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Radiofrequency ablation versus stereotactic body radiotherapy for recurrent hepatocellular carcinoma: a multicenter, propensity score matching analysis

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Abstract

Purpose This study aimed at analyzing and comparing the clinical efficacy and prognosis of stereotactic body radiotherapy (SBRT) and radiofrequency ablation (RFA) in the treatment of recurrent hepatocellular carcinoma (RHCC).

Methods Clinicopathological data of RHCC patients who underwent RFA or SBRT as treatment from three medical centers were retrospectively reviewed. The survival outcomes of patients who underwent SBRT were compared with those who underwent RFA. Using the Kaplan–Meier method, survival curves for the two groups of patients were generated, and the log-rank test was used to compare survival differences. Propensity score matching (PSM) analysis was used to match patients of the SBRT and RFA groups in a 1:1 ratio.

Results The SBRT group had a significantly better overall survival (OS) than the RFA group and no statistical differences were found in disease-free survival (DFS) in the two groups before and after PSM. After PSM, subgroup analysis demonstrated that, compared with the RFA group, the SBRT group had a significantly better OS in terms of tumor location in the subphrenic or subcapsular area, tumor size > 2.5 cm, and tumor proximity to major vessels ≤ 1 cm.

Conclusions SBRT appears to be an effective priority to RFA for RHCC patients especially when RFA is not feasible due to tumor location, size, and proximity to major vessels.

Keywords Recurrent hepatocellular carcinoma (RHCC), Survival outcomes, Propensity score matching (PSM), Stereotactic body radiotherapy (SBRT), Radiofrequency ablation (RFA)

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Introduction

Hepatocellular carcinoma (HCC) is a common malignant tumor of the digestive system and the third leading cause of cancer-related deaths worldwide [1, 2]. With significant advances in surgical technique over the recent decade, hepatectomy is currently one of the most effective treatment options for HCC [3]. Unfortunately, the prognosis of surgical resection is still compromised by a relatively high rate of intrahepatic recurrence, reaching as high as 70% within 5 years after surgery [4]. The management of recurrent HCC (RHCC) is pivotal in enhancing patients' long-term prognosis. However, limited clinical guidelines and consensus have been proposed for the treatment of RHCC. Improvement of the efficacy and prolongation of the survival for RHCC patients is the key and challenging aspect of current clinical research [5]. To date, there are large accounts of salvage treatment options for RHCC, such as repeat hepatectomy, liver transplantation, radiofrequency ablation (RFA), transarterial chemoembolization (TACE), stereotactic body radiation therapy (SBRT), chemotherapy, immunotherapy, etc. [6]. Currently, for localized disease, liver transplantation and hepatic resection are both adopted as the main curative treatments according to the Barcelona Clinic Liver Cancer staging system [7]. However, in clinical practice, most patients have lost the opportunity for re-surgical treatment [8]. Therefore, nonsurgical interventions have been explored [9].

Various local minimally invasive treatments for RHCC have been greatly developed in the past decade [10]. RFA is currently the main treatment for patients who are inoperable and have small HCCs, with fewer complications [5, 11]. The oncological outcomes of RFA are comparable to surgery in randomized trials [12]. However, RFA has some limitations, including tumor proximity to major vessels, size discrepancies, and limited accessibility of ultrasonography (US) [13]. In recent years, SBRT has become an emerging noninvasive modality to treat tumors not suitable for surgery or RFA [14], showing a potent local control ranging from 87 to 100% at 1–3 years [15, 16].

In this study, we conducted a multicenter retrospective study based on the data from three major cancer centers in China, aiming to analyze and compare the efficacy and safety of RFA and SBRT for RHCC, which may provide clinical reference and define a logical management algorithm for RHCC patients.

Materials and methods

Patients

From January 2015 to December 2021, a total of 219 patients who were admitted to the Eastern Hepatobiliary Surgery Hospital (EHBH), Fujian Provincial Hospital (FPH) and Xuzhou Municipal First People's Hospital (XMFPH) with RHCC were included in this study. The institutional review board of the participating hospitals approved this study. Written informed consent was obtained from all of the patients.

The inclusion criteria for the study were as follows: (1) age $\geq$ 18 years, (2) a history of hepatectomy for primary HCC, and RHCC $\leq$ 5 cm was diagnosed by American Association for the Study of Liver Diseases (AASLD) diagnostic criteria, (3) R0 resection of the primary tumor and absence of extrahepatic metastasis at first presentation, (4) no residual disease detected within the first 2 months after initial hepatectomy, (5) Child–Pugh class A or selected B (score $\leq$ 7). We excluded RHCC patients who had vascular invasion or distant metastasis when disease recurrence, recurrence within one month of SBRT or RFA treatment, hepatitis C virus (HCV) infection, and incomplete serological, pathological, or follow-up data. The treatment strategies and surgical methods for individual patient were based on the full discussions of multidisciplinary team (MDT) meetings at each medical center. Finally, a total of 174 patients were enrolled, including 99 patients in the RFA group and 75 patients in the SBRT group (Fig. 1).

Clinicopathological variables, including sex, age, body mass index (BMI), hepatitis B virus (HBV) infection, antiviral therapy, hypertension, diabetes mellitus, routine blood test, blood biochemical examination, serum alpha-fetoprotein (AFP), Child–Pugh class, cirrhosis, tumor number, tumor size, location and proximity to major vasculature, were collected.

Radiofrequency ablation (RFA)

RFA were routinely performed percutaneously using the Cool-tipTM RF Ablation System (Medtronic, USA) under local anesthesia. Using the intercostal or subcostal approach, a cooled-tip electrode was inserted under the guidance of ultrasound, with an intended ablative margin of at least 1 cm. All RFA procedures were performed by two experienced hepatologists with 5 years of experience performing RFA. When a viable RHCC lesion remained, due to an insufficient ablative effect observed at the 24-h Computed Tomography (CT) evaluation, additional RFA or resection was performed to achieve complete ablation or removal of the RHCC. Drain was placed only when clinically indicated.

Stereotactic body radiotherapy (SBRT)

The patient underwent free-breathing, time-averaged rapid scan CT (long-duration CT) with data acquisition every 6–8 s and reconstruction at 1-s intervals at the spinal position for radiation therapy planning CT. Patient immobilization was achieved using vacuum

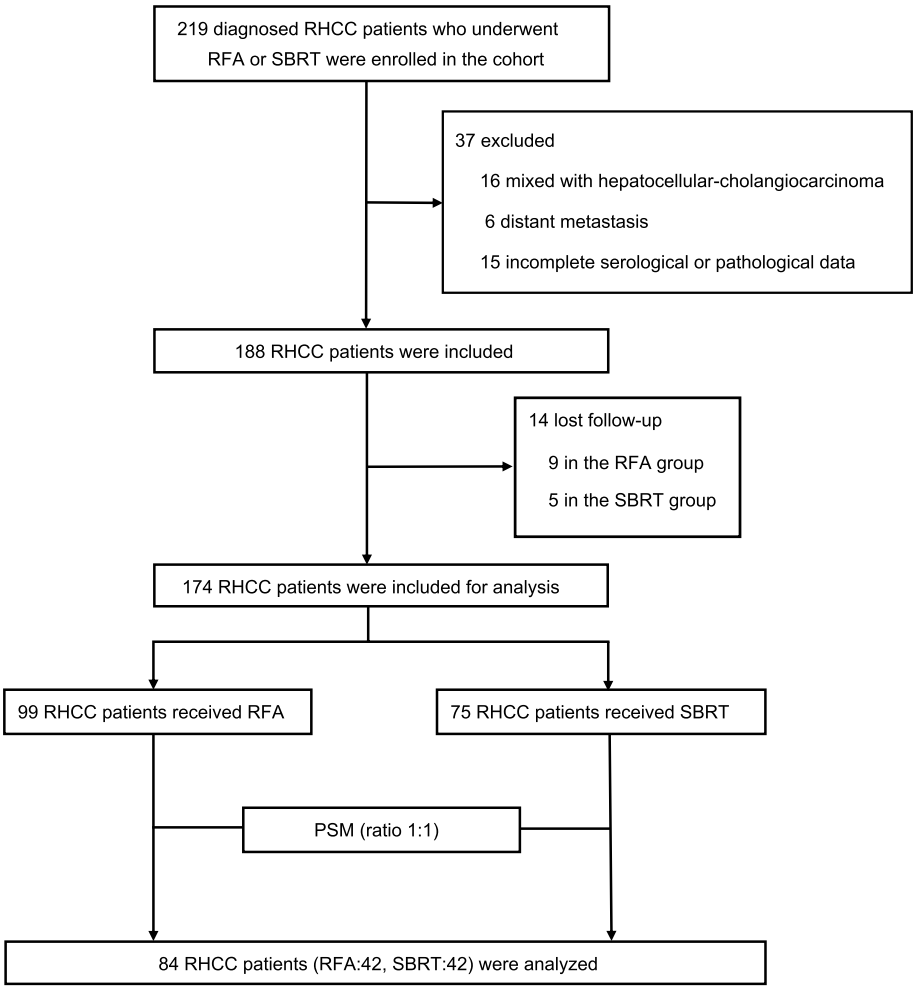

Fig. 1 Study flowchart survival. Abbreviations: RHCC, recurrent hepatocellular carcinoma; RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy; PSM, propensity score matching

pillows in combination with an α-cradle. Non-ionic contrast-enhanced 3-phase or 4-phase helical dynamic CT scans with abdominal compression were employed. Cone-beam CT was utilized before each treatment session to enhance setup precision. Treatment planning was based on contrast-enhanced 4D-CT imaging. The gross tumor volume (GTV) was delineated based on visible tumors identified across all respiratory phases of free-breathing CT and 4D-CT, supplemented by MRI information when available. An internal target volume (ITV) was generated and expanded isotropically by 6 mm to establish the planned target volume (PTV) based on variations in lesion size and location. Dose prescription was uniformly specified around the PTV during treatment planning. The prescribed dose, individual fraction dose, and fractionation schedule were determined based on lesion characteristics, with the number of lesions typically not influencing the prescribed dose. The most common schemes were 3×12.5 Gy (65%-isodose) in 56% and 5×8 Gy (80%-isodose) in 20% of the treated lesions delivered every other day. Implanted fiducials or lipiodol enhancement were contoured accordingly to receive a fiducial or lipiodol ITV, which was used for daily patient set-up.

Follow-up

Patients usually receive multiphase contrast-enhanced CT or Magnetic Resonance Imaging (MRI) scans and serum AFP tests 1 month after RFA or SBRT treatment to detect residual, recurrent, or metastatic tumors, and follow-up examinations were conducted every 3–6 months to monitor tumor progression. Tumor recurrence was described as the appearance of a new intra- or extrahepatic lesion. In case of recurrence of the tumor, follow-up

treatment was recommended by the multidisciplinary team. Once tumor recurrence occurred, aggressive management, including repeated surgery, TACE, RFA, SBRT, molecular targeted therapy, or immunotherapy, was adopted based on the stage of RHCC and liver function of patients. All patients were followed up regularly until December 1, 2022. The date of tumor recurrence, the date of last follow-up, and the date of death were recorded.

Study outcomes

Study outcomes included overall survival (OS), disease-free survival (DFS), and complications. In this study, OS was defined as the time interval from RFA or SBRT treatment to death from any cause or censoring at the last follow-up, and DFS was defined as the interval from RFA or SBRT treatment to recurrence in the liver or elsewhere, or censoring at the date of last follow-up (December 2022).

Postoperative complications, including nausea, wound infection, fever, bile fistula, pneumothorax, pleural effusion, ascites, intestinal fistula, upper gastrointestinal ulcer, dermatitis, radiation pneumonitis, needle tract seeding, hepatic hemorrhage, and hepatic failure.

Statistical analysis

Except for OS and DFS, all variables in this study are categorical variables. Categorical data were shown as frequencies and percentages, and compared using the Chi-square test or Fisher's exact test as appropriate. The Kaplan–Meier method was used to generate survival curves and the log-rank test was used to compare survival differences. Independent factors associated with DFS and OS were determined using Cox regression models. Hazard ratios (HRs) with corresponding 95% confidence intervals (95% CIs) were also estimated using Cox regression models. In Cox regression analysis, multivariate analysis was performed with variables yielding $P < 0.05$ in univariate analysis.

Propensity score matching (PSM) analysis was used to minimize the potential confounders and selection bias and balance the patient baseline characteristics between groups. A 1:1 match between the RFA and SBRT groups was performed. Variables including sex, age, BMI, HBV infection, antiviral therapy, hypertension, diabetes mellitus, routine blood test, blood biochemical examination, serum AFP, Child–Pugh class, cirrhosis, tumor number, tumor size, location and proximity to major vasculature were matched. A caliper width of 0.05 standard deviations was set to prevent poor matching.

Statistical significance was set as a p value < 0.05 at two-tailed level for all analyses. IBM SPSS Statistics for Windows, version 27.0 (IBMCorp., Armonk, N.Y., USA) was utilized for data analyses and visualization in our study.

Results

Baseline characteristics of the patients

The clinicopathological baseline characteristics are shown in Table 1. Among the 174 participants with RHCC, 99 patients underwent RFA, and 75 patients underwent SBRT. 85.6% were males and a total of 89.7% of patients had HBV infection. Compared with the RFA group, the SBRT group had a higher percentage of age > 60 (50.7% vs. 34.3%, $p = 0.032$), significantly fewer patients with diabetes melius (14.7% vs. 28.3%, $p = 0.028$) and hypertension (25.3% vs.41.4%, $p = 0.025$), a higher percentage of Child–Pugh class A (96.0% vs. 82.8%, $p = 0.003$), a higher percentage of creatinine ≤ 106 μmol/L (97.3%vs.89.9%, $p = 0.039$), a higher percentage of platelet count ≤ 100 × 10^9/L (26.7% vs. 12.1%, $p = 0.019$), a lower percentage of TBIL ≤ 17.1 μmol/L (74.7% vs. 87.9%, $p = 0.030$), a higher percentage of ALT ≤ 44 U/L (97.3%vs.81.8%), a lower percentage of PT > 13 s (6.7% vs. 18.2%, $p = 0.019$), a lower percentage of AFP > 400 μmol/L (18.7% vs. 33.3%, $p = 0.027$). After PSM, all these clinicopathological features were well balanced, and 42 cases in each group were matched and included in the analyses (Table 1).

Long term outcomes

The median follow-up time of the whole cohort was 48.0 months (95%CI 40.0–56.0 months), and approximately half of the patients ($n = 86$, 49.4%) died during follow-up. Before PSM, the OS of the SBRT group was significantly longer than that of the RFA group (median OS time, not reached vs. 41.6 months; 1-year, 98.7%vs.98.0%; 3-year, 77.3% vs.65.7%; 5-year, 73.3% vs.40.4%; $p = 0.026$; Fig. 2a). However, no significant differences for DFS were observed in the two groups (19.5 months vs. 27.1 months; 1-year, 78.7% vs. 89.9%; 2-year, 44.0% vs.55.6%;3-year, 34.7% vs.33.3%; $p = 0.481$; Fig. 2b).

After PSM, the OS of the SBRT group was also significantly better than the RFA group, while no significant differences for DFS were observed in the two groups (for OS: median OS time, not reached vs. 41.6 months; 1-year,97.6% vs.97.6%; 3-year,85.7% vs. 64.3%; 5-year,% 78.6vs. 40.5%; $p = 0.012$; Fig. 2c; for DFS: 28.1 months vs. 18.3 months; 1-year, 81.0% vs. 85.7%; 2-year, 57.1% vs.42.9%;3-year, 45.2% vs.28.6%; $p = 0.577$; Fig. 2d).

Independent risk factors associated with OS

As presented in Table 2, univariate and multivariate analyses demonstrated that different treatment methods (RFA or SBRT) on RHCC patients and tumor

Table 1 Baseline clinicopathological characteristics of RHCC patients with treatment of RFA or SBRT before and after PSM

Characteristics	Before PSM			After PSM		
	RFA	SBRT	*p* value	RFA	SBRT	*p*-value
	n = 99	*n* = 75		(*n* = 42)	(*n* = 42)	
Age > 60(%)	34(34.3%)	38(50.7%)	**0.032**[a]	19(45.2%)	19(45.2%)	1.000
Sex, male (%)	83(83.8%)	66(88.0%)	0.433	36(85.7%)	36(85.7%)	1.000
BMI > 24(%)	53(53.5%)	32(42.7%)	0.157	22(52.4%)	19(45.2%)	0.518
Diabetes melius (%)	28(28.3%)	11(14.7%)	**0.028**	9(21.4%)	6(14.3%)	0.399
Hypertension (%)	41(41.4%)	19(25.3%)	**0.025**	10(23.8%)	12(28.6%)	0.625
HBV infection (%)	86(86.9%)	70(93.3%)	0.151	37(88.1%)	37(88.1%)	1.000
Antiviral therapy (%)	85(85.9%)	65(86.7%)	0.879	37(88.1%)	33(78.6%)	0.247
Cirrhosis(%)	69(69.7%)	50(66.7%)	0.674	32(76.2%)	27(64.3%)	0.238
Child–Pugh class						
A	82(82.8%)	72(96.0%)	**0.003**	39(92.9%)	41(97.6%)	0.312
B	17(17.2%)	3(4.0%)		3(7.1%)	1(2.4%)	
Blood glucose (mmol/L)						
≤ 7	85(85.9%)	60(80.0%)	0.317	39(92.9%)	36(85.7%)	0.296
> 7	14(14.1%)	15(20.0%)		3(7.1%)	6(14.3%)	
Creatinine (μmol/L)						
≤ 106	89(89.9%)	73(97.3%)	**0.039**	41(97.6%)	40(95.2%)	0.562
> 106	10(10.1%)	2(2.7%)		1(2.4%)	2(4.8%)	
Hemoglobin(g/L)						
≤ 110	8(8.1%)	5(6.7%)	0.724	2(4.8%)	3(7.1%)	0.649
> 110	91(91.9%)	70(93.3%)		40(95.2%)	39(92.9%)	
Platelet count, x 10^9/L						
≤ 100	12(12.1%)	20(26.7%)	**0.019**	4(9.5%)	5(11.9%)	0.728
> 100	87(87.9%)	55(73.3%)		38(90.5%)	37(88.1%)	
TBIL (μmol/L)						
≤ 17.1	87(87.9%)	56(74.7%)	**0.030**	36(85.7%)	38(90.5%)	0.506
> 17.1	12(12.1%)	19(25.3%)		6(14.3%)	4(9.5%)	
ALT (U/L)						
≤ 44	81(81.8%)	73(97.3%)	**< 0.001**	41(97.6%)	40(95.2%)	0.562
> 44	18(18.2%)	2(2.7%)		1(2.4%)	2(4.8%)	
ALB (g/L)						
≤ 35	6(6.1%)	2(2.7%)	0.268	3(7.1%)	0(0.0%)	0.083
> 35	93(93.9%)	73(97.3%)		39(92.9%)	42(100.0%)	
PT (s)						
≤ 13	81(81.8%)	70(93.3%)	**0.019**	37(88.1%)	38(90.5%)	0.728
> 13	18(18.2%)	5(6.7%)		5(11.9%)	4(9.5%)	
AFP (ng/ml)						
≤ 400	66(66.7%)	61(81.3%)	**0.027**	33(78.6%)	32(76.2%)	0.797
> 400	33(33.3%)	14(18.7%)		9(21.4%)	10(23.8%)	
Tumor number						
Solitary	89(89.9%)	64(85.3%)	0.374	39(92.9%)	35(83.3%)	0.182
Multiple	10(10.1%)	11(14.7%)		3(7.1%)	7(16.7%)	
Tumor location						
Subphrenic or subcapsular	72(72.7%)	57(76.0%)	0.626	30(71.4%)	35(83.3%)	0.197
Other	27(27.3%)	18(24.0%)		12(28.6%)	7(16.7%)	
Tumor diameter						
≤ 2.5	58(58.6%)	35(46.7%)	0.121	26(61.9%)	19(45.2%)	0.129
> 2.5	41(41.4%)	40(53.3%)		16(38.1%)	23(54.8%)	

Table 1 (continued)

Characteristics	Before PSM			After PSM		
	RFA	SBRT	*p* value	RFA	SBRT	*p*-value
	n = 99	*n* = 75		(*n* = 42)	(*n* = 42)	
Tumor proximity to major vessels(cm)						
≤ 1	28(28.3%)	27(36.0%)	0.285	11(26.2%)	19(45.2%)	0.070
> 1	71(71.7%)	48(64.0%)		31(73.8%)	23(54.8%)	

Abbreviations: *RFA* radiofrequency ablation, *SBRT* stereotactic body radiotherapy, *PSM* propensity score matching, *SBRT* stereotactic body radiotherapy, *RFA* radiofrequency ablation, *BMI* body mass index, *HBV* hepatitis B virus, *ALT* alanine aminotransferase, *TBIL* total bilirubin, *ALB* albumin, *PT* prothrombin time, *AFP* alpha-fetoprotein

[a] The symbol bold reflected inside the table showed that *p*-value < 0.05, which means there was a significant difference between the two groups

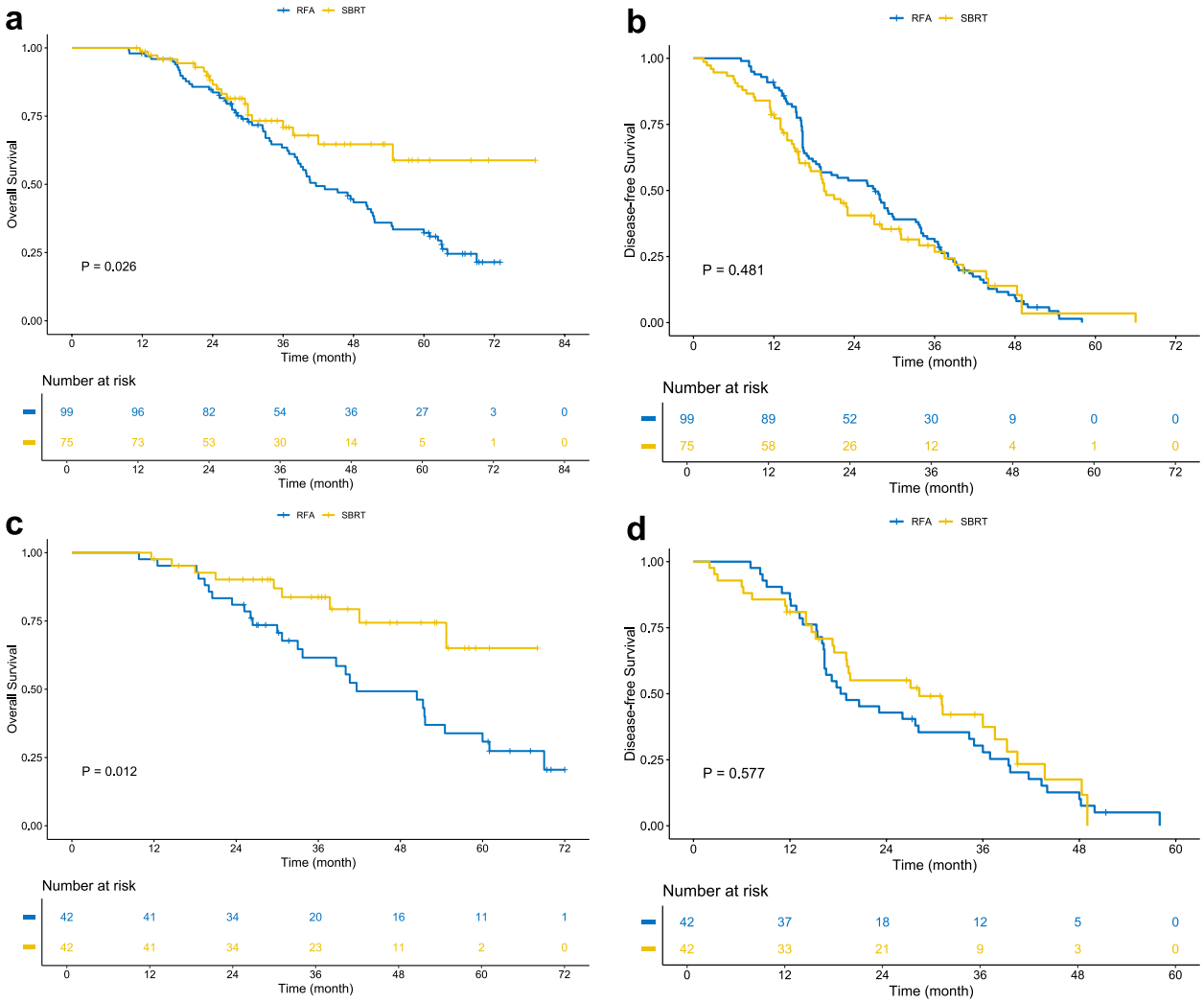

Fig. 2 OS and DFS of RHCC patients treated with RFA or SBRT before and after PSM. Notes: OS (**a**) and DFS (**b**) of RHCC patients before PSM. OS (**c**) and DFS (**d**) of RHCC patients after PSM. Abbreviations: OS, overall survival; DFS, disease-free survival; RHCC, recurrent hepatocellular carcinoma; RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy; PSM, propensity score matching

Table 2 Univariate and multivariate analysis of OS for patients with RHCC before and after PSM

Characteristic	HR Comparison	Before PSM						After PSM					
		Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
		HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	> 60 vs. ≤ 60,year	1.05	0.68–1.61	0.841				1.02	0.52–2.00	0.958			
Sex	Female vs. male	1.34	0.74–2.43	0.330				1.30	0.51–3.35	0.588			
BMI	> 24 vs. ≤ 24,kg/m^2	0.91	0.60–1.40	0.673				0.98	0.51–1.90	0.948			
Diabetes melius	Yes vs. no	1.18	0.73–1.91	0.495				1.34	0.63–2.87	0.449			
Hypertension	Yes vs. no	1.35	0.88–2.07	0.172				1.09	0.52–2.28	0.814			
HBV infection	Yes vs. no	1.48	0.71–3.06	0.294				3.10	0.74–12.97	0.121			
Antiviral therapy	Yes vs. no	1.67	0.86–3.24	0.128				2.93	0.90–9.62	0.076			
Cirrhosis	Yes vs. no	0.89	0.57–1.41	0.628				0.78	0.38–1.62	0.507			
Child–Pugh class	A or B	0.99	0.53–1.88	0.986				0.46	0.06–3.40	0.446			
Blood glucose	> 7 vs. ≤ 7,mmol/L	1.73	1.01–2.96	0.047				1.63	0.56–4.73	0.369			
Creatinine	> 106 vs. ≤ 106,μmol/L	1.34	0.64–2.77	0.436				1.28	0.17–9.42	0.810			
Hemoglobin	> 110 vs. ≤ 110,g/L	1.78	0.72–4.41	0.212				3.32	0.45–24.31	0.238			
Platelet count	> 100 vs. ≤ 100,× 10^9/L	0.99	0.55–1.78	0.965				1.03	0.36–2.94	0.952			
TBIL	> 17.1 vs. ≤ 17.1,μmol/L	0.80	0.43–1.51	0.491				0.86	0.30–2.44	0.777			
ALT	> 44 vs. ≤ 44,U/L	1.66	0.94–2.95	0.082				3.02	0.71–12.74	0.133			
ALB	> 35 vs. ≤ 35,g/L	1.04	0.45–2.39	0.932				0.77	0.23–2.55	0.668			
PT	> 13 VS. ≤ 13,s	0.92	0.51–1.66	0.777				0.94	0.33–2.66	0.902			
AFP	> 400 vs. ≤ 400,ng/ml	1.37	0.87–2.14	0.170				1.44	0.69–3.02	0.333			
Tumor number	Solitary vs. multiple	0.93	0.47–1.86	0.834				0.74	0.23–2.43	0.623			
Tumor location	Subphrenic or subcapsular vs.other	0.47	0.30–0.72	< 0.001	0.46	0.30–0.72	< 0.001	0.41	0.21–0.81	**0.011**	0.44	0.22–0.87	**0.019**
Tumor diameter	> 2.5 vs. ≤ 2.5,cm	0.83	0.54–1.27	0.385				1.31	0.67–2.57	0.432			
Tumor proximity to major vessels	> 1 vs. ≤ 1,cm	0.97	0.61–1.53	0.887				1.194	0.59–2.40	0.619			
Treatment methods	RFA vs.SBRT	1.76	1.06–2.92	**0.028**	1.78	1.07–2.94	**0.025**	2.58	1.20–5.53	**0.015**	2.43	1.13–5.22	**0.023**[a]

Abbreviations: *OS* overall survival, *RHCC* recurrent hepatocellular carcinoma, *PSM* propensity score matching, *HR* hazard ratio, *CI* confidence interval, *SBRT* stereotactic body radiotherapy, *RFA* radiofrequency ablation, *BMI* body mass index, *HBV* hepatitis B virus, *ALT* alanine aminotransferase, *TBIL* total bilirubin, *ALB* albumin, *PT* prothrombin time, *AFP* alpha-fetoprotein

[a] The symbol bold reflected inside the table showed that p-value < 0.05, which means there was a significant difference between the two groups

location were independent risk factors for OS before and after PSM.

Postoperative complications

Few toxicities were noted in patients in the SBRT and RFA groups (Table 3). In SBRT group, treatment-related toxicities included nausea ($n=2$, 2.7%), fever ($n=3$, 4.0%), pleural effusion ($n=1$, 1.3%) and dermatitis ($n=2$, 2.7%). All toxicities resolved after treatment; In RFA group, treatment-related toxicities included nausea ($n=3$, 3.0%), wound infection ($n=1$, 1.0%), fever ($n=8$, 8.1%), pneumothorax ($n=1$, 1.0%), pleural effusion ($n=2$, 2.0%), biliary fistula ($n=1$, 1.0%), ascites ($n=1$, 1.0%), hepatic hemorrhage ($n=3$, 3.0%), and needle tract seeding ($n=1$, 1.0%). All toxicities were resolved successfully after the interventional procedure.

Subgroup survival analysis in patients associated with tumor location, tumor size, tumor proximity to major vessels

Post-hoc subgroup analyses showed that, after PSM, the RHCC patients derived significant OS benefits from SBRT than those with RFA if the tumor was located in the subphrenic or subcapsular segments, and tumor diameter > 2.5 cm (both $p<0.05$) (Figs. 3a, 4c). The RHCC patients derived significant DFS benefits from SBRT if tumor proximity to major vessels ≤ 1 cm ($p<0.05$) (Fig. 5b).

Table 3 Postoperative short-term results of RHCC patients with treatment of RFA or SBRT before PSM

Characteristics	RFA ($n=99$)	SBRT ($n=75$)
Nausea	3	2
Wound infection	1	0
Fever	8	3
Pneumothorax	1	0
Pleural effusion	2	1
Radiation pneumonitis	0	0
Bile fistula	1	0
Ascites	1	0
Intestinal fistula	0	0
Upper gastrointestinal ulcer	0	0
Dermatitis	0	2
Hepatic hemorrhage	3	0
Needle tract seeding	1	0
Hepatic failure	0	0

Abbreviations: *RHCC* recurrent hepatocellular carcinoma, *RFA* radiofrequency ablation, *SBRT* stereotactic body radiotherapy, *PSM* propensity score matching

Discussions

HCC is one of the most common primary malignancies with a poor prognosis. The high incidence of recurrence in patients with RHCC has consistently compromised patient survival, making RHCC become a major global health problem. To the best of our knowledge, high-quality studies comparing the clinical efficacy and prognosis of RHCC patients who underwent RFA or SBRT are scarce. Therefore, in this study, we analyzed and compared the perioperative and long-term oncological outcomes among patients undergoing either RFA or SBRT, in order to determine which may be considered a preferred treatment option for RHCC.

The AASLD guidelines recommend RFA as the first choice for tumors < 2.5 cm [17], since RFA is based on the principle of frictional heat production by frequency waves. Heat conduction rates of RFA decrease as tumor size increases, resulting in inadequate tumor control. Previous studies have shown that tumors exceeding 2.5 cm in diameter are associated with local tumor progression after RFA [18, 19]. Besides, when the tumor is located close to a major blood vessel (i.e., the portal vein or a major branch of the hepatic vein), the lower blood temperature "cools" the tumor adjacent to the vessel, contributing to incomplete ablation and “heat-sink” effect [20–22]. Generally, it is widely accepted that RFA is technically challenging to visualize the tumor. RFA of tumors in either a subphrenic [23] or subcapsular [24, 25] location is associated with higher local recurrence [26–28] and risk of major complication rates [29, 30] due to the poor visibility under US guidance [23, 31]. When tumors are subcapsular and abutting vital organs such as the heart, stomach or other organs [32], they might cause reduction of energy application [33]. In our study, SBRT appears to be an effective priority to RFA with a significantly higher OS rate, probably because for patients undergoing hepatectomy for primary HCC, the tissues around the liver may be adherent after hepatectomy. Adhesion formation is a common complication after hepatectomy and may lead to abnormal connections of the stomach and intestinal tubes to the liver, causing the surgeon to be overly conservative in deciding the extent of ablation. When patients underwent RFA, the adherent tissues may interfere with the ultrasound images, resulting in inaccurate judgment of the tumor location and boundaries by the surgeon [34]. The anatomy of the liver can change significantly after hepatectomy for primary HCC, affecting the ultrasound-guided needle angle operated by the surgeon, which may affect ablation efficacy.

With advances in radiotherapy techniques, SBRT was more and more commonly and safely performed in clinical practice [35]. It is a highly precise technique of percutaneous radiation therapy delivered in a small number of

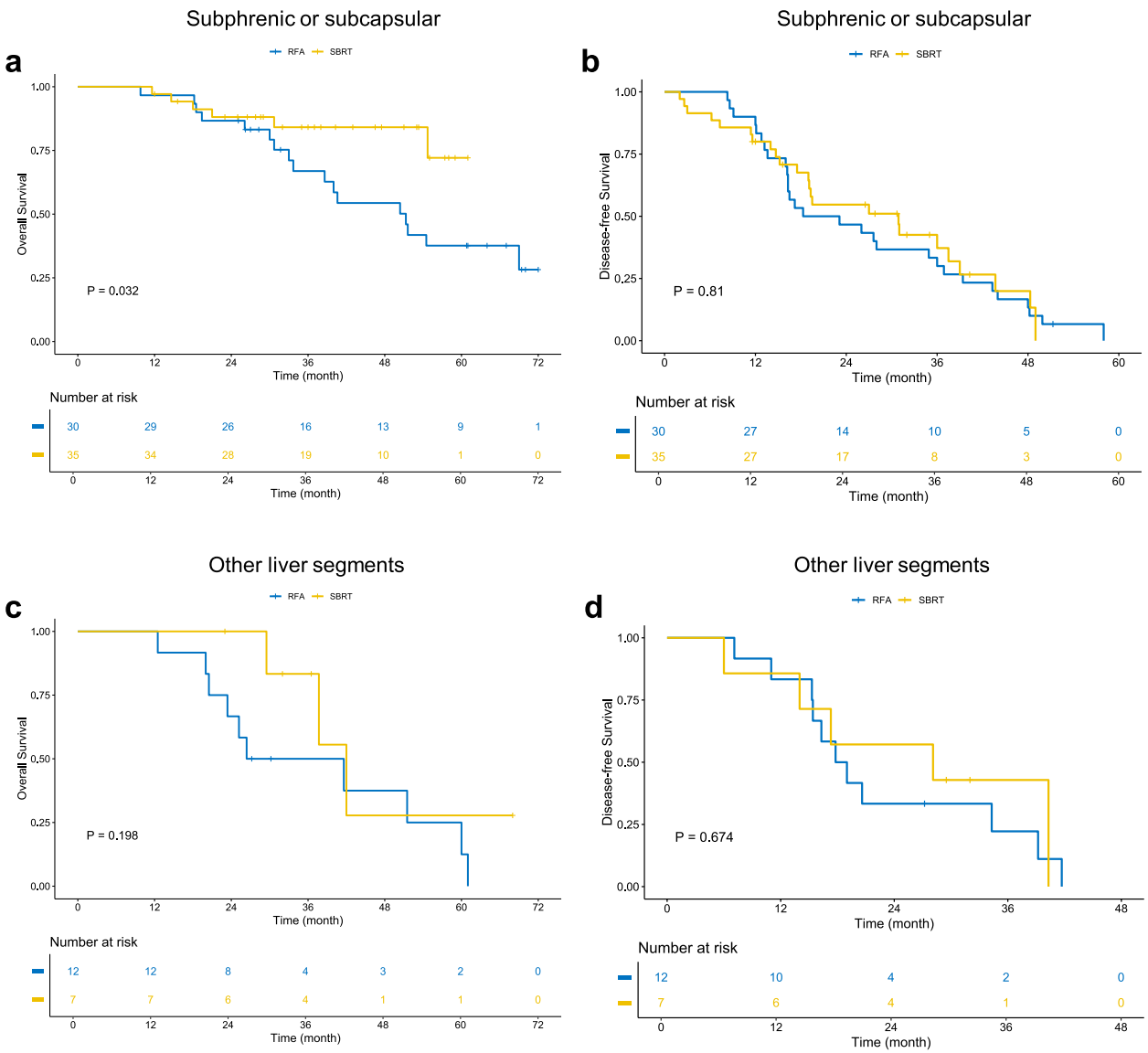

Fig. 3 Subgroup analysis OS and DFS based on tumor location. Notes: **a**, **b** Subgroup division according to subphrenic or subcapsular, and Kaplan–Meier analyses were performed for OS (**a**) and DFS (**b**) associated with RFA or SBRT. **c**, **d** Subgroup division according to other liver segments, and Kaplan–Meier analyses were performed for OS (**c**) and DFS (**c**) associated with RFA or SBRT. Abbreviations: RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy; OS, overall survival; DFS, disease-free survival

large fraction. The enhanced biological effecrtiveness of the large single doses maintains adequate tumor control, while sufficiently spares adjacent organs at risk due to its sharp dose fall-off outside the target. Increasing evidence have showed that SBRT can lead to improved tumor control and survival compared with conventional radiotherapy techniques [36], and that dose-escalated SBRT can further improve outcomes [37]. Therefore, based on our clinical experience, we performed three subgroup analyses to compare the prognosis and efficacy of RFA and SBRT in terms of tumor location, size and proximity to major vessels. Under CT guidance, the positioning function of SBRT is less affected by postoperative adhesions and more accurate than ultrasonography (US). Meanwhile, SBRT has a less damaging effect on the surrounding tissues [38, 39], which makes the doctor more active in formulating the tumor localization plan to achieve a better radiotherapy effect.

Subgroup analysis showed that the SBRT group provided better survival outcomes than the RFA group, for tumors located in the subphrenic area, tumors size > 2.5 cm, and tumor proximity to major

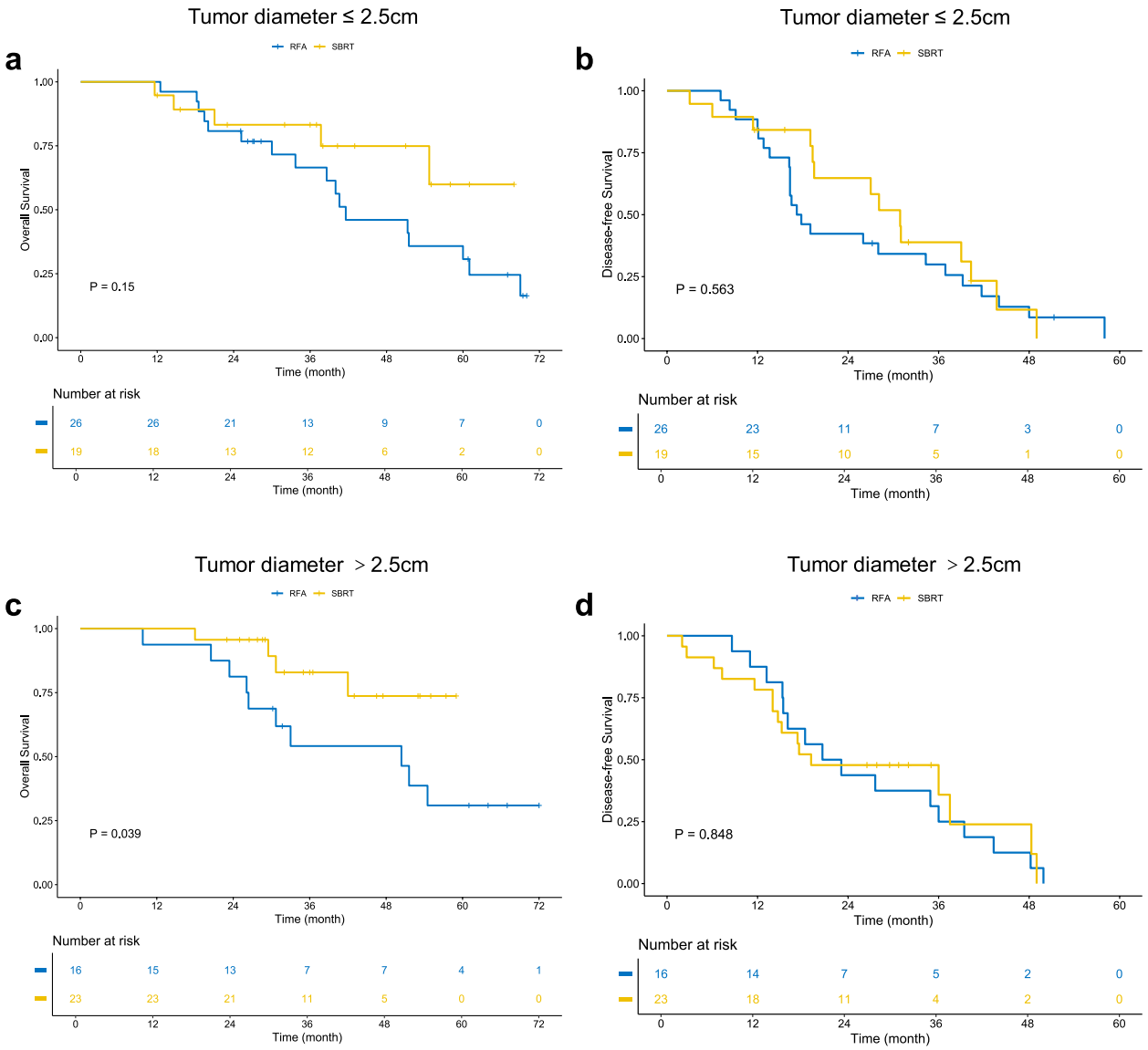

Fig. 4 Subgroup analysis OS and DFS based on tumor size. Notes: **a**, **b** Subgroup division according to tumor diameter ≤ 2.5 cm, and Kaplan–Meier analyses were performed for OS (**a**) and DFS (**b**) associated with RFA or SBRT. **c**, **d** Subgroup division according to tumor diameter > 2.5 cm, and Kaplan–Meier analyses were performed for OS (**c**) and DFS (**d**) associated with RFA or SBRT. Abbreviations: RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy; OS, overall survival; DFS, disease-free survival

vasculature ≤ 1 cm after PSM. Our study demonstrated that SBRT was efficacious for patients unfit for RFA due to the three factors mentioned above [40]. Besides, when tumors located in other liver segments, tumor size < 2.5 cm, and tumor proximity to major vasculature > 1 cm, the treatment of RHCC patients between RFA and SBRT showed comparable prognosis and efficacy. The median DFS and OS in this study appear to be somewhat worse than anticipated, we believe that, patients with unsatisfactory outcomes after RFA or SBRT treatment chose different subsequent treatment modalities, including hepatectomy, immunotherapy, TACE, etc. Different modalities of follow-up treatment after RFA or SBRT may have contributed to the difference in survival between the two groups.

Two modalities exhibited comparable feasibility in terms of toxicities. In recent years, physicians have gradually developed a mastery of technical expertise in both minimally invasive medical treatments and gained extensive clinical experience. In our study, both RFA and SBRT resulted in few complications which correspond to the findings of the previous study [41, 42]. A retrospective

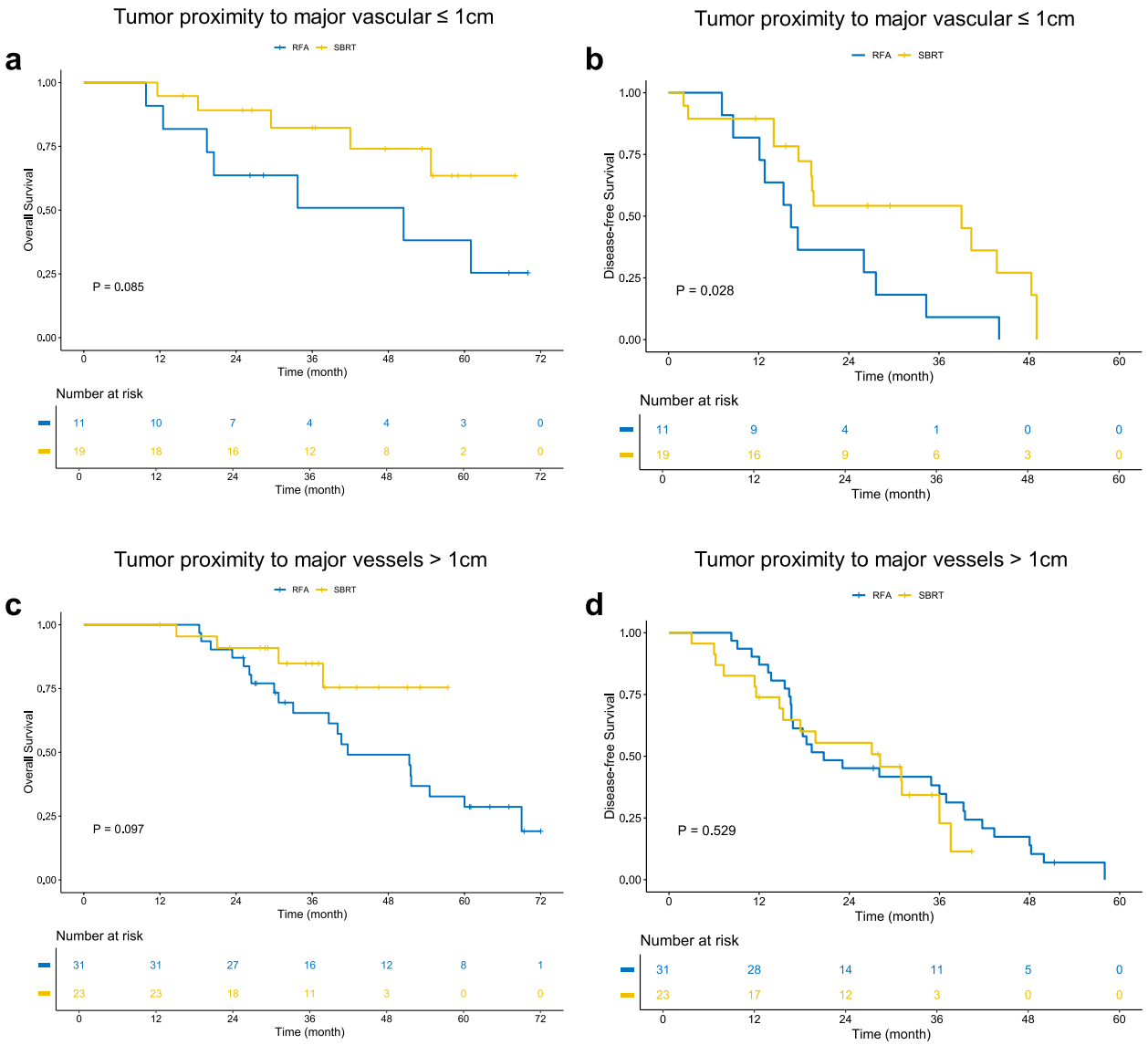

Fig. 5 Subgroup analysis OS and DFS based on tumor proximity to major vessels. Notes: **a**, **b** Subgroup division according to tumor proximity to major vascular ≤ 1 cm, and Kaplan–Meier analyses were performed for OS (**a**) and DFS (**b**) associated with RFA or SBRT. **c**, **d** Subgroup division according to tumor proximity to major vascular > 1 cm, and Kaplan–Meier analyses were performed for OS (**c**) and DFS (**d**) associated with RFA or SBRT. Abbreviations: RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy; OS, overall survival; DFS, disease-free survival

study indicated that both treatment modalities showed comparable survival rates with tolerable but distinct toxicities. SBRT, as a noninvasive approach, may be utilized to mitigate the adverse effects associated with RFA, such as hemorrhage, pneumothorax, and biliary fistula.

Several limitations should be acknowledged in this study. First of all, this is a nonrandomized retrospective study with its inherent selection bias and potential confounders. Even if a 1:1 propensity score matching was performed to minimize baseline differences between the RFA and SBRT groups, some other unbalanced variables might still exist. In our study, we set a caliber of 0.05 for PSM analysis, which reduces the success rate of the matching, so the sample size is reduced, making the study less statistically efficacious. Second, although the patients included in our study came from three high-volume medical centers, the sample size of the whole cohort was relatively small, which increases the risk of a beta error. Therefore, the results of our study still need to be further confirmed by high-quality, large sample randomized controlled trials with long-term follow-up.

Conclusion

The SBRT group had significantly better overall survival than the RFA group for RHCC. SBRT appears to be an effective alternative treatment modality especially when RFA is not feasible due to tumor location, size, or proximity to major vessels. Further prospective research needs to be designed and conducted.

Abbreviations

RHCC	Recurrent hepatocellular carcinoma
RFA	Radiofrequency ablation
SBRT	Stereotactic body radiotherapy
PSM	Propensity score matching
OS	Overall survival
DFS	Disease-free survival
HR	Hazard ratio
CI	Confidence interval
BMI	Body mass index
HBV	Hepatitis B virus
ALT	Alanine aminotransferase
TBIL	Total bilirubin
ALB	Albumin
PT	Prothrombin time
AFP	Alpha-fetoprotein.
CT	Computed tomography
US	Ultrasonography

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Authors' contributions

Conception and design: YM, SQC, WXG, ZHM, XLL; Administrative support: YM, SQC, WXG; Provision of study materials and patients: ZHM, XLL, FHL, JLZ, MLY, XCS, LG, JX, CDL, JS; Collection and assembly of data: ZHM, XLL; Data analysis and interpretation: ZHM, XLL, WXG; Manuscript writing: ZHM, WXG; Final approval of manuscript: All authors.

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Data availability

The data that support the findings of our study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol was performed in accordance with the ethical guidelines of the World Medical Association Declaration of Helsinki and approved by the Clinical Research Ethics Committee of the Eastern Hepatobiliary Surgery Hospital (Approval number: EHBHKY2022-H063-P001). Written informed consent was obtained before commencing RFA or SBRT for patients with RHCC.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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