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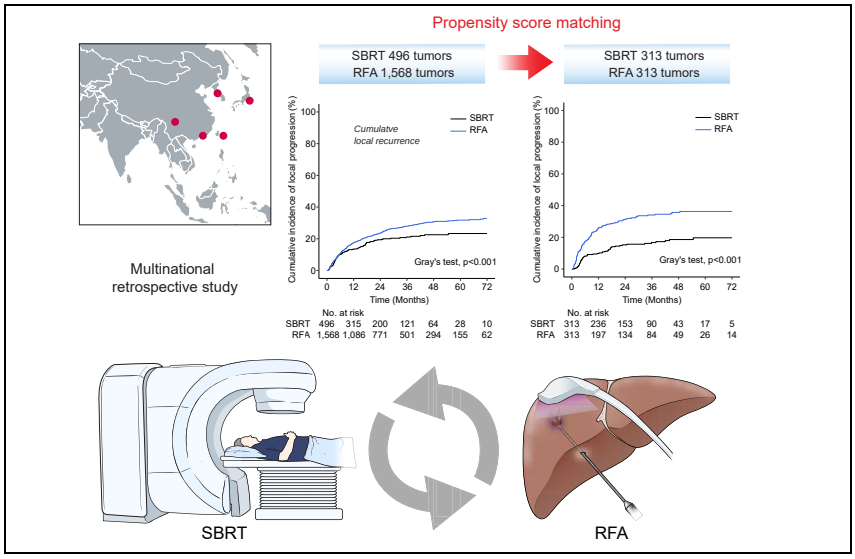
Stereotactic body radiation therapy *vs.* radiofrequency ablation in Asian patients with hepatocellular carcinoma

Graphical abstract



Highlights

- SBRT provided better local control than RFA among patients with HCC.
- Toxicity rates and survival outcomes were similar between these treatment modalities.
- SBRT is an effective alternative to RFA for larger tumors (>3 cm) in a subphrenic location (especially segment 8).

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Lay summary

It is currently not known what the best treatment option is for patients with unresectable hepatocellular carcinoma. Here, we show that stereotactic body radiation therapy provides better local control than radiofrequency ablation, with comparable toxicities. Stereotactic body radiation therapy appears to be an effective alternative to radiofrequency ablation that should be considered when there is a higher risk of local recurrence or toxicity after radiofrequency ablation.

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Stereotactic body radiation therapy *vs.* radiofrequency ablation in Asian patients with hepatocellular carcinoma

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See Editorial, pages 15–16

Background & Aims: Few studies have been conducted to compare the efficacies of stereotactic body radiation therapy (SBRT) and radiofrequency ablation (RFA). Thus, in this multinational study, we compared the effectiveness of SBRT and RFA in patients with unresectable HCC.

Methods: The retrospective study cohort included 2,064 patients treated in 7 hospitals: 1,568 and 496 in the RFA and SBRT groups, respectively. More than half of the patients (56.5%) developed recurrent tumors, mainly after transarterial chemoembolization (44.8%). Propensity score matching was performed to adjust for clinical factors (n = 313 in each group).

Results: At baseline, the SBRT group had unfavorable clinical features compared to the RFA group, including BCLC stage (B-C 65% *vs.* 16%), tumor size (median 3.0 cm *vs.* 1.9 cm), and frequent history of liver-directed treatment (81% *vs.* 49%, all p <0.001). With a median follow-up of 27.7 months, the 3-year cumulative local recurrence rates in the SBRT and RFA groups were 21.2% and 27.9%, respectively (p <0.001). After adjusting for clinical factors, SBRT was related to a significantly lower risk of local recurrence than RFA in both the entire (hazard ratio [HR] 0.45, p <0.001) and matched (HR 0.36, p <0.001) cohorts. In subgroup analysis, SBRT was associated with superior local control in small tumors (≤3 cm) irrespective of location, large tumors located in the subphrenic region, and those that progressed after transarterial chemoembolization. Acute grade ≥3 toxicities occurred in 1.6% and 2.6% of the SBRT and RFA patients, respectively (p = 0.268).

Conclusions: SBRT could be an effective alternative to RFA for unresectable HCC, particularly for larger tumors (>3 cm) in a subphrenic location and tumors that have progressed after transarterial chemoembolization.

Lay summary: It is currently not known what the best treatment option is for patients with unresectable hepatocellular carcinoma. Here, we show that stereotactic body radiation therapy provides better local control than radiofrequency ablation, with comparable toxicities. Stereotactic body radiation therapy appears to be an effective alternative to radiofrequency ablation that should be considered when there is a higher risk of local recurrence or toxicity after radiofrequency ablation.

Introduction

Although surgical resection can lead to long-term survival in early-stage HCC, many patients are not appropriate candidates. According to the current guidelines,[1,2] several non-surgical, locoregional treatments are available for localized HCC, including stereotactic body radiation therapy (SBRT), radiofrequency ablation (RFA), percutaneous ethanol injection, and transarterial chemoembolization (TACE).

There has been growing evidence to support the efficacy of SBRT, with a 2-year local control rate of 90%.[3] In prospective clinical trials, SBRT has demonstrated favorable local control, ranging from 87% to 100% at 1–3 years.[4–6] However, current guidelines do not recommend SBRT for early-stage HCC; RFA is recommended as the first-line option instead.

Few studies have been conducted to compare the efficacies of SBRT and RFA. Although physicians were intrigued by the results of a recent study comparing SBRT to RFA,[7] the efficacy of SBRT remains controversial[8–10] due to the lack of prospective randomized controlled trials. Herein, we performed a multinational study comparing the effectiveness of SBRT and RFA in patients treated at 7 tertiary-referral hospitals in 5 countries.

Keywords: Hepatocellular carcinoma; Stereotactic body radiation therapy; Radiofrequency ablation; Local control; Prognosis; Propensity score matching.
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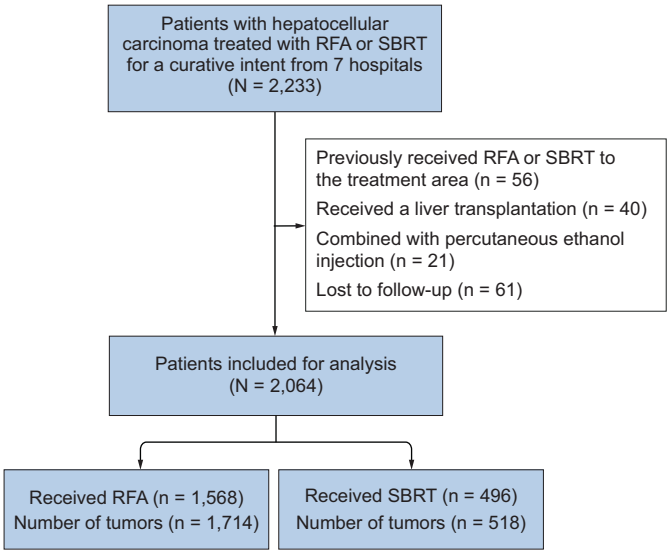

Fig. 1. CONSORT diagram.

Patients and methods

Study population

Patients from 7 hospitals (2 in Korea, 2 in Taiwan, 1 in China, 1 in Japan, and 1 in Hong Kong) were included in this study. The diagnosis of HCC was based on either radiological criteria (nodules >2 cm with radiological hallmarks or nodules of 1–2 cm identified using 2 coincidental techniques) or histological review. The inclusion criteria for the entire cohort were as follows: i) histologically or radiologically confirmed HCC; ii) RFA or SBRT with curative intent regardless of prior liver-directed treatment from January 1, 2010 through December 31, 2016; iii) age ≥15 years; and iv) maximum tumor diameter ≤6 cm for a single tumor or the sum of diameters being ≤6 cm for up to 3 lesions. Patients with a history of RFA or SBRT to the target area, who underwent liver transplantation, those with missing regular (at least every 6 months for 1 year) follow-up data, those treated with percutaneous ethanol injection combined with RFA, or with tumors with vascular invasion were excluded. A total of 2,064 patients, including 1,568 patients who underwent RFA for 1,714 tumors (RFA group) and 496 patients who underwent SBRT for 518 tumors (SBRT group), were identified and included (Fig. 1). For comprehensive statistical analysis, we selected the tumor with the largest size per patient. This study was approved by the institutional review boards of every participating institution, and the protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The requirement for informed consent was waived due to the retrospective study design.

Patient information, including sex, age, Eastern Cooperative Oncology Group (ECOG) performance status, HCC etiology, Child-Pugh class, pre-treatment alpha-fetoprotein (AFP), Barcelona Clinic Liver Cancer (BCLC) stage, tumor size, and status of previous liver-directed treatment, was collected from medical records. Tumor location was defined using Couinaud classification, and tumors located in the liver dome or near the diaphragm (within 0.1 cm of the diaphragm) were defined as subphrenic tumors.[11]

Treatment modality

The optimal treatment modality was discussed and determined by each institutional multidisciplinary team. Local therapies including either surgery or alternative approaches (SBRT, RFA, or TACE) were considered on an individual basis.

Various treatment plans for SBRT (including dose and fractionation schedules) have been employed among institutions. These approaches have been adopted based on the effective irradiated liver volume and dose constraints for dose-limiting gastrointestinal toxicity. For most institutions, peripheral isodose (typically 70–85%) covering the planning target volume is prescribed.[12] SBRT was delivered using CyberKnife (CyberKnife; Accuray, Sunnyvale, CA, USA) (n = 158; 31.9%), Tomotherapy (Hi-Art TomoTherapy; Accuray, Madison, WI, USA) (n = 124; 25.0%), volumetric modulated arc therapy (Elekta VMAT; Elekta, Stockholm, Sweden) (n = 113; 22.8%), and three-dimensional conformal radiotherapy (n = 101; 20.4%). The median gross tumor volume and planning target volume were 22.5 (IQR 6.1–72.0) ml and 59.7 (IQR 24.8–146.1) ml, respectively. The median equivalent dose in 2.0-Gy fractions (α/β of 10) was 72.0 (IQR 65.6–88.0) Gy, and the median biologically effective dose was 86.4 (IQR 78.8–105.6) Gy.

RFA procedures in all institutions were performed percutaneously under ultrasound guidance. One to three needles were inserted with optimal positioning to achieve complete ablation, allowing complete ablation of the tumor with a 0.5 to 1.0 cm margin. Each treatment was repeated following repositioning until the tumor was visibly ablated. Immediate additional RFA was also permitted unless complete ablation was achieved (included as 1 treatment).

Follow-up

After treatment completion, all patients were assessed every 3 months for 1 year and at least every 6 months thereafter. Radiologic responses were defined using the modified Response Evaluation Criteria in Solid Tumors[13] based on dynamic contrast-enhanced CT (98.5%) or MRI (21.1%) findings. Multiphasic MRI was performed only when recurrent tumors were equivocally viable (LR-TR Equivocal).[14] Local progression was defined when a newly developed contrast-enhanced lesion (LR-TR viable) was detected at the treated sites: ablated sites for the RFA group and the 95% isodose line for the SBRT group. Intrahepatic progression outside of the planning target volume or ablation site was defined as an out-field failure. Treatment-related toxicity was graded according to the Common Terminology Criteria for Adverse Events (ver. 4.03).[15]

Statistical analysis

To compare differences in patient characteristics between the 2 groups, Pearson's Chi-square or Fisher's exact test were used to analyze categorical variables and the Mann-Whitney *U* test (non-normally distributed data) or Student's *t* test (normally distributed data) was employed to compare continuous variables.

Time-to-local recurrence and time-to-death from the first date of treatment were the primary outcomes, to compare the effectiveness of the 2 treatments. Both events (local recurrence or death) or censoring were evaluated at the last follow-up date. Since patients who died cannot progress, we performed a competing risks analysis to estimate the cumulative local recurrence rate (CLRR). We used Gray's test to compare CLRR and cumulative mortality rates (CMRs) between the 2 treatment groups. Fine-Gray subdistribution hazard models were used to estimate hazard ratios (HRs) comparing the risks of local recurrence and death with or without adjustment for covariates.

Propensity score matching (PSM) analysis was performed to minimize the effects of potential confounders and selection biases. Propensity scores were calculated using a multivariable logistic regression model including sex, age, performance status, viral etiology, Child-Pugh class (A *vs.* B or C), pre-treatment AFP and des-gamma carboxyprothrombin, BCLC stage, tumor size, and previous liver-directed treatment (yes *vs.* no). Following the estimation of propensity scores, the tumors were matched using 1:1 nearest neighbor matching with a caliper distance set at 0.05 standard deviations of the logit of the propensity score. Non-matched results were discarded. Standardized mean difference was used to evaluate the balance of covariate distribution between the 2 groups. After matching, McNemar's test was used to analyze categorical variables, while the Wilcoxon signed-rank test (non-normally distributed data) or paired *t* test (normally distributed data) were employed to compare continuous variables. Stratified Cox proportional hazards models were used for univariable and multivariable analyses. A 2-tailed *p* value of <0.05 was considered statistically significant. All statistical analyses were performed using R (version 3.4.4; R Foundation for Statistical Computing, Vienna, Austria). cmprisk and Matching packages were used for the competing risks analysis and PSM, respectively.

Results

Baseline characteristics

Patient and tumor characteristics are listed in Table 1. Among 2,064 patients, 72.2% were male, the median patient age was 64.9 (IQR 57.3–72.8) years, and 21.5% (444/2,064) were diagnosed by histologic review. The most common HCC etiology was chronic HBV infection (61.1%, 1,261/2,064), followed by chronic HCV infection (27.2%, 562/2,064). Most patients presented with well-compensated liver function (Child-Pugh class A, 88.3%). Median tumor size was 2.0 (IQR 1.5–2.8) cm, and 20.6% (425/2,064) of patients had tumors >3 cm. Additionally, 44.8% (924/2,064) of patients received prior liver-directed treatment; TACE was the most common previous treatment. The SBRT group had unfavorable factors compared to the RFA group, such as advanced stage (BCLC stage B or C), elevated AFP, larger tumor size, and larger proportion of patients who received previous liver-directed treatments. The distribution of tumor locations by liver segment are summarized in Table S1. In both groups, segment 8 was the most common tumor location (22.2% SBRT group; 23.7% RFA group). After PSM, there were 313 tumors in each group, with an adequate balance of all characteristics (Fig. S1). Most patients in the matched cohort were HBV/HCV carriers (85.1%, 533/626), Child-Pugh class A (87.9%, 550/626), and received previous liver-directed treatments (83.2%, 521/626). Additionally, BCLC stage was evenly distributed in the matched cohort.

Cumulative local recurrence rate

The median follow-up for all patients was 27.7 (IQR 13.8–45.6) months, and the follow-up period did not differ between the 2 groups (SBRT 22.2 [IQR 9.8–37.6] months; RFA: 29.6 [IQR 15.2–48.0] months, $p = 0.056$). The 2-year CLRRs were 19.4% and 23.7% in the SBRT and RFA groups, respectively ($p < 0.001$, Fig. 2, Table S2). In the entire cohort, treatment with RFA (HR 0.45; 95% CI 0.35–0.58; $p < 0.001$) was a significantly unfavorable factor for local control, along with advanced stage, elevated AFP level, previous liver-directed treatment, and tumor size >3 cm (Table 2). After PSM, SBRT was associated with a lower CLRR; the 2-year CLRRs were 16.4% and 31.1% in the SBRT and RFA groups, respectively (Table S2). Multivariable analysis after PSM demonstrated that treatment modality attributed to local control, favoring SBRT (HR 0.36; 95% CI 0.25–0.50; $p < 0.001$).

Cumulative mortality rate

Before PSM, patients in the SBRT group showed higher CMR than patients in the RFA group (2-year CMR: 25.7% *vs.* 18.9%, $p < 0.001$, Table S2, Fig. 3). Although SBRT increased the risk of death compared to RFA (HR 1.57) in univariable analysis, there was no statistical difference in multivariable analysis. Instead, age, Child-Pugh class, AFP level, and prior liver-directed treatments significantly influenced overall survival (all $p < 0.05$, Table 3). However, after PSM, treatment modality had little effect on CMR; the 2-year CMRs were 22.4% and 28.9% in the SBRT and RFA groups, respectively ($p = 0.308$, Table S2, Fig. 3). Additionally, Child-Pugh class B or C, frequent liver-directed treatments, and larger tumor size (>3 cm) showed a poor survival trend in the matched cohort (Table 3).

Exploratory subgroup analysis

For further analysis according to tumor location, SBRT had superior efficacy to RFA for tumors in segment 8 (Table S1, Fig. S2). Furthermore, tumors in the subphrenic region showed higher CLRR after RFA than after SBRT (2-year CLRR: 23.0% *vs.* 15.3%, $p = 0.005$). In the subgroup analysis stratified by tumor location and size (Table S3, Fig. S3), SBRT was associated with better local control than RFA, except with large tumors (>3 cm) located in the non-subphrenic area (177/2,064, 8.6%), after adjusting for clinical factors. This difference in CLRR was significant especially for large tumors located in the subphrenic region; the 2-year CLRRs were 18.7% and 32.1% in the SBRT and RFA groups, respectively ($p = 0.019$). In addition, SBRT was a favorable factor for both recurrent and treatment-naïve tumors (Table S4). In subsequent analysis according to previous liver-directed treatment modalities, both SBRT and RFA showed comparable local control for recurrent tumors after previous RFA to other sites, surgery, sorafenib administration, and percutaneous ethanol injection (Fig. S4). However, recurrent tumors after previous TACE showed inferior local control after RFA compared to the SBRT ($p = 0.001$).

According to the subgroup analysis in each treatment group (Table S5), only advanced stage was identified as a prognostic factor for SBRT ($p < 0.001$). Tumor size was not related to local control in the SBRT group. However, large tumor size was related to higher local recurrences in the RFA group ($p = 0.030$). Elevated AFP levels and frequent previous liver-directed treatments were identified as significant prognostic factors for CLRR in the RFA group ($p < 0.05$). Additionally, there was no difference in AFP response within 3 months post-treatment (median ratio of post-treatment AFP to pre-treatment AFP; 0.860 [SBRT] *vs.* 0.845 [RFA], $p = 0.082$).

Toxicity

Any-grade acute toxicities were noted in 167 (33.7%) and 331 (21.1%) patients in the SBRT and RFA groups, respectively (Table 4). All patients in the SBRT and RFA groups completed the planned treatment without severe toxicity. Although the overall incidence of toxicities of any grade was higher after SBRT ($p < 0.001$), there was no significant difference in the rates of grade 3–4 toxicity (1.6% *vs.* 2.6%, $p = 0.268$). There was a significant

Table 1. Baseline characteristics of the RFA- and SBRT-treated groups before and after PSM.

	Before PSM				After PSM			
	RFA (n = 1,568)	SBRT (n = 496)	*p* value	SMD*	RFA (n = 313)	SBRT (n = 313)	*p* value	SMD*
Sex, n (%)			0.025	0.120			0.926	0.015
Female	456 (29.1)	118 (23.8)			77 (24.6)	75 (24.0)		
Median age [IQR], years	64.9 [57.3–72.6]	65.0 [57.3–74.6]	0.296	0.050	67.3 [59.4–74.0]	65.8 [58.7–75.0]	0.511	0.064
ECOG PS, n (%)			<0.001	0.288			0.601	0.081
0	681 (43.4)	251 (50.6)			177 (56.5)	174 (55.6)		
1	847 (54.0)	210 (42.3)			124 (39.6)	131 (41.9)		
2~3	40 (2.6)	35 (7.1)			12 (3.8)	8 (2.6)		
Etiology, n (%)			0.313	0.077			0.519	0.092
HBV	968 (61.7)	293 (59.1)			166 (53.0)	180 (57.5)		
HCV	426 (27.2)	136 (27.4)			99 (31.6)	88 (28.1)		
NBNC	174 (11.1)	67 (13.5)			48 (15.3)	45 (14.4)		
Child-Pugh class, n (%)			0.012	0.128			0.714	0.039
A	1401 (89.3)	422 (85.1)			273 (87.2)	277 (88.5)		
B–C	167 (10.7)	74 (14.9)			40 (12.8)	36 (11.5)		
BCLC stage, n (%)			<0.001	1.181			0.942	0.050
0	559 (35.7)	80 (16.1)			82 (26.2)	79 (25.2)		
A	758 (48.3)	92 (18.5)			79 (25.2)	80 (25.6)		
B	127 (8.1)	105 (21.2)			70 (22.4)	66 (21.1)		
C	124 (7.9)	219 (44.2)			82 (26.2)	88 (28.1)		
Median platelet count [IQR], ($\times 10^3/\mu l$)	114.0 [78.0;154.0]	115.0 [76.0–159.3]	0.518	0.072	109.0 [77.0–148.0]	114.0 [74.0–162.0]	0.203	0.181
Median AFP [IQR], ng/ml	11.91 [4.60–62.30]	26.50 [5.81–242.75]	<0.001	0.131	10.37 [4.37–60.00]	14.70 [4.80–95.45]	0.132	0.003
>1 tumor treated, n (%)	132 (8.4)	21 (4.2)	0.003	0.173	23 (7.3)	19 (6.1)	0.632	0.051
Median tumor size [IQR], cm	1.90 [1.50–2.50]	3.00 [1.80–5.20]	<0.001	0.831	2.20 [1.60–3.20]	2.10 [1.50–3.10]	0.287	0.026
>3 cm, n (%)	186 (11.9)	239 (48.2)	<0.001	0.863	83 (26.5)	82 (26.2)	1.000	0.007
Prior liver-directed treatment, n (%)			<0.001	0.711			0.521	0.06
Yes	766 (48.9)	401 (80.8)			257 (82.1)	264 (84.3)		
Details of prior liver-directed treatment, n (%)								
RFA	129 (8.2)	115 (23.2)	<0.001	0.420	50 (16.0)	75 (24.0)	0.016	0.201
TACE	552 (35.2)	372 (75.0)	<0.001	0.873	171 (54.6)	249 (79.6)	<0.001	0.550
Surgery	301 (19.2)	145 (29.2)	<0.001	0.236	102 (32.6)	98 (31.3)	0.797	0.027
Sorafenib	2 (0.1)	15 (3.0)	<0.001	0.234	2 (0.6)	7 (2.2)	0.179	0.134
PEI	30 (1.9)	32 (6.5)	<0.001	0.228	7 (2.2)	22 (7.0)	0.008	0.229

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; NBNC, non-HBV/HCV; PEI, percutaneous ethanol injection; PSM, propensity score matching; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy; SMD, standardized mean difference; TACE, transarterial chemoembolization.

*Standardized mean difference was used to evaluate the balance of covariate distribution between two groups. After matching, McNemar's test was used to analyze categorical variables and Wilcoxon signed-rank test (non-normally distributed data) or paired *t* test (normally distributed data) was employed to compare continuous variables. A 2-tailed *p* value of less than 0.05 was considered statistically significant.

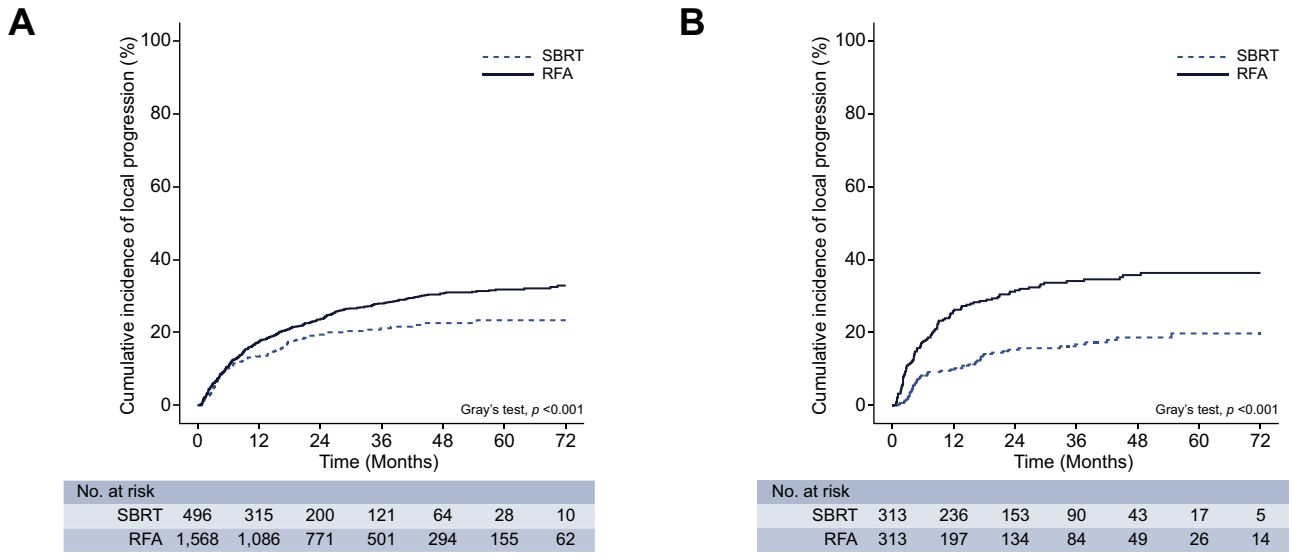

Fig. 2. Cumulative local recurrence rates after SBRT and RFA in patients with hepatocellular carcinoma. (A) Before PSM, and (B) after PSM. Difference was tested using Gray's test. A 2-tailed *p* value of less than 0.05 was considered statistically significant. RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy.

Table 2. Prognostic factors for local recurrence before and after PSM.

	Univariable analysis			Multivariable analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Before PSM**						
Treatment (RFA *vs.* SBRT)	0.73	0.58–0.91	0.005	0.45	0.35–0.58	<0.001
Sex (Male *vs.* female)	0.86	0.71–1.04	0.125	0.85	0.70–1.05	0.127
Age (<median *vs.* ≥median)	0.94	0.79–1.11	0.444	0.99	0.83–1.18	0.921
ECOG PS (0–1 *vs.* 2–3)	1.31	0.83–2.07	0.244	1.16	0.72–1.87	0.545
Etiology (HBV/HCV *vs.* NBNC)	0.74	0.55–0.98	0.039	0.75	0.56–1.02	0.064
Child-Pugh class (A *vs.* B–C)	1.05	0.80–1.38	0.702	0.85	0.64–1.13	0.274
BCLC stage (0–A *vs.* B–C)	1.51	1.26–1.81	<0.001	1.68	1.34–2.1	<0.001
AFP*	1.06	1.03–1.09	<0.001	1.06	1.04–1.09	<0.001
Previous treatment (no *vs.* yes)	1.18	1.00–1.40	0.051	1.22	1.01–1.47	0.036
Size (≤3 cm *vs.* >3 cm)	1.25	1.02–1.54	0.030	1.16	0.91–1.49	0.222
After PSM**						
Treatment (RFA *vs.* SBRT)	0.40	0.30–0.53	<0.001	0.36	0.25–0.50	<0.001
Sex (Female *vs.* Male)	0.87	0.60–1.26	0.459	0.71	0.41–1.23	0.221
Age (<median *vs.* ≥median)	0.78	0.57–1.08	0.141	0.89	0.55–1.42	0.623
ECOG PS (0–1 *vs.* 2–3)	1.50	0.60–3.74	0.384	0.98	0.35–2.75	0.968
Etiology (HBV/HCV *vs.* NBNC)	0.49	0.29–0.85	0.010	0.51	0.25–1.05	0.067
Child-Pugh class (A *vs.* B–C)	1.47	0.89–2.44	0.134	1.57	0.82–2.99	0.173
BCLC stage (0–A *vs.* B–C)	2.34	1.40–3.91	0.001	2.00	1.11–3.58	0.020
AFP*	1.07	1.00–1.13	0.043	1.10	1.00–1.20	0.040
Previous treatment (no *vs.* yes)	0.58	0.34–0.99	0.047	0.87	0.42–1.78	0.697
Size (≤3 cm *vs.* >3 cm)	1.00	0.67–1.49	0.990	0.95	0.55–1.63	0.849

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; NBNC, non-HBV/HCV; PSM, propensity score matching; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy.

*AFP was treated as a continuous variable. The foreparts of the parentheses were set as the reference groups in the multivariable analysis. **Fine-Gray subdistribution hazard models were used to estimate hazard ratios comparing risks of local recurrence with or without adjustment for covariates. After PSM, stratified Cox proportional hazards models were used for univariable and multivariable analyses. A 2-tailed *p* value of less than 0.05 was considered statistically significant.

difference in toxicity profiles: 37 patients (7.4%) treated with SBRT experienced either abdominal distension or pain and 3 (0.6%) experienced grade 3–4 duodenal ulcer. Biliary fistula after SBRT in 1 patient resolved successfully after interventional procedure. Acute treatment-related toxicities after RFA included hepatic hemorrhage (n = 125, 8.0%), pleural effusion (n = 37, 2.4%), biliary fistula (n = 20, 1.3%), skin burn (n = 13, 0.8%), pneumothorax (n = 6, 0.4%), and pleural hemorrhage (n = 4, 0.3%). Twenty-nine patients (5.8%) in the SBRT group and 83 (5.3%) in the RFA group experienced late toxicities. Fifteen patients (1.0%) in the RFA group experienced grade 3–4 toxicities, including pleural effusion (n = 10) and biliary fistula (n = 5). Although patients with grade 1 or 2 fistula recovered after interventional management (percutaneous bile duct drainage or

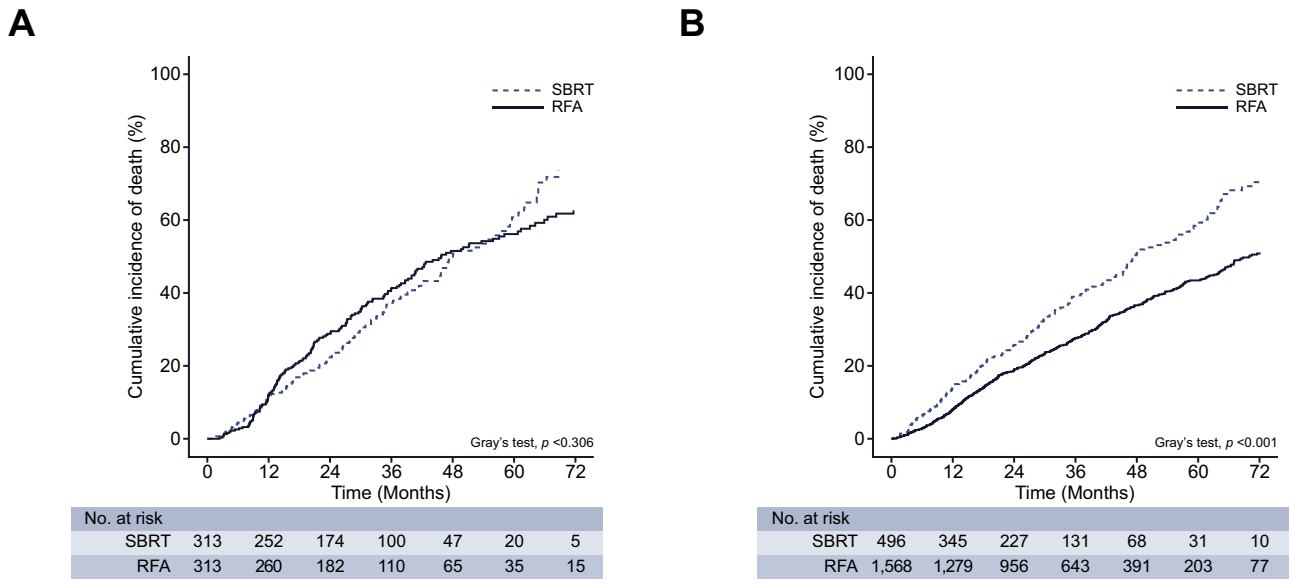

Fig. 3. Cumulative mortality rates after SBRT and RFA in patients with hepatocellular carcinoma. (A) Before PSM, and (B) after PSM. Difference was tested using Gray's test. A 2-tailed *p* value of less than 0.05 was considered statistically significant. RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy.

Table 3. Prognostic factors for overall survival before and after PSM.

	Univariable analysis			Multivariable analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Before PSM**						
Treatment (RFA *vs.* SBRT)	1.57	1.36–1.81	<0.001	1.19	1.01–1.41	0.042
Sex (female *vs.* male)	0.91	0.78–1.05	0.196	0.88	0.76–1.03	0.111
Age (<median *vs.* ≥median)	1.21	1.06–1.39	0.004	1.24	1.09–1.42	0.001
ECOG PS (0–1 *vs.* 2–3)	1.90	1.32–2.72	<0.001	1.38	0.93–2.04	0.108
Etiology (HBV/HCV *vs.* NBNC)	1.19	0.96–1.48	0.106	1.14	0.92–1.40	0.229
CTP class (A *vs.* B–C)	1.96	1.61–2.38	<0.001	1.92	1.59–2.33	<0.001
BCLC stage (0–A *vs.* B–C)	1.45	1.26–1.67	<0.001	0.94	0.78–1.13	0.480
AFP*	1.05	1.03–1.07	<0.001	1.05	1.02–1.07	<0.001
Previous treatment (no *vs.* yes)	1.81	1.58–2.08	<0.001	1.63	1.41–1.89	<0.001
Size (≤3 cm *vs.* >3 cm)	1.28	1.09–1.50	0.003	1.09	0.89–1.33	0.401
After PSM**						
Treatment (RFA *vs.* SBRT)	0.86	0.70–1.06	0.164	0.85	0.67–1.07	0.163
Sex (female *vs.* male)	1.06	0.76–1.46	0.737	0.81	0.56–1.18	0.272
Age (<median *vs.* ≥median)	1.15	0.85–1.56	0.353	1.38	0.96–1.97	0.079
ECOG PS (0–1 *vs.* 2–3)	1.75	0.71–4.31	0.223	1.05	0.41–2.68	0.925
Etiology (HBV/HCV *vs.* NBNC)	0.73	0.47–1.12	0.147	0.70	0.44–1.12	0.138
CTP class (A *vs.* B–C)	2.82	1.69–4.72	<0.001	2.79	1.67–4.67	<0.001
BCLC stage (0–A *vs.* B–C)	1.13	0.77–1.65	0.538	1.00	0.62–1.61	0.997
AFP*	1.04	0.98–1.09	0.172	1.06	1.00–1.13	0.067
Previous treatment (no *vs.* yes)	1.40	0.81–2.43	0.234	1.86	0.96–3.64	0.068
Size (≤3 cm *vs.* >3 cm)	1.46	0.98–2.17	0.061	1.57	0.98–2.51	0.061

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; NBNC, non-HBV/HCV; PSM, propensity score matching; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy.
*AFP was treated as a continuous variable. The foreparts of the parentheses were set as the reference groups in the multivariable analysis. **Fine-Gray subdistribution hazard models were used to estimate hazard ratios comparing risks of death with or without adjustment for covariates. After PSM, stratified Cox proportional hazards models were used for univariable and multivariable analyses. A 2-tailed *p* value of less than 0.05 was considered statistically significant.

endoscopic stenting), 5 patients with grade 3/4 fistula eventually underwent either cholecystectomy with choledocoplasty (n = 3) or Roux-en-Y hepaticojejunostomy (n = 2). A change in the Child-Pugh score >2 points at 3 months post-treatment was more frequent in the SBRT group than in the RFA group (11.2% *vs.* 4.7%, *p* <0.001, Table S6). These changes were restored at 6 months post-treatment (6.3% *vs.* 8.1%, *p* = 0.278).

Discussion

In the current multinational study, we compared a retrospective cohort of 2,064 HCC patients with 2,064 tumors treated with either SBRT or RFA. Although the SBRT group had more unfavorable factors (stage, tumor size, and prior liver-directed treatment) than the RFA group, SBRT provided better local control than RFA in the entire cohort. This was more evident in the

Table 4. Acute and late toxicity in patients treated by SBRT or RFA.

	SBRT (n = 496)			RFA (n = 1,568)		
	Grade 1–2	Grade 3–4	Total	Grade 1–2	Grade 3–4	Total
Acute toxicity (within 3 months)						
Fatigue	39 (7.9)	0 (0.0)	39 (7.9)	28 (1.8)	0 (0.0)	28 (1.8)
Nausea	44 (8.9)	1 (0.2)	45 (9.1)	17 (1.1)	0 (0.0)	17 (1.1)
Anorexia	30 (6.0)	0 (0.0)	30 (6.0)	22 (1.4)	0 (0.0)	22 (1.4)
Burn	0 (0.0)	0 (0.0)	0 (0.0)	13 (0.8)	0 (0.0)	13 (0.8)
Wound infection	0 (0.0)	0 (0.0)	0 (0.0)	8 (0.5)	0 (0.0)	8 (0.5)
Gastrointestinal toxicity						
Esophagitis	3 (0.6)	0 (0.0)	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal distension	17 (3.4)	0 (0.0)	17 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal pain	18 (3.6)	2 (0.4)	20 (4.0)	10 (0.6)	0 (0.0)	10 (0.6)
Diarrhea	4 (0.8)	0 (0.0)	4 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Duodenal ulcer	4 (0.8)	3 (0.6)	7 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatobiliary toxicity						
Biliary fistula	0 (0.0)	1 (0.2)	1 (0.2)	15 (1.0)	5 (0.3)	20 (1.3)
Hepatic failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	34 (2.2)	34 (2.2)
Hepatic hemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	125 (8.0)	0 (0.0)	125 (8.0)
Intra-abdominal hemorrhage	0 (0.0)	1 (0.2)	1 (0.2)	6 (0.4)	1 (0.1)	7 (0.4)
Pulmonary toxicity						
Pleural hemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)	1 (0.1)	4 (0.3)
Pneumothorax	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.4)	0 (0.0)	6 (0.4)
Pleural effusion	0 (0.0)	0 (0.0)	0 (0.0)	37 (2.4)	0 (0.0)	37 (2.4)
Total	159 (32.1)	8 (1.6)	167 (33.7)	290 (18.5)	41 (2.6)	331 (21.1)
Late toxicity (after 3 months)						
Pneumonitis	20 (4.0)	0 (0.0)	20 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	5 (1.0)	0 (0.0)	5 (1.0)	27 (1.7)	0 (0.0)	27 (1.7)
Anorexia	3 (0.6)	0 (0.0)	3 (0.6)	21 (1.3)	0 (0.0)	21 (1.3)
Biliary fistula	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.4)	5 (0.3)	11 (0.7)
Pleural effusion	0 (0.0)	0 (0.0)	0 (0.0)	9 (0.6)	10 (0.6)	19 (1.2)
Burn	1 (0.2)	0 (0.0)	1 (0.2)	5 (0.3)	0 (0.0)	5 (0.3)
Total	29 (5.8)	0 (0.0)	29 (5.8)	68 (4.3)	15 (1.0)	83 (5.3)

RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy.
Data are presented as n (%).

matched cohort. Both treatment modalities showed comparable survival rates with tolerable but distinct toxicities.

Several studies have also compared the outcomes in patients with HCC undergoing SBRT and RFA using PSM.[7,9,16,17] Wahl *et al.*[7] investigated local control rates in 83 tumors treated with SBRT and 249 tumors treated with RFA. They reported that SBRT had better local control than RFA for tumors ≥2 cm and comparable local control for tumors <2 cm. However, this study had a relatively short follow-up and a relatively small sample size in the SBRT group, which increased the risk of a beta error. Rajyaguru *et al.*[9] analyzed survival in 3,684 and 296 patients who underwent RFA and SBRT, respectively, using data from the National Cancer Database. They reported that RFA resulted in better survival than SBRT after PSM analysis. However, local control could not be assessed, and as local control can affect survival, this is a major drawback of database-based investigations.[18] Recently, a single-institution study retrospectively reviewed 736 tumors treated with RFA and 114 tumors treated with SBRT.[16] SBRT provided better local control for tumors >2 cm and tumors located in the subphrenic area. Hara *et al.*[17] compared tumors ≤3 cm treated with SBRT (221 tumors) or RFA (474 tumors). They showed that SBRT was efficacious for patients unfit for RFA due to tumor location. Further, they specifically reported tumor location and liver toxicity in each treatment group but did not analyze the prognostic value of the treatment modality after adjusting for multiple clinical factors. In this multinational study, we externally validated the efficacy of SBRT over RFA in HBV/HCV endemic areas. The SBRT group had poorer baseline factors than the RFA group, reflecting the current status of SBRT in real practice. Despite unfavorable conditions, SBRT was associated with lower local recurrences. This result was even reproduced in the entire independent 2,232 tumors (Table S7). Further, SBRT and RFA showed comparable mortality rates. It is generally recognized that most patients with HCC encounter multiple failure events, not only at the treatment site but also at out-field intrahepatic sites. Therefore, subsequent treatments, such as repeated RFA, TACE, or systemic treatment, are commonly performed after initial single local treatment in clinical practice. Consequently, lower CLRR may not simply be translated into survival benefit.

In this study, we identified that large tumors (especially >3 cm) located in the subphrenic region exhibited a suboptimal local control rate in the RFA group (2-year CLRR of 32.1%) compared to that in the SBRT group (2-year CLRR of 18.7%). Additionally, tumor size was a prognostic factor for local failure after RFA but not after SBRT. Heat conduction produced by frequency waves in RFA decreases with increasing tumor size.[19–21] Therefore, the AASLD guidelines recommend RFA as the first choice in tumors <2.5 or 3.0 cm.[1] However, with the emergence of high-precision image-guided radiotherapy (IGRT), SBRT could deliver a highly curative dose to tumors irrespective of tumor size.[12,22] Tumors located in the subphrenic region or near the diaphragm are associated with a higher rate of local recurrence after RFA due to invisibility under ultrasound guidance when performed by non-expert physicians.[16,23] Additionally, it is easy to damage the lung basal area when ablating tumors in these

locations, resulting in pleural hemorrhage, pneumothorax, and pleural effusion.[24,25] Recently, several technical advances in RFA methods using artificial ascites, pleural effusion, and real-time virtual sonography can depict tumors invisible by conventional ultrasonography.[26–28] Additionally, SBRT could deliver an adequate radiation dose safely to tumors even in subphrenic locations using various IGRT methods. Our findings demonstrate that SBRT, under IGRT, might be better for treating large tumors located in the subphrenic area.

In recurrent HCC, the available local treatment options are somewhat limited.[22] In our series, there was no significant difference in outcomes for tumors treated with prior RFA to other sites, surgery, sorafenib, and percutaneous ethanol injection. However, compared to SBRT, RFA showed reduced efficacy for recurrent tumor after previous TACE. There are several reports that RFA as a salvage treatment option could result in lower local control rates.[16,29,30] Furthermore, recent prospective trials have suggested that application of SBRT in LR-TR viable tumors after repeated TACE could be a treatment option.[31–33] Therefore, we postulate that SBRT could be an effective treatment modality for recurrent HCC tumors, especially after TACE.

Given distinct toxicity profiles in the RFA group, physicians should consider factors other than tumor size when deciding on the local treatment modality. The incidence of biliary tract damage in the acute phase after RFA was 1.3%, and 11 patients in the RFA group showed long-standing biliary fistula in the current study. Tumors within 1 cm of the major bile duct or hilar tumors are easily affected by thermal damage or direct mechanical damage.[25] Conversely, the rate of biliary complications associated with SBRT was nearly negligible.[34] Additionally, pulmonary toxicities were observed in 2.9% of RFA group patients, and 10 patients who underwent RFA experienced grade 3–4 late pulmonary toxicities.

A frequent decline in Child-Pugh score 3 months post-treatment was observed in the SBRT group, but this pattern reversed after another 3 months. The irradiation volume in SBRT is larger than the ablated area after RFA, which could translate into liver function deterioration.[35] However, radiation-induced liver disease could be avoided if an adequate and precise SBRT plan is developed under the following strict patient selection criteria: more than 700 ml of uninvolved liver, tolerable liver function, and minimum distance (5 mm) from the organ at risk (the stomach and duodenum).[12] Additionally, IGRT with respiratory motion management (breath-hold techniques, 4-dimensional CT, or respiratory gating) could also decrease toxicities and improve the therapeutic ratio. Growing evidence suggests that with long-term follow-up, appropriate patient selection, and advanced radiation therapy techniques, these toxicities could be further avoided.[36–38]

Due to the nature of this multi-institutional retrospective study design, we could not obtain the detailed reason for each treatment. Additionally, there are several limitations of the current study. Even after collecting multi-institutional data and performing PSM analysis to reduce the effect of potential biases, confounders may still exist. Several non-medical factors such as socio-economic status, patient preference, and cost may have influenced the decision for local treatment. Since both modalities require technical expertise, treatment outcomes may show significant variation among institutions; this has been reported in a registry-based study.[9] Current study also showed a wide variation in local recurrence rates among institutions (Fig. S5). Additionally, the relatively short follow-up period in the SBRT group could overestimate the clinical outcomes, and lack of independent review for imaging studies could have affected the difference in the local recurrence results. Therefore, further well-controlled prospective randomized trials are still needed. In summary, both SBRT and RFA could provide comparable local control for HCC. However, SBRT achieved better local control than RFA after adjusting for clinical factors. Both modalities showed comparable mortality rates. In conclusion, SBRT could be an effective alternative to RFA for unresectable HCC, particularly for larger tumors (>3 cm) in a subphrenic location.

Abbreviations

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CLRR, cumulative local recurrence rate; CMR, cumulative mortality rates; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; HR, hazard ratio; IGRT, image-guided radiotherapy; PSM, propensity score matching; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study concept and design: J.S.; Acquisition of data: N.K., J.C., J.D.L., Y.L.S., W.Y.H., T.K., V.H.L., Z.C.Z., R.Z., C.S.K., J.Y.W.; Analysis and interpretation of data: N.K., I.J., S.J.H., J.S.; Drafting of the manuscript: N.K., J.S.; Critical revision of the manuscript for important intellectual content: All authors; Statistical analysis: N.K., I.J., S.J.H.; Funding acquirement: J.S.; Administrative, technical, or material support: J.C., J.D.L., Y.L.S., W.Y.H., T.K., V.H.L., Z.C.Z., R.Z., C.S.K., J.Y.W., J.S.; Study supervision: J.S.

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Supplementary data

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Author names in bold designate shared co-first authorship

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