$). Overall survival 1 and 2 years after treatment was 70% and 53% after RFA and 74% and 46% after SBRT.

Conclusion

Both RFA and SBRT are effective local treatment options for inoperable HCC. Although these data are retrospective, SBRT appears to be a reasonable first-line treatment of inoperable, larger HCC.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the third leading cause of cancer mortality worldwide, and incidence and mortality are increasing.[1,2] Although surgical management is the standard of care, most patients with HCC are not surgical candidates and are managed with nonsurgical locoregional interventions.[3-5] These treatments include regional arterial therapies and local ablative therapies, including radiofrequency ablation (RFA), stereotactic body radiation therapy (SBRT), percutaneous ethanol injection (PEI), microwave ablation, and cryoablation.

RFA achieves rates of local control between 70% and 90% for small tumors[6-8] but achieves complete necrosis in only 30% to 40% of tumors larger than 3 cm.[9,10] SBRT is an emerging noninvasive alternative to RFA with similar local control rates.[11-14] Unlike RFA, increasing tumor size has not been reported to correlate with increased local failures for SBRT.[11,15] Although patients with localized HCC who do not undergo surgery are typically candidates for both SBRT and RFA, there are no data comparing these modalities. We therefore summarized our institutional experience with RFA and SBRT for HCC and hypothesized that patient- or tumor-specific factors, including tumor size, might differentially predict for local failure in RFA and SBRT.

PATIENTS AND METHODS

Data Collection and Modality Selection

As part of an institutional review board–approved study, patients receiving liver SBRT from 2004 to 2012 at the University of Michigan were identified from a prospective departmental database. Patients receiving percutaneous or laparoscopic RFA over this same period were identified from the institutional cancer center registry using Current Procedural Terminology (CPT-4) codes (47370, 47380, 47382) and International Classification of Diseases (ICD-9) codes (155.0, 155.2). Clinical records were reviewed to verify patient and tumor characteristics, treatment details, and clinical outcomes. Treatment decisions were made at the discretion of the institutional multidisciplinary liver tumor board, which generally followed National Comprehensive Cancer Network guidelines. Typically, RFA was the first choice for tumors smaller than 3 to 4 cm. SBRT was first choice for tumors not visualized by ultrasound (US), abutting a vessel or the luminal GI tract, or after RFA failure.

RFA Treatments

Percutaneous RFA was performed under general anesthesia using the Cool-tip Ablation System (Covidien-Medtronic, Minneapolis, MN). Using US guidance, electrodes were placed within the tumors while avoiding critical structures during temporary suspension of respiration. Two to three needles were placed within the tumor or at its margin. Grounding was achieved with two or more 1,000-cm^2 grounding pads placed on the skin. Electrodes were attached to a 500 kHz generator capable of producing up to 200 W. Tissue impedance was continuously monitored during the ablation, and generator output was adjusted to generator maximum power or until circuit impedance increased. Once impedance increased more than 10 ohms, current was stopped and reapplied for a pulsed RF application. Tumor temperature was measured with a thermocouple within each electrode after each ablation. Target tumor temperature after ablation was 60°C. Tumors were heated with an intended 5-mm ablation cavity margin surrounding the tumor. US imaging was used to confirm ablation of the visualized tumor. Lesions larger than 2.5 cm were considered for follow-up ablation sessions. Post-RFA imaging was performed 4 to 6 weeks post-procedure, and residual disease was typically re-ablated.

SBRT Treatments

Patients underwent contrast-enhanced computed tomography (CT) simulation while immobilized using a customized vacuum body mold. Active breathing control or four-dimensional CT simulations were used depending on patient tolerance and generated a gross tumor volume or internal target volume, which was set equal to the clinical target volume. For tumors not well-visualized on CT scan, a pretreatment diagnostic magnetic resonance imaging study was registered to the planning CT.[16] The planning target volume (PTV) was typically constructed by expanding the clinical target volume by 5 mm radially and 8 mm craniocaudally.[17] SBRT was planned using three-dimensional conformal techniques, generally with eight to 16 nonopposed noncoplanar, static 6- and 16-MV beams. Radiotherapy dose was prescribed to the isodose surface covering 99.5% of the PTV, typically 75% to 85% of the maximum PTV dose, accepting regional underdosing when necessary to satisfy normal tissue limits. Patients were treated with either three (46%) or five (53%) fractions delivered two to three times per week with median doses of 30 or 50 Gy with a range of 27 to 60 Gy. The five-fraction regimen was typically administered to tumors that were larger, central, or near critical structures. The median biologically equivalent dose for all patients was 100 Gy assuming an α/β ratio of 10. Dose limits to 0.5 cc of the duodenum, stomach, and heart were 24, 22.5, and 30 Gy for three fractions, with a limit of less than 30 cm^3 of the chest wall receiving $\geq$ 30 Gy. For five-fraction plans, the limits were 30, 27.5, 52.5, and 35 Gy, respectively. In some cases, intrahepatic fiducials were placed percutaneously before SBRT. Daily image guidance was accomplished using either orthogonal x-rays for fiducial alignment or cone beam CT for alignment of local liver anatomy.

Follow-Up

Patients underwent clinical evaluation, liver function testing, and imaging with liver CT or magnetic resonance imaging beginning 3 months (SBRT) or 6 weeks (RFA) after completion of therapy and every 3 months thereafter. Adverse events were defined as grade 3+ events according to the National Institutes of Health–defined Common Terminology Criteria for Adverse Events during the 30 days after treatment (acute) or at all later time points (late biliary and luminal GI toxicity). Freedom from local progression (FFLP) was defined as the absence of progressive disease by the Response Evaluation Criteria in Solid Tumors criteria within or at the PTV margin for patients receiving SBRT and the absence of recurrence within or adjacent to the ablation zone for patients receiving RFA. Tumors that required multiple ablations due to residual disease were not counted as failures unless there was progression at a later date. Patients who progressed locally received salvage therapy at the discretion of the tumor board with varied modalities including RFA, SBRT, radioembolization, transarterial chemoembolization, or sorafenib, with a general sequence of local therapies followed by regional followed by systemic.

Statistics

The RFA and SBRT groups were compared at the patient and lesion level. *t* Tests were used for normal variables, Wilcoxon Mann-Whitney tests for ordinal but nonnormal variables, *z*-tests for two population proportions, and χ^2 tests for multinomial variables. The primary end point was FFLP defined at the lesion level as the time from treatment initiation until subsequent local progression or last follow-up. Overall survival was calculated at the patient level as the time from first treatment (with SBRT or RFA) until death from any cause or last follow-up. FFLP and overall survival were summarized with the Kaplan-Meier method. The effect of treatment and other covariates on FFLP was modeled using mixed-effects Cox models with patient-level random effects to adjust for the correlation between lesions within the same patient.[18] We applied inverse probability of treatment weighting (IPTW) to the Kaplan-Meier method and Cox models for FFLP to adjust for potential imbalances in treatment assignment.[19] The treatment probabilities (propensity) were calculated from a logistic regression using a set of covariates deemed likely to have affected the original treatment decisions, including tumor size, platelet counts, performance status, and number of prior treatments. All of these variables were included, regardless of statistical significance. To allow the treatment effect on FFLP to vary with tumor size, we fit separate models to tumors less than or greater than 2 cm (a predefined threshold) and also included a treatment by tumor size interaction term in the overall model. Both univariate and multivariate models were fit with variables selected a priori. Logistic regression models were used to model increased Child-Pugh score (any increase *v* none) as a function of treatment and other covariates. Patient-level random effects were used to account for within-patient correlation, and IPTW was used to adjust for potential imbalance in treatment assignment. Analyses were performed using R (version 3.1.1; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient Characteristics

A total of 332 discrete liver tumors were identified within 224 patients with nonmetastatic HCC, including 249 tumors treated with RFA in 161 patients and 83 tumors treated with SBRT in 63 patients (Table 1). Patients receiving RFA had higher rates of cirrhosis (96% *v* 78%; $P < .001$) and lower AFP levels (8.8 *v* 18.6; $P = .04$) than patients treated with SBRT. Patients treated with RFA

Table 1. Patient Characteristics

Characteristic	RFA	SBRT	*P*
No. of patients	161	63	—
No. of lesions	249	83	—
No. of lesions treated per patient			.13
Median	1	1	
Range	1-6	1-4	
No. of lesions treated per patient			.14
1	109	49	
2	33	9	
> 2	19	5	
Age, years			.09
Median	60	62	
Range	31-81	35-85	
Sex, male	117 (72.7)	54 (85.7)	.04
Race			.18
White	132 (82.0)	36 (57.1)	
African American	14 (8.7)	2 (3.2)	
Asian	7 (4.3)	1 (1.6)	
Other/unknown	8 (5.0)	24 (38.1)	
Liver transplant	34 (21.1)	4 (6.3)	.01
Type of RFA			—
Percutaneous	242 (97.2)	—	
Intraoperative	7 (2.8)	—	
Use of fiducials in SBRT			—
Yes	—	21 (25.3)	
No	—	62 (74.7)	
Cirrhosis	238 (95.6)	65 (78.3)	< .001
Liver disease			.14
Hepatitis B	24 (9.6)	3 (3.6)	
Hepatitis C	149 (59.8)	44 (53.0)	
Alcoholic cirrhosis	21 (8.4)	10 (12.0)	
NAFLD	13 (5.2)	1 (1.2)	
Other	21 (8.4)	3 (3.6)	
Child-Pugh score			.003
Mean	6.9	6.2	
Child-Pugh score			.003
A	121 (49.6)	57 (68.7)	
5	78 (32.0)	35 (42.2)	
6	43 (17.6)	22 (26.5)	
B	103 (42.2)	24 (28.9)	
7	32 (13.1)	9 (10.8)	
8	40 (16.4)	11 (13.3)	
9	31 (12.7)	4 (4.8)	
C	20 (8.2)	2 (2.4)	
10	12 (4.9)	2 (2.4)	
11	4 (1.6)	—	
12	3 (1.2)	—	
14	1 (0.4)	—	
AFP			.04
Median	8.8	18.6	
Range	1.4-42,630.0	1.4-6,256.0	
Platelet counts			.62
Median	92	97	
Range	25-505	19-293	
No. of prior liver-directed therapies			< .001
Median	0	2	
Range	0-7	0-7	
Tumor diameter, maximum, cm			.14
Median	1.8	2.2	
Range	0.6-7.0	0-10.0	
Tumor diameter, maximum, cm			.21
< 2 cm	137 (55.0)	39 (47.6)	
≥ 2 cm, < 3 cm	57 (22.9)	21 (25.6)	
≥ 3 cm, < 5 cm	52 (20.9)	19 (23.2)	
≥ 5 cm	3 (1.2)	3 (3.7)	
T stage			.32
T1	123 (49.8)	38 (45.8)	
T2	121 (49.0)	40 (48.2)	
T3a	3 (1.2)	—	
T3b	—	5 (6.0)	
Follow-up for all patients, months			.01
Median	20.0	13.0	
Range	0-112.8	0.5-86.5	
Follow-up for living patients, months			.001
Median	50.9	27.0	
Range	3.5-112.8	0.5-86.5	

(continued in next column)

Table 1. Patient Characteristics (continued)

NOTE. Data presented as No. (%) unless otherwise noted.
Abbreviations: AFP, alpha-fetoprotein; NAFLD, nonalcoholic fatty liver disease; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy.

had fewer prior liver-directed treatments, including surgical resection, RFA, SBRT, conventional radiotherapy, transarterial chemoembolization, and radioembolization (median, 0 *v* 2; $P <$ .001) than patients treated with SBRT, as well as longer follow-up (median, 20 *v* 13 months; $P = .01$). Tumors were similarly sized and predominantly T1 or T2 in both RFA and SBRT groups (1.8 *v* 2.2 cm median maximum diameter; $P = .14$). Patients were treated with SBRT or RFA contemporaneously throughout the time range studied. To correct for potential imbalances in treatment assignments, we performed IPTW, which decreased the differences between groups (Appendix Table A1, online only).

Local Control and Survival

The 1- and 2-year FFLP was 83.6% and 80.2% for tumors treated with RFA and 97.4% and 83.8% for tumors treated with SBRT, respectively (Fig 1). Twenty tumors (8%) treated with RFA showed residual disease after first ablation. Eight of these were re-ablated within 12 weeks and were not counted as local failures.

In IPTW univariate analysis, treatment modality was associated with local progression (hazard ratio [HR], 2.63; $P = .016$ for RFA *v* SBRT). After adjusting for treatment type, tumor size was the only covariate predictive of local progression (HR, 1.36 per cm; $P = .029$; Table 2). Child-Pugh score and number of previous treatments, both of which differed between SBRT and RFA groups, did not affect local progression. When patients treated with RFA and SBRT were analyzed separately, increasing tumor size predicted failure with RFA (HR, 1.54 per cm; $P = .006$) but not with SBRT (HR, 1.21 per cm; $P = .617$). We also investigated whether fiducial use for image guidance related to treatment failure with SBRT. With fiducials, 0 of 21 treatments were associated with local failure compared with six of 62 treatments without fiducials ($P = .15$).

Because of the discrepancy in size dependence, we explored how SBRT performed relative to RFA as tumor size varied. With regard to FFLP, the relative performance of SBRT compared with RFA improved with increasing tumor size (Fig 2). We then stratified our data into tumors smaller than 2 cm and those 2 cm or larger, which is a threshold similar to that used in prior RFA trials.[20] For tumors smaller than 2 cm, there was no significant difference between RFA and SBRT in FFLP (HR, 2.50; 95% CI, 0.72 to 8.67; $P = .15$; Fig 3A), but for tumors 2 cm or larger, RFA was

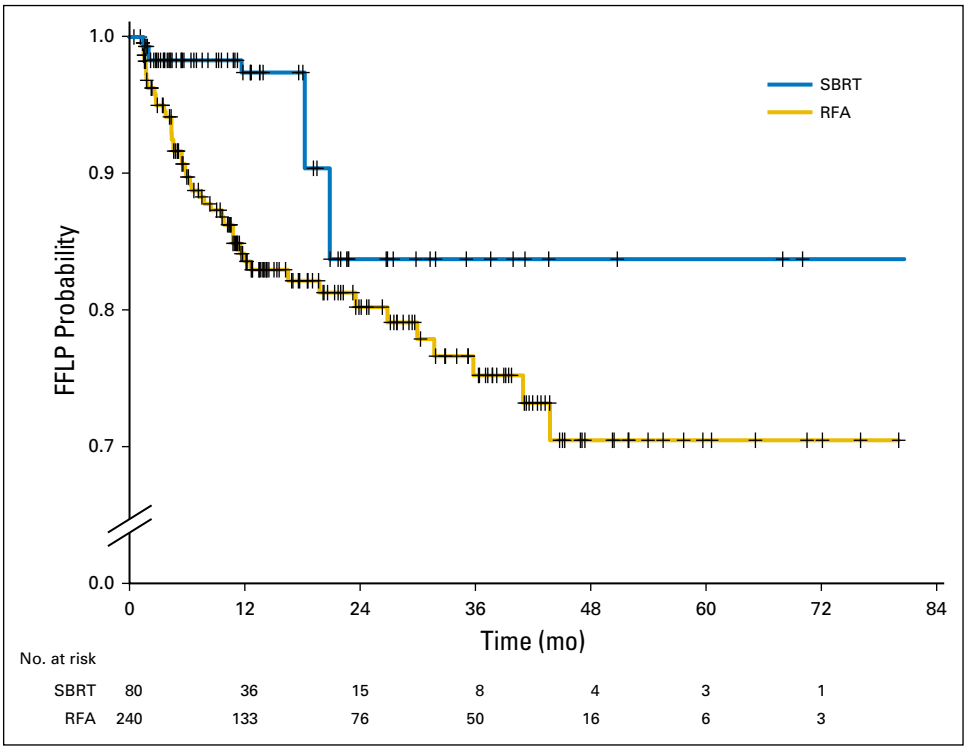

Fig 1. Freedom from local progression (FFLP) by treatment modality. RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy.

associated with significantly worse FFLP (HR, 3.35; 95% CI, 1.17 to 9.62, P = .025; Fig 3B).

On multivariate analysis (Table 3), treatment with RFA (HR, 3.84; P = .002) was significantly associated with inferior local control, whereas increasing tumor size (HR, 1.35; P = .055) and an increasing number of prior liver-directed therapies (HR, 1.25; P = .055) were marginally significant. Overall survival at 1 and 2 years was 69.6% and 52.9% after RFA and 74.1% and 46.3% after SBRT, with no significant difference between treatment groups.

Adverse Events

Eighteen grade 3+ acute adverse events were observed in the RFA group (11% of treatments). These complications included pneumothorax (n = 1), sepsis (n = 2), duodenal and colonic perforation (n = 2), and bleeding (n = 3) and resulted in two deaths within 1 month of treatment (one from hemothorax, and one from GI bleeding). In the SBRT group, three grade 3+ acute toxicities were observed (5% of treatments; P = .31 *v* RFA) including radiation-induced liver disease (n = 1), GI bleeding (n = 1), and worsening ascites (n = 1). The case of GI bleeding after SBRT was likely due to anatomic changes of the gall bladder, which was adjacent to the tumor and displaced bowel from the high-dose region at the time of simulation but decompressed during treatment, potentially increasing dose to the duodenum. No deaths were seen as a consequence of SBRT. The rates of late grade 3+ biliary toxicity were similar in the RFA and SBRT groups at 1 (2.3% *v* 3.3%; P = .7) and 2 years (6% *v* 3.3%; P = .38). The rates of late grade 3+ luminal GI toxicity were also similar in the RFA and SBRT groups at 1 (3.4% *v* 5.4%; P = .49) and 2 years (6.4% *v* 8.3%; P = .66). There were no late grade 5 adverse events in either group.

Table 2. Univariate Analysis of Variables Predictive for Local Progression

	All Lesions			RFA			SBRT		
Variable	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Treatment									
RFA *v* SBRT	2.63	1.20 to 5.75	.016	—	—	—	—	—	—
Age	1.02	0.98 to 1.06	.407	1.02	0.98 to 1.06	.439	1.01	0.91 to 1.11	.858
Tumor size	1.36	1.03 to 1.80	.029	1.54	1.13 to 2.09	.006	1.21	0.57 to 2.54	.617
Child-Pugh score	0.92	0.73 to 1.15	.452	0.92	0.75 to 1.15	.485	0.93	0.34 to 2.57	.898
AFP	1.14	0.98 to 1.32	.082	1.12	0.97 to 1.30	.116	1.23	0.86 to 1.76	.260
No. prior treatments	1.19	0.95 to 1.48	.124	1.04	0.83 to 1.31	.707	1.48	0.82 to 2.65	.190
SBRT dose	—	—	—	—	—	—	0.91	0.81 to 1.02	.110

NOTE. Age (per year), tumor size (per cm), Child-Pugh Score (per point), AFP (per doubling), No. prior treatments (per treatment), and SBRT dose (per Gy) were treated as continuous variables. Data in the All Lesions column has been corrected for treatment modality. Dashes indicate not applicable.
Abbreviations: RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy; HR, hazard ratio; AFP, alpha-fetoprotein.

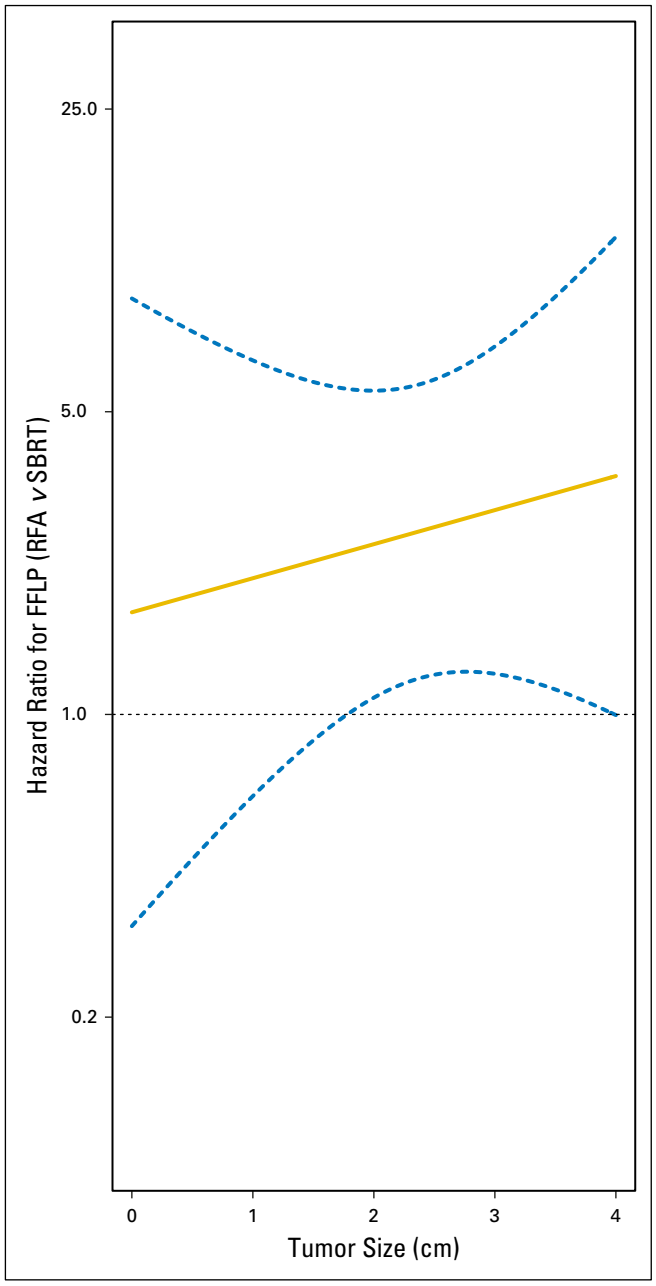

Fig 2. Freedom from local progression (FFLP) by treatment modality by tumor size. Solid line represents hazard ratio estimate, and dashed lines represent 95% CIs. *y*-axis is plotted on a logarithmic scale (base = 5). RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy.

To assess for treatment-related effects on liver function, we analyzed CP scores after RFA or SBRT. Baseline CP scores were slightly worse in the RFA group (mean, 6.9 *v* 6.2; Table 1). Three months after treatment, mean CP scores worsened by 0.2 and 0.5 for RFA- and SBRT-treated patients ($P = .17$), and 12 months after treatment, CP scores worsened by 0.3 and 1.2 ($P = .005$). Because RFA- and SBRT-treated patients differed in a number of other factors we fit a logistic regression model with random effects and the same IPTWs used for FFLP analysis to assess the relationship between treatment type and decreased CP scores while adjusting for treatment modality, number of prior treatments, pretreatment CP score, and tumor size. An increasing number of prior treatments was significantly associated with CP worsening of one or more points at 3 or 12 months (odds ratio, 2.11 per each before treatment; $P = .002$). In this multivariate model, treatment modality did not predict for CP worsening (odds ratio, 1.02 for RFA *v* SBRT; $P = .97$). Total dose of radiation did not predict for CP worsening within the SBRT group.

DISCUSSION

SBRT and RFA are the two primary treatments for patients with unresectable localized HCC, but until now they have not been directly compared. In our series, SBRT provided higher FFLP than RFA on univariate and multivariate analysis. However, we believe it would be incorrect to suggest that all unresectable HCCs be treated with SBRT. RFA provides excellent local control for tumors smaller than 2 cm but has difficulty controlling lesions larger than 3 cm.[9,10,20] Therefore, we stratified tumors by size and found that SBRT had improved control over RFA for tumors 2 cm or larger but that differences were not significant for tumors smaller than 2 cm. These results suggest that both SBRT and RFA are excellent choices for smaller tumors but that SBRT may be preferred for larger tumors. Prospective, randomized clinical trials are needed to compare these two modalities, especially for larger tumors, although we are unaware of any such ongoing trials.

Our local control rates with RFA and SBRT compare favorably with the published literature. The largest published prospective SBRT experience for HCC from the Princess Margaret Hospital reports 1- and 2-year local control rates of 87% and 74% for 102 patients and no size dependence.[11] Smaller retrospective reports show similar rates of local control.[21,22] For RFA, our excellent rate of local control for tumors smaller than 2 cm agrees with literature reports for RFA and other local ablative treatments.[20,23,24] Similarly, our decreased rate of local control with RFA for larger lesions is consistent with literature reports of high rates of incomplete necrosis in larger HCCs.[9,10] Given this concordance, we believe that the higher control after SBRT for larger lesions in our series is likely due to intrinsic differences between modalities rather than unusually ineffective RFA or effective SBRT at our institution.

The decreased efficacy of RFA for larger lesions is likely due to increasing distance from the heat source and incomplete coagulative necrosis, although other technical factors could contribute. In contrast, tumor size does not correlate with local control for SBRT, which is consistent with other reports.[11] This lack of size dependence for SBRT local control is also observed in lung cancer.[25,26] Interestingly, older studies with lower doses of radiation and larger lung tumors did find a size dependence for SBRT.[27,28] Therefore, the SBRT doses used in our study were likely sufficiently high, such that the size threshold for local failure is above the size of tumors investigated. Although our series contained many tumors up to 5 cm in diameter, only three tumors were larger than 5 cm. Therefore, further study is needed to determine whether SBRT provides similar rates of local control in tumors larger than 5 cm. The use of sufficiently ablative RT doses may also explain why there was no dose-response relationship with respect to local control, and this observation is consistent with contemporaneous results from the Princess Margaret Hospital.

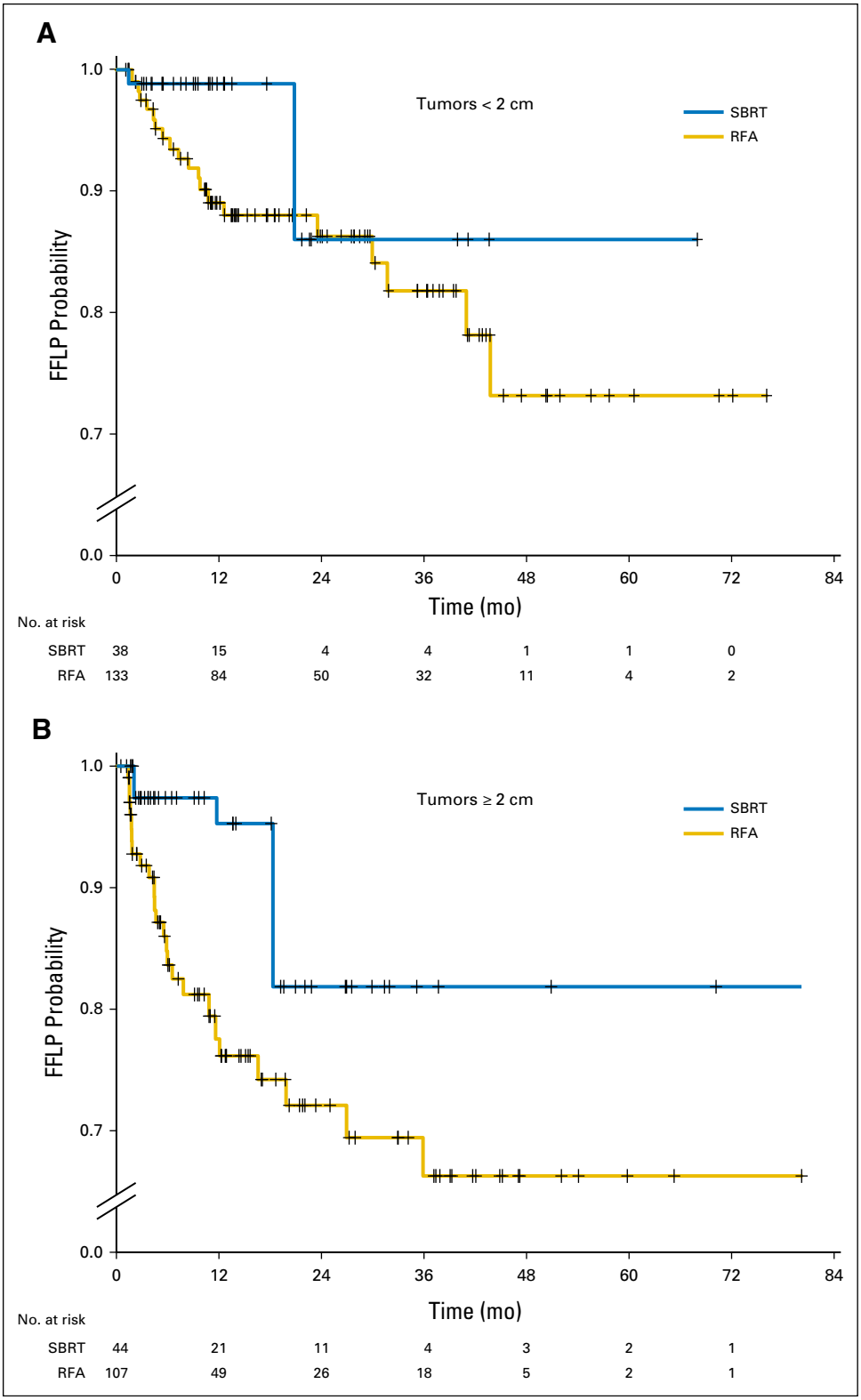

Fig 3. (A) Freedom from local progression (FFLP) for tumors smaller than 2 cm by treatment modality. (B) FFLP for tumors ≥ 2 cm by treatment modality. RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy.

Without fiducials, SBRT-treated patients experienced local failure nearly 10% of the time compared with 0% when fiducials were used. Although not statistically significant, we believe this finding highlights the importance of using excellent image guidance when performing SBRT.

SBRT was associated with one case of radiation-induced liver disease and, on univariate analysis, a small but significant decline in CP score not seen with RFA. However, a multivariate regression showed that the number of prior treatments was the only variable that predicted for CP worsening. Both treatment modalities were

Table 3. Multivariate Cox Proportional Hazards Analysis of Factors Associated With Local Progression

	HR	95% CI	*P*
Treatment			
RFA *v* SBRT	3.84	1.62 to 9.09	.002
Age	1.01	0.97 to 1.06	.514
Tumor size	1.35	0.99 to 1.84	.055
Child-Pugh score	0.95	0.74 to 1.22	.703
AFP	1.12	0.97 to 1.30	.130
No. prior treatments	1.25	1.00 to 1.56	.055

NOTE. Age (per year), tumor size (per cm), Child-Pugh score (per point), AFP (per doubling) and No. prior treatments (per treatment) were treated as continuous variables.
Abbreviations: AFP, alpha-fetoprotein; HR, hazard ratio; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy.

associated with low and similar rates of late adverse events. Compared with SBRT, RFA was associated with a nonsignificant increase in acute adverse events and treatment-related deaths. These results suggest that SBRT might be a better option for medically unfit patients who are likely to poorly tolerate invasive procedures such as RFA.

There are several limitations of the current study in addition to its retrospective nature. Although the two treatment populations were well balanced with respect to multiple factors, patients undergoing SBRT had, on the average, received more prior therapies and were less likely to proceed to transplantation. These observations may help explain why overall survival was similar between the two groups despite improved local control in larger lesions with SBRT. There was also shorter follow-up in the SBRT group, which could obscure late effects. Last, there could be unaccounted-for differences between the SBRT and RFA groups (eg, proximity to heat sinks or location within liver) that could explain the benefit of SBRT for larger tumors.

In sum, our results show that SBRT and RFA both provide excellent local control for small HCC but that SBRT may have an advantage for tumors 2 cm and larger. The overall toxicity was minimal for both modalities. Together, these findings highlight the need for a randomized trial comparing SBRT to percutaneous ablation for unresectable localized HCC and suggest that in the absence of such data, SBRT may be the preferred treatment for larger HCC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org

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Provision of study materials or patients: Theodore S. Lawrence, Mary Feng
Collection and assembly of data: Daniel R. Wahl, Matthew H. Stenmark, Erqi L. Pollom, Elaine M. Caoili, Mary Feng
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Outcomes After Stereotactic Body Radiotherapy or Radiofrequency Ablation for Hepatocellular Carcinoma

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Appendix

Table A1. IPTW-Adjusted Patient Characteristics

	Unadjusted		Post-IPTW	
	RFA	SBRT	RFA	SBRT
Cirrhosis (%)	95.6	78.3	92.3	91.2
Child-Pugh (mean)	6.91	6.19	6.86	6.25
AFP (median)	8.8	18.6	9.22	12.68
Prior treatments, n				
Median	0	2	0	1.12
Mean	0.76	1.8	0.96	1.58

Abbreviations: IPTW, inverse probability of treatment weighting; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy; AFP, alpha fetal protein.