Research article

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Stereotactic body radiotherapy is an alternative to radiofrequency ablation for single HCC ≤5.0 cm

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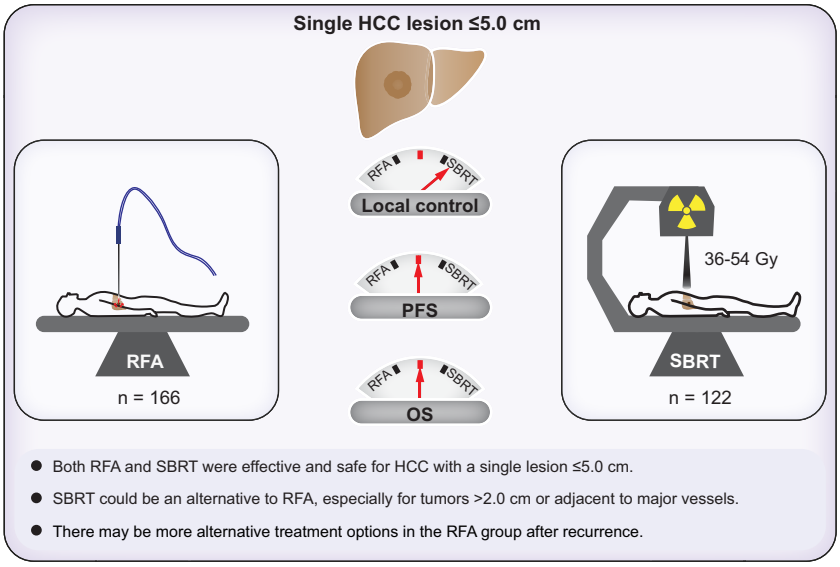
Graphical abstract



Highlights:

- Both RFA and SBRT were effective and safe in patients with a single HCC ≤5 cm.
- We found that distant recurrence had a significant effect on PFS and OS in the SBRT group.
- There may be more alternative treatment options following recurrence/progression in those treated with RFA.
- SBRT could be an alternative treatment to RFA, especially for tumors >2.0 cm or adjacent to major vessels.

Impact and implications:

Stereotactic body radiation therapy (SBRT) may be used as an alternative treatment to thermal ablation for patients with BCLC stage A hepatocellular carcinoma (HCC) who are not candidates for surgical resection, including those with tumours >3 cm and those with 1 to 3 tumours. This study focused on HCC patients with a specific tumour burden, namely a single lesion ≤5.0 cm, demonstrating that SBRT could be an effective and safe alternative to radiofrequency ablation (RFA), especially for those with tumours >2.0 cm or adjacent to major vessels. The findings of this study provided robust empirical evidence supporting the utilization of SBRT in treating small HCC, while also establishing a solid foundation for future prospective clinical investigations.

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Stereotactic body radiotherapy is an alternative to radiofrequency ablation for single HCC ≤5.0 cm

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Background & Aims: Radiation therapy has been refined with increasing evidence of the benefits of stereotactic body radiation therapy (SBRT) in treating hepatocellular carcinoma (HCC). In this study, we aimed to evaluate whether SBRT could serve as an alternative to radiofrequency ablation (RFA) for small HCC with a single lesion ≤5.0 cm.

Methods: Patients with a single HCC lesion ≤5.0 cm who received RFA or SBRT were included. Cumulative local/distant recurrence rate, progression-free survival, overall survival, adverse events and subsequent treatments after recurrence were analyzed.

Results: A total of 288 patients receiving RFA (n = 166) or SBRT (n = 122) were enrolled. The baseline characteristics between the two groups were comparable. The cumulative local recurrence rate in the SBRT group was significantly lower than that in the RFA group (hazard ratio [HR] 0.30, 95% CI 0.16–0.57, p <0.001), especially for patients with tumours >2.0 cm (HR 0.20, 95% CI 0.08–0.50, p <0.001) or adjacent to major vessels (HR 0.29, 95% CI 0.13–0.66, p <0.001). Cumulative distant recurrence rate, progression-free survival and overall survival were not significantly different between the two groups (all p >0.050). Adverse events were mild and easily reversible. However, more patients in the SBRT group suffered from Child-Pugh score and total bilirubin increases. More treatment options after recurrence or progression might be available for patients in the RFA group compared to those in the SBRT group (p <0.001).

Conclusions: Both RFA and SBRT were effective and safe for HCC with a single lesion ≤5.0 cm. SBRT could be an alternative treatment to RFA, especially for tumours >2.0 cm or adjacent to major vessels.

Introduction

Liver cancer is the second leading cause of cancer-related death worldwide, and its incidence and mortality rates are increasing. Hepatocellular carcinoma (HCC) represents about 90% of primary liver cancers and arises from various etiological factors.[1–3] In the Chinese population, HCC frequently manifests in conjunction with hepatitis and cirrhosis.[1,3,4] Certain patients are not suitable candidates for surgery or transplantation due to impaired liver function, tumour location or size limitations, donor scarcity, and other factors. For individuals with small HCC lesions, radiofrequency ablation (RFA) is recommended as the alternative treatment and offers excellent local control rates ranging from 70% to 90%.[2,5–8] However, RFA treatment is greatly affected by cirrhosis, tumour size, location, and is associated with potential complications such as incomplete ablation, needle tract seeding, bleeding, and damage to adjacent organs.[9–13]

Stereotactic body radiation therapy (SBRT) was considered as a potential curative treatment for HCC, especially for patients unfit for surgery and ablation.[2,3,14–17] Previous studies have demonstrated that SBRT is a safe and effective treatment for HCC that is associated with similar local control rates as RFA.[18–23] In addition to X-ray radiation therapy, a prospective study has demonstrated that proton beam radiotherapy is non-inferior to RFA in terms of local progression-free survival and safety for the treatment of recurrent HCC (size <3 cm, number ≤2).[24] Nevertheless, it has been observed that there were imbalances in baseline characteristics among the retrospective studies, including variations in tumour number, size, and location as well as liver function among other factors. Furthermore, there was a dearth of reporting or comparison regarding the progression modality after treatment and subsequent treatments for progressive disease which may impact clinical decision-making.

In this study, we aimed to evaluate whether SBRT could serve as an alternative to RFA for small HCC with a single lesion ≤5.0 cm by comparing survival outcomes, treatment toxicities,

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progression modality after treatment and the subsequent treatments for progressive disease.

Patients and methods

Study population

From January 2017 to January 2020, a total of 288 consecutive patients diagnosed with HCC and treated with RFA or SBRT at Sun Yat-sen University Cancer Center were included in this retrospective study. Patients meeting all the following criteria were included: 1) histologically or radiologically diagnosed HCC; 2) solitary lesion ≤5.0 cm, without distant metastases or vascular invasion; 3) ECOG PS score 0 or 1; 4) Child-Pugh A or B; 5) received RFA or SBRT with curative intent; 6) comprehensive patient medical record data, inclusive of a minimum 6-month follow-up period. The exclusion criteria were as follows: 1) a history of other malignancies; 2) receiving other HCC-related treatments; 3) a history of RFA or SBRT to the target area; 4) other serious non-neoplastic diseases. SBRT was administered to patients who encountered challenges in surgical or RFA procedures due to the following factors: 1) tumour located in the subphrenic region without satisfactory ultrasound imaging; 2) tumours situated close to the gallbladder or gastrointestinal organs; 3) previous repeated surgical interventions or RFA procedures; 4) relative contraindications to surgery or ablation including hypersensitivity to anesthetics, impaired coagulation function, thrombocytopenia, presence of pacemakers etc.; 5) patient refusal of invasive procedures. Patient information, including sex, age, Child-Pugh class, tumour size, etiology, prior liver-directed treatment, pre- and post-treatment liver function (total bilirubin [TB], aspartate aminotransferase, alanine aminotransferase, and albumin levels, as well as prothrombin time etc.), alpha-fetoprotein and follow-up data, were collected. The albumin-bilirubin (ALBI) score was calculated according to the formula ([$\log_{10}$ bilirubin (in μmol/L) × 0.66] + [albumin (in g/L) × -0.085]), with ALBI grades assigned as follows: Grade 1, ≤-2.60; Grade 2, <-2.60 to ≤-1.39; and Grade 3, >-1.39.[25] This work was approved by the ethics committee.

Procedures

RFA

For the RFA group, pre-treatment necessitated the utilization of enhanced ultrasound in conjunction with enhanced CT or MRI. The standard procedures and details were as described previously.[5,26] RFA was performed using conscious analgesic sedation (continuous intravenous anesthesia) and local anesthesia. The ablation procedures were performed percutaneously under real-time ultrasound guidance. During the procedure, a hyperechoic area surrounding the electrode was observed on real-time ultrasound monitoring. To ensure complete coverage of the presumed necrotic volume, the electrode was repetitively inserted into multiple sites to accommodate larger tumours. The procedure was finished when the hyperechoic area was completely covered and exceeded the original lesion. At the end of the procedure, the electrode was slowly pulled out using the thermal hemostatic effect of the electrode tip to prevent the liver and skin needle tract from bleeding. Patients who were found to have residual tumours on imaging after 1 month and received RFA again were also included in this study.

SBRT

For the SBRT group, pre-treatment enhanced CT and MRI are required. Notably, contrast-enhanced CT scans were performed after stabilizing the respiratory curve in the supine position, and 4D software was applied to sort the CT data into respiratory cycles, dividing each respiratory cycle into 10 phases to obtain 10 sets of CT sequences. The target area was delineated based on four-dimensional CT scans. The gross tumour volume (GTV) is defined as an imaging-observable intrahepatic lesion; the internal target volume is formed by the fusion of the GTV in 10 respiratory phases; the planning target volume (PTV) is formed by the outward expansion of the internal target volume by 0.6 cm in all directions. Normal liver is defined as the volume of the whole liver minus the volume of the GTV and is used as a reference for dose assessment. Normal liver volume and organs at risk (OARs) are crucial parameters for dose evaluation, and treatment should be administered at the maximum attainable dosage while adhering to established dose standards. OARs include the liver, kidney, stomach, small intestine, spinal cord, and heart. Dosimetric targets: for PTV, V95% ≥95%, Dmax ≤110%, Dmin ≥90%; for OARs, the mean dose to the normal liver <13 Gy, V15Gy <35%; bilateral kidney Dmean <6 Gy; oesophageal D0.5cc <21 Gy; gastric D0.5cc <21 Gy; small intestine D0.5cc <21 Gy; colon D0.5cc <24 Gy; heart D0.5cc <30 Gy; rib D0.5cc <39 Gy; spinal Dmax <18 Gy. Further evaluation and optimization of the radiotherapy plan was based on dose-volume histograms and dose distribution of tomography.

Treatment was performed using an Elekta Versa HDTM linear accelerator (MLCi2 80 leaves, 0.5 cm MLC) with 6-MV X-rays, using the geometric center of the PTV as the field center point. The prescribed dose was defined as the average dose to the PTV, maximizing the dose to the target area while meeting the dosimetric objectives. The total dose of radiotherapy is 36–54 Gy, administered on alternate days and completed in three fractions.[26]

Follow-up and assessments

Clinical symptoms, blood routine, liver function, alpha-fetoprotein, and tumour assessment (via contrast-enhanced multiphasic CT or MRI) were performed at the first month after the treatment, every 3 months for the following 2 years, and every 6 months thereafter for the RFA group. Patients treated with SBRT were assessed every 3 months for 2 years and at least every 6 months thereafter. The long-term dynamic monitoring of tumour markers and imaging examinations after SBRT is crucial for accurately assessing the response of local lesions.[27]

The primary endpoint was the cumulative recurrence rate (CRR, including local and distant recurrence). The secondary endpoint was progression-free survival (PFS, defined as the time from the date of first treatment to the date of local or intrahepatic recurrence, distant metastases, or death from any cause), overall survival (OS, defined as the time from the date of first treatment to the date of death from any cause), treatment-

related adverse events (AEs), and the subsequent treatments for recurrent disease.

In this study, local recurrence was defined as the re-emergence of tumour activity *in situ* or within 1.0 cm of the margin of loss of activity of the treated lesion under CT or MRI. Distant recurrence was defined as the presence of new lesions elsewhere within the liver or extrahepatic metastases, excluding local recurrence. Irrespective of its type, the first recurrence was treated as an event, serving as the criterion for determining the primary endpoint in this analysis. Lesions located ≤1.0 cm from major vessels such as the main trunk, primary or secondary branches of the hepatic vein, portal vein, biliary system, or the posterior inferior hepatic vena cava were categorized as tumours adjacent to major vessels. The tumour responses were assessed using the modified RECIST criteria.[28] Treatment-related toxicity was graded according to CTCAE v4.0.

Statistical analysis

We used χ^2 test or Fisher's exact test to evaluate categorical variables and the Mann-Whitney *U* test or Student's *t* test to compare continuous variables between two groups. Given that cumulative local recurrence rate (CLRR) and cumulative distant recurrence rate (CDRR) were considered as competing events, we assessed the cumulative recurrence rate using the competing risk model and Fine and Gray's non-parametric test. Survival outcomes and hazard ratios (HRs) were estimated using the Kaplan-Meier method and a Cox proportional hazard model, respectively. Statistical significance was defined as a two-tailed *p* value <0.05. All statistical analyses were performed using R (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria) and SPSS 25.0 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

The baseline characteristics of patients in both groups were presented in Table 1. A total of 288 patients were involved in this study, including 166 patients treated with RFA and 122 patients treated with SBRT. Among the 288 patients, the median age was 56 years (IQR 48.0–63.0) and 87.5% were male. Most patients (94.8%) had chronic HBV infection. The majority of patients presented with well-compensated liver function (Child-Pugh grade A or ALBI grade 1). Approximately half (47.2%) of patients had recurrent tumours. The mean tumour size was 2.16 ± 0.90 cm, with 48.3% of patients presenting with tumours larger than 2.0 cm in diameter. The median follow-up duration was 40.0 months (IQR 30.5–53.4) in the RFA group and 30.9 months (IQR 26.7–38.2) in the SBRT group. The delivered dosages of the SBRT group were presented in Table S1.

Cumulative recurrence rate

After treatment, residual disease was observed in three patients from the RFA group and six patients from the SBRT group. During the follow-up period, the RFA group exhibited local progressive disease in one patient and stable disease in two patients. On the other hand, the SBRT group had three patients with local progressive disease, one with a partial response of the local lesion combined with intrahepatic recurrence, and two with stable disease.

When considering the 279 patients with no residual disease after treatment, local recurrence was observed in 47 (28.8%) of 163 patients in the RFA group and 6 (5.2%) of 116 patients in the SBRT group. Distant recurrence was observed in 41 patients in the RFA group (25.2%, including two cases of lung metastasis and one lymph node metastasis) and 34 patients in the SBRT group (29.3%, including one lung metastasis, one lymph node metastasis, one cervical spine metastasis, and one iliac metastasis). Both local and distant recurrences were detected in five patients in the RFA group and one patient in the SBRT group.

According to Fine and Gray's test, no significant differences in CRR were observed between the two groups (HR 0.71, 95% CI 0.49–1.02, $p = 0.058$, Fig. 1A). At 1 year, CRR in the RFA group was 24.5% (95% CI 17.9%–31.2%) compared with 23.4% (95% CI 15.6%–31.1%) in the SBRT group, and at 3 years it was 52.0% (95% CI 44.1%–60.0%) compared with 39.4% (95% CI 29.8%–49.0%), with Gray's test $p = 0.77$ and $p = 0.09$, respectively (Fig. 1A). Considering two patterns of tumour recurrence, we analyzed the CLRR and CDRR separately (Fig. S1A). CLRR in the SBRT group was significantly lower than that in the RFA group (HR 0.30, 95% CI 0.16–0.57, p <0.001, Fig. 1B), while CDRR was similar between groups (HR 1.30, 95% CI 0.84–2.02, $p = 0.204$, Fig. S1B).

The subgroup analyses were conducted based on tumour size and location. Grouped by tumour size, patients treated with SBRT had lower CLRR than RFA in both subgroups (lesions ≤2.0 cm: HR 0.32, 95% CI 0.11–0.95, $p = 0.035$; lesions 2.1–5.0 cm: HR 0.20, 95% CI 0.08–0.50, p <0.001; Fig. 1C,D). Regardless of whether the lesions were adjacent to major vessels, patients in the SBRT group exhibited a lower CLRR than those in the RFA group (lesions adjacent to major vessels: HR 0.29, 95% CI 0.13–0.66, p <0.001; lesions non-adjacent to major vessels: HR 0.31, 95% CI 0.11–0.89, $p = 0.016$, Fig. 1E,F). For lesions in the subphrenic or subcapsular area, SBRT was associated with lower CLRR than RFA (HR 0.16, 95% CI 0.04–0.72, $p = 0.007$, Fig. 1G). However, the benefits of SBRT were particularly pronounced in patients with tumours larger than 2.0 or those located adjacent to major vessels.

In the 2.1–5.0 cm size subgroup, the SBRT group exhibited a significantly higher CDRR compared to the RFA group (HR 1.97, 95% CI 1.04–3.73, $p = 0.035$, Fig. S1D), and no statistically significant difference in CDRR was observed between the two treatments in other subgroups (all p >0.050, Figs S1C and 1E–G). However, in contrast to the RFA group, distant recurrences in the SBRT group predominantly occurred within 2 years, followed by a significant decrease thereafter.

The results of univariate and multivariate analysis showed that SBRT (HR 0.22, 95% CI 0.10–0.50, p <0.001) and elevated PLT level (HR 0.995, 95% CI 0.99–0.999, $p = 0.018$) were associated with improved CLRR, while larger tumour size (HR 1.60, 95% CI 1.21–2.12, $p = 0.001$) was associated with poorer CLRR. Additionally, increasing age (HR 1.03, 95% CI 1.01–1.05, $p = 0.030$) was identified as a risk factor for CDRR (Table 2).

Progression-free survival and overall survival

During the follow-up period, progressive diseases were observed in 92 patients in the RFA group and 48 patients in the SBRT group out of a total of 288 patients. Thirteen patients in

Table 1. Baseline characteristics of patients in the RFA group and SBRT group.

	RFA, n = 166	SBRT, n = 122	*p* values
Sex, n (%)			0.928[#]
Female	20 (12.0)	16 (13.1)	
Male	146 (88.0)	106 (86.9)	
Age (years), median (IQR)	55.0 (48.0∼63.0)	56.0 (50.0 ∼63.0)	0.434[*]
ECOG score, n (%)			
0	162 (97.6)	120 (98.4)	0.972[#]
1	4 (2.4)	2 (1.6)	
Etiology, n (%)			0.673[#]
HBV	159 (95.8)	114 (93.4)	
HCV	1 (0.6)	1 (0.8)	
Unknown	6 (3.6)	7 (5.7)	
HBV-DNA level (log_{10}), n (%)			0.392[#]
0	111 (66.9)	86 (70.5)	
1–2	7 (4.2)	8 (6.6)	
>2	46 (27.7)	25 (20.5)	
Unknown	2 (1.2)	3 (2.5)	
Antiviral therapy, n (%)			0.768[#]
First-line	146 (88.0)	105 (86.1)	
Second-line	20 (12.0)	17 (13.9)	
Pre-treatment, n (%)			0.122[#]
Newly diagnosed	90 (54.3)	62 (50.8)	
Surgery ± TACE	45 (27.1)	28 (23.0)	
RFA ± TACE	17 (10.2)	13 (10.6)	
Surgery + RFA ± TACE	10 (6.0)	18 (14.8)	
TACE	4 (2.4)	1 (0.8)	
Tumour size, cm, n (%)	2.08 ± 0.80	2.27 ± 1.02	0.073[ϕ]
≤2.0	88 (53.0)	61 (50.0)	0.699[#]
2.1–5.0	78 (47.0)	61 (50.0)	
Location, n (%)			0.671[#]
Adjacent to major vessels	94 (56.6)	73 (59.8)	
Non-adjacent to major vessels	72 (43.4)	49 (40.2)	
Child-Pugh grade, n (%)			0.788[#]
A	165 (99.4)	120 (98.4)	
B	1 (0.6)	2 (1.6)	
ALBI grade, n (%)			0.052[#]
1	147 (88.6)	97 (79.5)	
2	19 (11.4)	25 (20.5)	
AFP, ng/ml, n (%)			0.093[#]
<25	98 (59.0)	72 (59.0)	
25–200	41 (24.7)	20 (16.4)	
>200	27 (16.3)	30 (24.6)	
PIVKA-II, mAU/ml, n (%)			0.125[#]
≤40	91 (54.8)	55 (45.1)	
>40	72 (43.4)	61 (50.0)	
Unknown	3 (1.8)	6 (4.9)	

AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; PIVKA-II, prothrombin induced by vitamin K absence-II; PLT, platelet; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy; TACE, transarterial chemoembolization.
Entecavir, tenofovir and tenofovir alafenamide fumarate were classified as first-line antiviral treatments.
[#]*p* values were calculated using a χ^2 test.
[*]*p* values were calculated using the Mann-Whitney *U* test.
[ϕ]*p* values were calculated using Student's *t* test.

the RFA group and 11 patients (one patient died of cardiovascular disease) in the SBRT group died of tumour progression.

The median PFS time was 32.6 months in the RFA group and not reached in the SBRT group. The Kaplan-Meier analyses showed that 1-year PFS rates were 75.3% (95% CI 71.7%–78.9%) in the RFA group and 76.1% (95% CI 72.2%–80.0%) in the SBRT group (p = 0.790, Fig. 2A); the 3-year PFS rates were 48.1% (95% CI 44.2%–52.0%) in the RFA group and 59.2% (95% CI 54.9%–63.5%) in the SBRT group (p = 0.140, Fig. 2A). In subgroup analyses stratified by tumour size and location, PFS in all subgroups was comparable in the RFA and SBRT groups (all p >0.050, Fig. 2C–G, Table S2). However, SBRT showed a trend of leading to better PFS when tumours were adjacent to major vessels. The univariate and multivariate analyses showed that an elevated PLT level (HR 0.995, 95% CI 0.992–0.998, p <0.001) was significantly associated with improved PFS, whereas the effect of treatment modality only suggested a trend towards better PFS with SBRT (HR 0.71, 95% CI 0.49–1.03, p = 0.07) (Table 3).

OS was similar between the SBRT and RFA groups (HR 1.60, 95% CI 0.69–3.72, p = 0.233) (Fig. 2B). The 3-year OS rates in the RFA group and SBRT group were 93.5% (95% CI 93.2%–93.8%) and 90.4% (95% CI 89.8%–90.4%), respectively. Univariate and multivariate analyses showed that increasing age and tumour size were associated with poorer OS (Table 3).

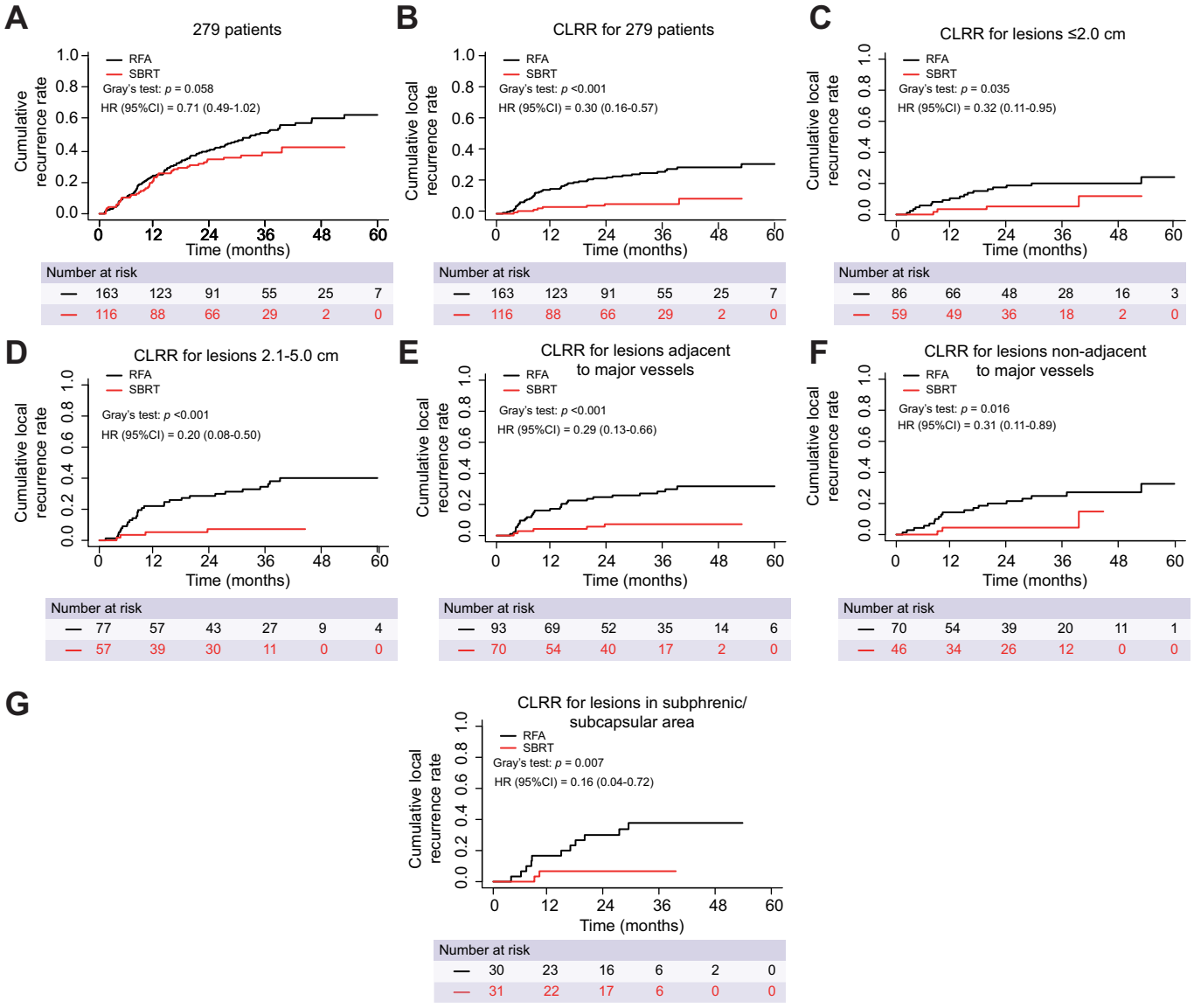

Fig. 1. Cumulative recurrence rates of overall and subgroup analysis in the RFA and SBRT group. (A) CRR in all 279 patients. (B) CLRR in all 279 patients. (C) CLRR in patients with lesions ≤2.0 cm. (D) CLRR in patients with lesions 2.1-5.0 cm. (E) CLRR in patients with lesions adjacent to major vessels. (F) CLRR in patients with lesions non-adjacent to major vessels. (G) CLRR in patients with lesions in the subphrenic or subcapsular area. The Competing risk model and Fine and Gray's test were used. CLRR, cumulative local recurrence rate; CRR, cumulative recurrence rate; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy.

Table 2. Multivariate analysis of variables predictive for recurrences.

	Cumulative local recurrence rate		Cumulative distant recurrence rate	
	HR (95% CI)	*p* values	HR (95% CI)	*p* values
RFA or SBRT	0.22 (0.10–0.50)	**<0.001**	1.34 (0.85–2.10)	0.21
Age	0.98 (0.96–1.01)	0.14	1.03 (1.01–1.05)	**0.03**
HBV-DNA level	1.24 (0.88–1.75)	0.23	0.80 (0.57–1.11)	0.18
Pre-antitumour treatment	1.01 (0.86–1.19)	0.92	1.02 (0.91–1.13)	0.79
Tumour size	1.60 (1.21–2.12)	**0.001**	0.88 (0.66–1.16)	0.36
Adjacent to major vessels, yes *vs*. no	0.99 (0.54–1.81)	0.97	0.94 (0.58–1.53)	0.80
Child-Pugh scores	0.52 (0.14–1.95)	0.33	1.37 (0.83–2.25)	0.22
PLT level	0.995 (0.99–0.999)	**0.018**	0.997 (0.99–1.00)	0.13
AFP level	1.08 (0.73–1.60)	0.69	1.25 (0.94–1.66)	0.12

AFP, alpha-fetoprotein; HR, hazard ratio; PLT, platelet; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy.
HR was calculated using Fine-Gray sub-distribution hazard model. Statistically significant *p* values are displayed in bold.

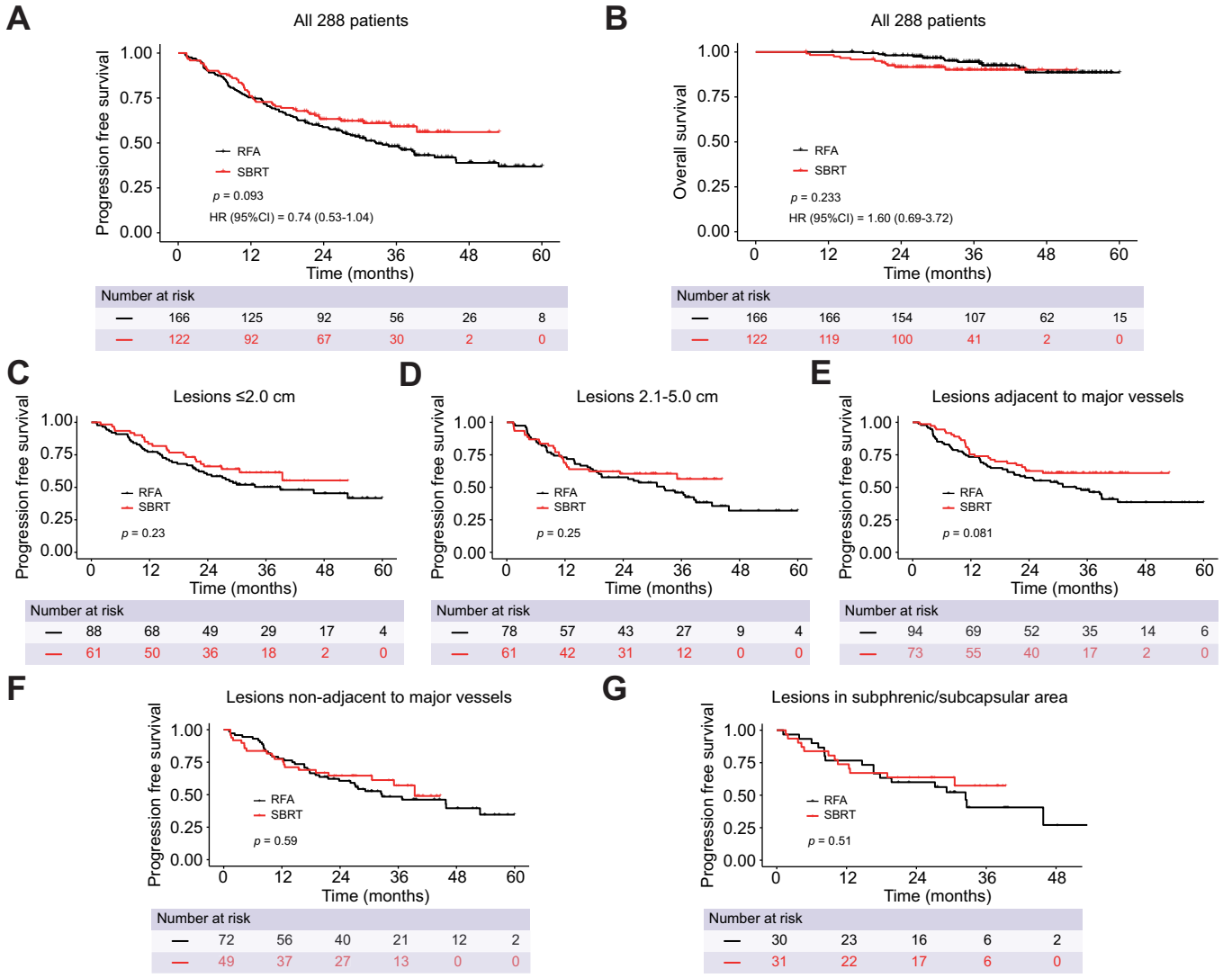

Fig. 2. Kaplan-Meier curves in the RFA and SBRT group. (A) PFS in all 288 patients. (B) OS in all 288 patients. (C) PFS in patients with lesions ≤2.0 cm. (D) PFS in patients with lesions 2.1-5.0 cm. (E) PFS in patients with lesions adjacent to major vessels. (F) PFS in patients with lesions non-adjacent to major vessels. (G) PFS in patients with lesions in the subphrenic or subcapsular area. Kaplan-Meier method and Cox proportional hazard model were used. OS, overall survival; PFS, progression-free survival; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy.

Adverse events

The AEs or toxicities occurring within 1 year after treatment were summarized in Table 4. In the RFA group, needle track seeding and liver abscess (infection) were observed in two patients and one patient, respectively. Two patients in the SBRT group suffered from intercostal neuritis. Patients in both groups received the treatment without severe AEs or toxicities, and there were no instances of acute hepatic failure or bleeding events. Notably, there was a difference in AEs profiles: nausea and fatigue more commonly occurred within 3 months in the

Table 3. Multivariate analysis of variables predictive for PFS and OS.

	PFS rate		OS rate	
	HR (95% CI)	*p* values	HR (95% CI)	*p* values
RFA or SBRT	0.71 (0.49–1.03)	0.07	0.97 (0.37–2.56)	0.95
Age	1.01 (0.99–1.02)	0.49	1.08 (1.03–1.14)	**0.003**
Pre-antitumour treatment	1.03 (0.94–1.13)	0.50	1.15 (0.93–1.43)	0.19
Tumour size	1.16 (0.96–1.42)	0.13	1.72 (1.05–2.80)	**0.03**
Adjacent to major vessels, yes *vs.* no	0.90 (0.63–1.30)	0.58	0.61 (0.24–1.52)	0.29
Child-Pugh scores	0.92 (0.53–1.57)	0.75	1.04 (0.44–2.45)	0.93
PLT level	0.995 (0.992–0.998)	**<0.001**	0.995 (0.998–1.003)	0.21
AFP level	1.20 (0.96–1.48)	0.11	1.38 (0.80–2.40)	0.25

AFP, alpha-fetoprotein; HR, hazard ratio; PFS, progression-free survival; PLT, platelet; OS, overall survival; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy. Cox proportional hazards models were used for univariable and multivariable analyses. Statistically significant *p* values are displayed in bold.

Table 4. Adverse events in patients treated by RFA or SBRT.

	RFA, n = 166				SBRT, n = 122				*p* values
Change of CTCAE scores	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	
PLT decrease	13 (8.0)	2 (1.2)	0	0	22 (18.2)	2 (1.7)	1 (0.8)	0	0.117
Hb decrease	2 (1.2)	0	0	0	3 (2.5)	2 (1.7)	0	0	0.137
ALT increase	7 (4.3)	1 (0.6)	0	0	10 (8.3)	2 (1.7)	0	0	0.236
AST increase	8 (4.9)	0	0	0	12 (9.9)	0	1 (0.8)	0	0.078
TB increase	19 (11.7)	1 (0.6)	0	0	23 (19.2)	8 (6.7)	0	0	**0.005**
ALB decrease	1 (0.6)	0	0	0	2 (1.6)	0	0	0	0.348
Nausea	5	0	0	0	24	0	0	0	**<0.001**
Pain	22	0	0	0	2	0	0	0	**0.001**
Fatigue	0	0	0	0	8	0	0	0	**0.003**
Child-Pugh score increase	-1	0	1	2	-1	0	1	2	**0.016**
	5 (3.1)	151 (93.2)	5 (3.1)	1 (0.6)	1 (0.8)	103 (85.8)	14 (11.7)	2 (1.7)	
Intercostal neuritis				0				2	NA
Abscess				1				0	NA
Needle track seeding				2				0	NA
HBV-DNA level increase				0				0	NA

ALT, alanine aminotransferase; AST, aspartate aminotransferase; Hb, hemoglobin; PLT, platelet; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy.
Data are shown as n (%). *p* values were calculated using a χ^2 test or Fisher's exact test. Statistically significant *p* values are displayed in bold.

patients treated with SBRT, while pain on the day of treatment was commonly observed in the patients treated with RFA. However, all these AEs were transient and could be well managed with or without treatment. No elevation in HBV-DNA levels was observed among HBV-infected patients receiving regular antiviral medication. In terms of liver function indicators, more patients in the SBRT group suffered from transient TB and Child-Pugh score increased (p = 0.005 and p = 0.016 respectively).

Treatment after tumour recurrence or progression

Among the 288 patients, residual diseases, recurrent diseases, or progressive diseases were observed in 94 patients in the RFA group and 50 patients in the SBRT group (Table 5). The predominant treatment modality for these patients was ablation, with 43 patients (45.7%) from the RFA group and 16 patients (32.0%) from the SBRT group undergoing ablation. Other treatment options such as surgery, transarterial chemoembolization (TACE), SBRT, systemic therapy, and liver transplant were also available based on individual clinical presentations at the time of tumour recurrence or progression. More than half of the recurrent patients in both groups received potentially radical treatments including ablation, surgery, transplantation or SBRT (73.4% patients in the RFA group and 56.0% patients in the SBRT group). In summary, more patients in the RFA group received these 'potentially' radical treatments (p <0.001) after recurrence or progression.

Table 5. Treatment after recurrence or progression.

Treatment	RFA, n = 94	SBRT, n = 50	*p* value
Ablation	43 (45.7%)	16 (32.0%)	**<0.001**
Surgery	16 (17.0%)	7 (14.0%)	
SBRT	9 (9.6%)	5 (10.0%)	
TACE	11 (11.7%)	7 (14.0%)	
Systemic therapy	4 (4.3%)	5 (10.0%)	
Liver transplant	1 (1.1%)	0 (0.0%)	
Ongoing monitoring	4 (4.3%)	7 (14.0%)	
Unknown	6 (6.4%)	3 (6.0%)	

RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy; TACE, transarterial chemoembolization.
Data are shown as n (%). *p* values were calculated using Fisher's exact test. Statistically significant *p* values are displayed in bold.

Discussion

For small HCCs that are not suitable for surgical resection, there may be a dilemma when considering ablation due to tumour size, tumour location, severity of cirrhosis, and risk of bleeding. Therefore, alternative treatment options for these cases need to be explored. In this study, we conducted a comparative analysis of CLRR, CDRR, PFS, OS, AEs, and subsequent treatments for recurrent disease following RFA or SBRT in patients with a solitary HCC ≤5.0 cm. Although the CDRR, PFS, and OS were similar between the two groups, the CLRR was significantly lower in the SBRT group compared to the RFA group, especially for patients with tumours >2.0 cm or adjacent to major vessels. The AEs or toxicities were acceptable in both groups, while the RFA group appeared to have more available treatment options after recurrence.

Tumour size and location are the critical determinants impacting oncologic outcomes for patients with HCC undergoing ablation. Previous studies have demonstrated that SBRT is associated with better local control than RFA for patients with larger tumours, such as those exceeding 2.0 or 3.0 cm in diameter.[18–22] In the present study, although SBRT was associated with better local control rates than RFA, regardless of tumour size, this advantage was particularly pronounced in patients with tumours exceeding 2.0 cm. Consistent with previous studies, we also observed that for subphrenic tumours, SBRT exhibited better CLRR than RFA. For tumours adjacent to major vessels, 'heat sink' could lead to more incomplete ablation and local recurrence.[29] Therefore, we performed a more detailed subgroup analysis based on the adjacency of tumours to large blood vessels. Our results demonstrated that irrespective of tumour location, SBRT yielded superior local control rates compared to RFA. Notably, the benefits of SBRT were particularly striking for patients with tumours adjacent to major vessels. Furthermore, SBRT showed a trend of achieving better PFS when tumours were adjacent to major vessels.

It was reported that the previous treatment histories would influence oncologic outcomes for patients undergoing ablation or SBRT.[19] However, in the present study, there was no difference in local and distant recurrence rates between the two groups regardless of whether prior curative treatment (curative treatment: surgery or RFA; palliative treatment: TACE) had been received (Fig. S2A-D). This could potentially be attributed to the inclusion of a substantial proportion of patients with tumour BCLC B–C stage, TNM stage T2-T3, and Child-Pugh class B–C in Kim's study.[19]

As reported by others, we also noticed that the lower CLRR did not lead to better PFS and OS in the SBRT group. We proposed that intrahepatic and/or extrahepatic metastases greatly contributed to similar PFS and OS outcomes. Despite having lower CLRR compared to the RFA group, there was a trend towards higher CDRR in the SBRT group (25.3% *vs.* 29.3%). A possible reason might be that we preferred to assign patients with poorer liver conditions (potentially worse ALBI scores) or larger tumours (Table S3) to the SBRT group. Cirrhosis and larger tumour size in the SBRT group might lead to poorer CDRR. Studies suggested that when tumours grow larger than 2.0 cm, the incidences of satellite nodule and microvascular invasion are increased dramatically.[1,30,31] SBRT might have advantages in local control rate, but it cannot overcome the biological characteristics of a high intrahepatic recurrence rate of HCC. Therefore, reducing rates of distant recurrence remains crucial for improving the oncologic outcomes of HCC.

Secondly, SBRT may potentially exert deleterious long-term effects on liver condition. Unlike most solid tumours, patients with HCC often present with concurrent hepatitis and cirrhosis due to HBV infection.[32] Effective management of these comorbidities has been shown to reduce recurrence rates and improve OS.[33,34] We report a very high prevalence of HBV infection (94.8%) among our patients, with no observed elevation in HBV-DNA levels following treatment with regular antiviral medication. However, our results demonstrated that the PLT level, one of the indicators of cirrhosis, significantly influenced CLRR and PFS. The presence of thrombocytopenia and cirrhosis may impact the assessment of lesion necrosis during ablation procedures and the administration of high-dose radiotherapy, thereby influencing the local treatment efficacy, underscoring the importance of managing cirrhosis during HCC treatment and follow-up. Although all AEs in both groups were transient and could be well managed with or without treatment, a higher proportion of patients in the SBRT group suffered from TB and Child-Pugh score increases ($p = 0.005$ and $p = 0.016$, respectively). It is important to note that retrospective studies are subject to underreporting, potentially overlooking minor adverse events that patients or physicians may not have documented. Furthermore, atrophy of the liver and destruction of the liver structure can be observed after SBRT (Fig. S1H,I). The occurrence of biliary tract injury may result in elevated TB levels and liver atrophy, highlighting the necessity to further investigate the long-term radiotherapy-induced toxicity.

Thirdly, appropriate treatments after recurrence or progression are important for better survival. Previous studies did not analyze the available treatment options for patients after recurrence or progression. It has been reported that the treatments with the greatest OS benefit for patients with intrahepatic recurrent HCCs were salvage liver transplantation and repeat hepatectomy, followed by RFA, SBRT, and TACE.[35] In the present study, we found that 73.4% of patients in the RFA group and 56.0% in the SBRT group had opportunities to receive 'potentially' curative treatment, suggesting that these patients may have more treatment options available to them. Overall, the post-relapse treatment profiles were similar, but the RFA group appeared to have more available treatments, including curative ones. This discrepancy may be attributed to the compromised liver conditions observed in patients from the SBRT group. Another possible reason might be the atrophy of the liver tissue at the irradiated field limiting the application of RFA and surgery (Fig. S1H). Furthermore, in cases of local recurrences, the feasibility of repeated radiotherapy may be limited by dosage constraints, resulting in fewer treatment options. In contrast, a key benefit of RFA is its capacity for repeated treatments, which can be particularly advantageous for managing recurrent tumours.

Compared to previous studies, the present study exhibited some strengths. Firstly, our focus was on patients with a single tumour ≤5.0 cm, ensuring comparable baseline characteristics and liver function between the two groups. Patients with a single tumour were treated with SBRT without unnecessary liver damage due to overlapping irradiation fields caused by multiple tumours. Secondly, we provided more comprehensive analyses of relapse patterns and subsequent treatments, which greatly improved the panoramic view of the pros and cons of RFA and SBRT for treating small HCC.

Although our study was conducted at a stage when both SBRT and RFA were well-developed, there are several limitations. Firstly, this retrospective study encountered inherent challenges in assigning treatment to patients, such as patients with severe cirrhosis receiving SBRT. Secondly, the relatively small sample size and single-center data collection may result in selection bias. Thirdly, the relatively short follow-up period made it impossible to assess the long-term effects of SBRT, including efficacy and side effects. However, based on previous studies and the data observed in our cohort, we believe that SBRT is an effective treatment with tolerable long-term side effects.[36] The fourth point to note was the high prevalence of HBV infection (94.8%) observed among our cohort, leaving unknown whether a similar trend exists for HCC caused by other etiologies. Lastly, we were unable to assess the effects on liver volume and tissue structure within the irradiated field after SBRT treatment.[37] Therefore, further prospective randomized trials are needed.

In summary, SBRT resulted in better CLRR than RFA and comparable CDRR, PFS, and OS. The AEs or toxicities were minimal in both groups, and the RFA group may had more alternative treatment options after recurrence. SBRT could be an effective and safe alternative treatment to RFA for patients with HCC with a single lesion ≤5.0 cm, especially for tumours >2.0 cm or adjacent to major vessels.

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Abbreviations

AEs, adverse events; CRR, cumulative recurrence rate; CDRR, cumulative distant recurrence rate; CLRR, cumulative local recurrence rate; GTV, gross tumour volume; HCC, hepatocellular carcinoma; OARs, organs at risk; OS, overall survival; PFS, progression-free survival; PTV, planning target volume; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy; TACE, transarterial chemoembolization.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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

Authors' contributions

Study concept and design (ZYJ, XM and CMS); conduct of the study (YZT, LSL, HL and CJB); acquisition of data (YZT, LSL, HL); analysis and interpretation of data (YZT, LSL, HL and WJC); drafting of the manuscript (YZT, LSL, HL and PYX); critical revision of the manuscript for important intellectual content (All authors); final approval (All authors).

Data availability statement

The data are available from the corresponding author on reasonable request.

Statement of ethics

The study protocol conforms to the Declaration of Helsinki and Good Clinical Practice Guidelines. This study protocol was reviewed and the need for informed consent was waived by the Ethics Committee of Sun Yat-sen University Cancer Center.

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Supplementary data

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Author names in bold designate shared co-first authorship

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