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Radiofrequency Ablation Therapy versus Stereotactic Body Radiation Therapy for Naive Hepatocellular Carcinoma (≤5cm): A Retrospective Multi-Center Study

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Purpose: Radiofrequency ablation (RFA) is a micro-invasive treatment for early-stage HCC patients. Stereotactic body radiation therapy (SBRT) has also been proven an effective and safe treatment for HCC patients. This multi-center study is to compare the efficacy of computed tomography (CT)-guided RFA and CT-based SBRT in naïve HCC patients with tumor diameters ≤5 cm.

Patients and Methods: This retrospective cohort study included 1001 treatment-naïve HCC patients from three hospitals or medical centers. The patients received RFA (n = 481) or SBRT (n = 520) treatment between December 2011 and May 2019. Furthermore, subgroup analyses of all patients were conducted based on Couinaud's classification of liver segments.

Results: After matching, the local control (LC) rates of the SBRT group were better than those of the RFA group (p=0.024*), which mainly referred to the patients whose tumors were located in the S7/S8 (p=0.006*). Among patients with tumors located in S1, nineteen patients (19/21) underwent SBRT. The 1-, 3- and 5-year LC rates were 100%, 87.8% and 87.8% in the SBRT group, and the 1-, 3- and 5-year OS rates were 100%, 69.8% and 69.8%, respectively. Moreover, the OS rates in S5/S6 group in RFA were higher than those in SBRT group.

Conclusion: The LC rates were better in the SBRT group than in the RFA group for the patients with lesions localized in S7/S8, and SBRT could also be a therapeutic option for patients with lesions in S1. Moreover, patients with tumors located in S5/S6 were better candidates for RFA treatment than SBRT.

Keywords: Stereotactic body radiation therapy, Computed tomography-guided radiofrequency, Naive hepatocellular carcinoma, Couinaud's segmentation

Introduction

According to the Global Cancer Statistics 2020, primary liver cancer is the sixth most common cancer and the third leading cause of cancer-related death worldwide.[1] Radiofrequency ablation therapy is a minimally invasive and time-saving treatment that can be applied to cure recurrent lesions or new intrahepatic lesions in a short period of time. Previous studies have shown that stereotactic body radiation therapy (SBRT) is an effective and safe treatment for HCC patients who refuse or are unsuitable for other treatments.[2,3] Since radiotherapy is usually based on CT images, comparing CT-guided RFA with SBRT would yield more objective and accurate results. However, after reviewing the

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available publications, we found few studies comparing the effects of computed tomography (CT)-guided radiofrequency ablation (RFA) and SBRT for HCC patients, especially the effects in naive cases.

In addition, Couinaud's segmentation is based on the identification of the three hepatic veins and the plane passing by the portal vein bifurcation; this is the most widely used classification since it is better suited for surgery and more accurate for localizing and monitoring intraparenchymal lesions.[4] Accordingly, in a previous study,[5] when a tumor was located across two or more Couinaud's segments, the location of the tumor center was defined as the representative location. Our team found that this segmentation method could also roughly reflect the anatomical relationship between the tumor and surrounding organs. Among the eight segments, S1 includes the liver caudate lobe, S2/S3 includes the lateral segment of the left liver and is closer to the stomach, S4 includes the medial segment of left lobe of the liver, S7/S8 includes the right upper lobe and is closer to the lung and large bile duct, and S5/S6 includes the right lower lobe and is closer to the duodenum and colon. This segmentation approach suggests to the organs at risk (OARs) that need to be considered when performing RFA and SBRT, so it was also applied to RFA and SBRT in this study.

To sum up, we conducted this study to compare the efficacy of CT-guided RFA and CT-based SBRT in treatment-naïve HCC patients and to further explore the efficacy of both treatments in different Couinaud's segmentations.

Material and Methods

This study included a total of one thousand and one consecutive patients from December 2011 to May 2019 in three hospitals. Among them, 481 patients were in the RFA group, and 520 cases were in the SBRT group. The patients met the following criteria: (1) diagnosed with HCC by radiologists according to imaging examinations, laboratory tests or pathology, in which diagnosis criteria followed Practice Guidance by the American Association for the Study of Liver Diseases;[6] (2) had a single tumor with a lesion diameter ≤5 cm; (3) scored as Child-Pugh A or B7-8; (4) did not receive any prior therapy; (5) did not have portal vein tumor thrombus or distant metastasis; (6) treated with oral adefovir, entecavir or tenofovir, if infected with HBV; treated with peginterferon plus ribavirin or sofosbuvir and velpatasvir, infected with HCV; (7) had platelet counts $\geq 50\times10^9$/L at enrollment or after platelet raising therapy before RFA or SBRT; and (8) (of the patients who received SBRT) had a residual liver volume of equal to or greater than 700 cc. All patients provided written informed consent for the therapeutic procedures.

The Treatment Procedure in the SBRT Group

We applied CyberKnife (Accuray, USA) to realize stereotactic body radiation therapy (SBRT). Three to four fiducial markers were implanted in normal liver tissue located in close proximity to the lesion. After the location of treatment was determined using CT simulation, a radiation oncologist contoured the gross tumor volume (GTV) and outlined the organs at risk (OARs, including the stomach, normal liver, esophagus, duodenum, kidneys, spinal cord and bowel). The GTV was expanded by 3–5 mm to define the planning target volume (PTV). The prescribed doses were 48–55 Gy/5-8 fx, and the isodose curve encompassed 95~100% of the GTV. The radiation therapy plans were calculated using the CyberKnife Multiplan system (version 4.0.2 and version 4.1.0).

The Treatment Procedure in the RFA Group

RFA procedures (RITA, USA; Olympus corporation, JAPAN; Blade, China) were performed percutaneously under CT guidance. For RFA, the interventional radiologists used bipolar radiofrequency ablation probes with active tips of 30–40 mm measuring 1.8 mm in diameter, a 1–250 W output power, a 470 kHz frequency, and three bipolar channels. A CT scan was used for localization during RFA treatment, CT scanning was performed after probe insertion to ensure accurate positioning, and RFA was performed. The ablation mode for multiple overlapping regions was performed using the technique of Chen et al[7] if the largest tumor diameter was greater than 3 cm. During RFA treatment, interventional radiologists considered that the ablation was completed when previous tumor lesions were well covered by treated regions.

Follow-Up and Subsequent Therapies

Toxicity reactions were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.[8] All patients were followed up every three months until May 2024 or death, whichever occurred first. The follow-up items included physical examination, imaging (lung CT, abdominal contrast-enhanced CT/MRI and other required imaging on a per-patient basis), and laboratory tests (liver function, routine blood test, coagulation function, serum alpha fetoprotein, etc). Tumor response was evaluated by senior radiologists based on changes in tumor size, arterial stage intensification, etc. in contrast-enhanced images. When the tumors recurred or progressed, the patient then chose to receive repeat SBRT, repeat RFA, hepatic resection, targeted therapy or immunotherapy depending on their condition.

Statistical Analysis

Overall survival period was defined as from the date of beginning RFA/SBRT to the date of final follow-up visit or death. Progression-free survival period was from the date of beginning RFA/SBRT to the date of tumor progression or death. Local control period was starting from the date of RFA/SBRT to the date of treated lesion progression or patient death. Distant metastasis-free period was assessed from the date of beginning RFA/SBRT to the date of untreated lesion progression or patient death. Propensity score-matching analysis was applied to minimize the effect of selection biases and potential confounders. The propensity score was calculated using a multivariable logistic regression model including patient characteristics. After PS estimation, the tumors were matched using the "matchit" function in the R package Matchit, with the parameter "method" set to "cardinality". Survival rates were calculated using the Kaplan–Meier method. The comparison between SBRT- and RFA-treated groups was performed using the Log rank test. Univariate and multivariable hazard ratios were evaluated using the Cox proportional hazard model. The $\chi 2$ test or Fisher's exact test was used to compare baseline variables between the two groups. A P value < 0.05 was considered to indicate statistical significance. All statistical analyses were performed with SPSS ver. 24.0 (IBM Corp., NY, Armonk, USA) and with RStudio using R Version 4.1.2 (RStudio, Boston, MA, USA).

Results

The characteristics of the 1001 patients are shown in Table 1. Before matching, tumor diameters and AFP values in SBRT group were larger and higher than in the RFA group. In contrast, the platelet count in the SBRT group was higher than that in the RFA group. The median overall survival periods were 41 months and 43 months in SBRT group and RFA group, respectively. In addition, the median progression-free survival periods were 29 months and 30 months in SBRT and RFA group, respectively. The results showed the OS rates in SBRT group were worse than those of the RFA group

Table 1 The Characteristics of Patients Before and After Matching in This Study

	Before Matching			After Matching		
	SBRT (N=520)	**RFA (N=481)**	**p value**	**SBRT (N=374)**	**RFA (N=374)**	**p value**
Sex						
Female	118 (22.7%)	126 (26.2%)	0.197	81 (21.7%)	97 (25.9%)	0.170
Male	402 (77.3%)	355 (73.8%)		293 (78.3%)	277 (74.1%)	
Age (years)						
Mean (SD)	55.4 (9.87)	54.4 (9.55)	0.108	54.8 (9.77)	54.1 (9.60)	0.360
Median [Min, Max]	55.0 [26.0, 88.0]	54.0 [22.0, 87.0]		54.0 [26.0, 88.0]	54.0 [22.0, 82.0]	
Tumor Diameter (cm)						
Mean (SD)	2.46 (1.06)	1.73 (0.744)	<0.001	1.94 (0.654)	1.90 (0.734)	0.110
Median [Min, Max]	2.30 [0.500, 5.00]	1.60 [0.400, 4.70]		1.90 [0.500, 3.80]	1.70 [0.500, 4.70]	
Location Group						
S1 (Caudate lobe)	19 (3.7%)	2 (0.4%)	<0.001	7 (1.9%)	2 (0.5%)	0.310
S2/S3	81 (15.6%)	60 (12.5%)		51 (13.6%)	55 (14.7%)	
S4	73 (14.0%)	40 (8.3%)		48 (12.8%)	37 (9.9%)	

(*Continued*)

Table 1 (Continued).

	Before Matching			After Matching		
	SBRT (N=520)	**RFA (N=481)**	**p value**	**SBRT (N=374)**	**RFA (N=374)**	**p value**
S5/S6	180 (34.6%)	175 (36.4%)		131 (35.0%)	142 (38.0%)	
S7/S8	167 (32.1%)	204 (42.4%)		137 (36.6%)	138 (36.9%)	
Background of hepatitis						
None			15 (2.9%)	11 (2.3%)	7 (1.9%)	8 (2.1%)
PBC			3 (0.6%)	5 (1.0%)	1 (0.3%)	4 (1.1%)
HBV	460 (88.5%)	399 (83.0%)	0.037	338 (90.4%)	319 (85.3%)	0.160
HCV	34 (6.5%)	58 (12.1%)		24 (6.4%)	40 (10.7%)	
ALD	8 (1.5%)	8 (1.7%)		4 (1.1%)	3 (0.8%)	
Platelet count (10^9/L)						
Mean (SD)	123 (59.9)	109 (62.9)	<0.001	119 (58.8)	118 (61.2)	0.550
Median [Min, Max]	117 [24.0, 331]	90.0 [14.0, 391]		114 [24.0, 331]	110 [16.0, 330]	
ALBI grade						
1	155 (29.8%)	100 (20.8%)	<0.001	104 (27.8%)	99 (26.5%)	0.630
2	349 (67.1%)	324 (67.4%)		257 (68.7%)	257 (68.7%)	
3	16 (3.1%)	57 (11.9%)		13 (3.5%)	18 (4.8%)	
AFP value (ng/mL)						
Mean (SD)	317 (1310)	117 (327)	<0.001	158 (420)	142 (365)	0.290
Median [Min, Max]	14.7 [0.823, 20,000]	8.62 [0.610, 3810]		11.4 [0.850, 5470]	9.98 [0.610, 3810]	
Child–Pugh score						
5	432 (83.1%)	332 (69.0%)	<0.001	305 (81.6%)	298 (79.7%)	0.770
6	61 (11.7%)	74 (15.4%)		47 (12.6%)	48 (12.8%)	
7	20 (3.8%)	54 (11.2%)		18 (4.8%)	21 (5.6%)	
8	7 (1.3%)	21 (4.4%)		4 (1.1%)	7 (1.9%)	
ECOG PS score						
0	387 (74.4%)	374 (77.8%)	0.098	286 (76.5%)	290 (77.5%)	0.710
1	109 (21.0%)	78 (16.2%)		73 (19.5%)	65 (17.4%)	
2	24 (4.6%)	27 (5.6%)		15 (4.0%)	18 (4.8%)	
3	0 (0%)	2 (0.4%)		0 (0%)	1 (0.3%)	

(Figure 1A, p = 0.021*). There was no difference in PFS rates and DMFS rates between two groups (PFS rates: Figure 1B, p = 0.111; DMFS rates: Figure 1D, p = 0.189). The LC rates in SBRT group were better than those of the RFA group (Figure 1C, p = 0.033*). After matching, three hundred seventy-four patients were selected from each group. The

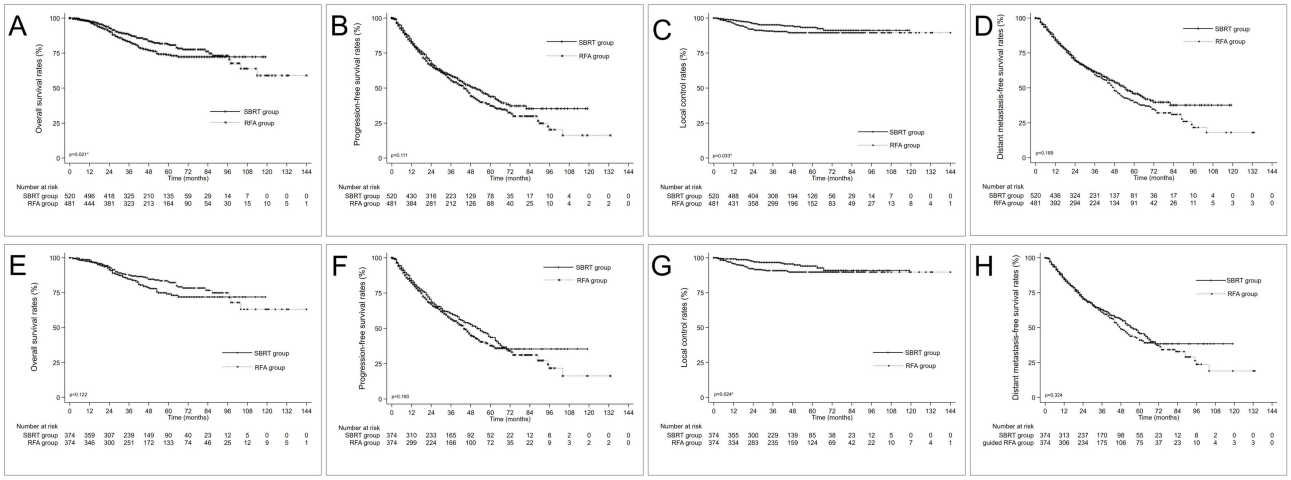

Figure 1 The overall survival curves between the SBRT and RFA groups before and after matching. (**A**–**D**) survival curves rates before matching; (**E-H**) survival curves rates after matching.

LC rates of the SBRT group were better than those of the RFA group (Figure 1G, p = 0.024*), and there was no difference in OS rates, PFS rates and DMFS rates between the two groups (OS rate: Figure 1E, p = 0.122; PFS rate: Figure 1F, p = 0.160; DMFS: Figure 1H, p = 0.324). The metastases and subsequent therapies in different Couinaud's segmentation were showed in Table 2

Based on Couinaud's segmentation method, we divided the eight segmentations into five groups. Among the patients with tumors located in S1, nineteen (19/21) underwent SBRT. The 1-, 3- and 5-year LC rates were 100%, 87.8% and 87.8% in the SBRT group, and the 1-, 3- and 5-year OS rates were 100%, 69.8% and 69.8%, respectively. The 1-, 3- and 5-year PFS rates were 77.8%, 55.6% and 47.6%, and the DMFS rates were 83.3%, 61.1% and 52.4%, respectively. The data of matching results in the other groups were shown in Table 3. As is shown in Figure 2, after matching, we found that patients with tumors located in S7/S8 had better LC rates when treated by SBRT rather than RFA (Figure 2D–7D), and there was no difference in LC rates between treatment groups among patients with lesions located in other subgroups. We also found that patients with tumors located in S5/S6 had better OS rates in RFA group than those of the SBRT group (Figure 2C–5). The survival rates results were shown in Supplementary Table 1.

Toxicity and Complications

Three hundred sixty-one (75.0%) patients in the RFA group experienced abdominal pain after the procedure and recovered within 3 days. Perihepatic hemorrhage occurred in forty-seven patients (9.8%), and most of these hemorrhages were absorbed within 1 week. Pneumothorax and hydrothorax occurred in forty-two patients (8.7%) and were absorbed within 1 week. Transient liver dysfunction, which mainly manifested as a decrease in albumin and elevation of transaminase, occurred in one hundred ninety-seven patients (40.9%). Among them, one hundred and nineteen cases (24.7%) experienced liver toxicities of Grade ≥3, mainly manifested as more than fivefold increase in alanine aminotransferase. Of these patients with abnormal liver function, one hundred fifty-six patients (32.4%) recovered within 2 weeks, and forty-one patients (8.5%) recovered within 4 weeks.

All patients in the SBRT group completed the radiation therapy plan. Grade 1–2 acute toxicity reactions, including fatigue, vomiting, anorexia and abdominal pain, occurred in one hundred and sixty-three patients (31.3%). Forty-one (7.9%) were diagnosed with radiation-induced liver disease (RILD).

Discussion

Locoregional therapy plays a leading role in the management of 50% to 60% of HCC patients and is considered a potentially curative therapy for small HCC, along with surgical resection and liver transplantation.[9,10] As we knew, RFA is suitable for HCC patients with cirrhosis because it can protect the normal liver, preserve liver volume, and maintain liver function. Previous studies and our studies have shown that SBRT is also an effective treatment for early-stage HCC patients.[2,11] The results of a single-center study we previously published showed that there was no statistical difference in matching survival outcomes between SBRT and HR in patients with early-stage HCC.[12] Both RFA and HR are first-line treatment options for early-stage liver cancer. Based on the comparison with HR, we conducted this comparative study of SBRT and RFA and found that both were effective treatments. Different from previous studies, this study is a multi-center research, and the number of patients included is larger due to the prolonged time span. Meanwhile, Couinaud's anatomical division is the most widely applied classification for functional liver anatomy in liver surgery, which is found to also affect therapeutic effects of SBRT and RFA.

Several research groups have conducted studies comparing SBRT and RFA. Rajyaguru DJ et al[13] conducted an observational study and suggested that treatment with RFA yields superior survival to SBRT for nonsurgically managed patients with stage I or II HCC. However, they only compared the OS rates of the two groups, without comparisons of LC, due to the scarcity of some data in their database. We considered that RFA and SBRT are both local therapies, so the LC rates are not negligible, and the choice of treatment after tumor recurrence is also an important factor affecting OS rates, so we compared LC rates in our observation. Our results showed that the LC rates of patients in the SBRT group were higher than the corresponding rates in the RFA group. Moreover, there was no significant difference in OS rates between the two groups.

Table 2 The Metastases and Subsequent Therapies in Two Group

	S1		S2 and S3		S4		S5 and S6		S7 and S8	
	SBRT (19)	RFA (2)	SBRT (81)	RFA (60)	SBRT (73)	RFA (40)	SBRT (180)	RFA (175)	SBRT (167)	RFA (204)
Number of patients with metastases	9 (47.4%)	2 (100.0%)	44 (54.3%)	39 (65.0%)	34 (46.6%)	14 (35.0%)	84 (46.7%)	110 (62.9%)	73 (43.7%)	98(48.0%)
Metastasis locations										
Intrahepatic metastasis alone	7 (36.8%)	1 (50.0%)	38 (47.0%)	36 (92.3%)	31 (42.5%)	13 (32.5%)	76 (42.2%)	98 (56.0%)	61 (36.5%)	85 (41.7%)
Extrahepatic and/or multiple organ metastasis	2 (10.6%)	1 (50.0%)	6 (7.3%)	3 (7.7%)	3 (4.1%)	1 (2.5%)	8 (4.4%)	12 (6.9%)	12 (7.2%)	13 (6.4%)
Subsequent therapies										
Single treatment	5 (55.5%)	1 (50.0%)	29 (65.9%)	17 (43.6%)	20 (58.9%)	9 (64.3%)	49 (58.3%)	68 (61.9%)	45 (61.6%)	53 (54.1%)
Hepatic resection	0 (0.0%)	0 (0.0%)	1 (2.3%)	0 (0.0%)	2 (5.9%)	0 (0.0%)	3 (3.57%)	0 (0.0%)	1 (1.4%)	0 (0.0%)
Trans-arterial chemoembolization	1 (11.1%)	0 (0.0%)	4 (9.1%)	4 (10.3%)	4 (11.8%)	3 (21.4%)	13 (15.5%)	13 (11.8%)	6 (8.2%)	9 (9.2%)
Radio-frequency ablation	1 (11.1%)	1 (50.0%)	4 (9.1%)	11 (28.2%)	2 (5.9%)	6 (42.9%)	6 (7.1%)	47 (42.7%)	5 (6.8%)	35 (35.7%)
CyberKnife SBRT	2 (22.2%)	0 (0.0%)	20 (45.5%)	1 (2.6%)	12 (35.3%)	0 (0.0%)	27 (32.1%)	6 (5.5%)	32 (43.8%)	8 (8.2%)
Target therapy/immune therapy	1 (11.1%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	1 (1.4%)	0 (0.0%)
Liver transplantation	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
Multiple treatments	2 (22.2%)	0 (0.0%)	5 (11.4%)	11 (28.2%)	4 (11.8%)	3 (21.4%)	10 (11.9%)	21 (19.1%)	11 (15.1%)	23 (23.4%)
Conservative treatment	2 (22.2%)	1 (50.0%)	10 (22.7%)	11 (28.2%)	10 (29.4%)	2 (14.3%)	25 (29.8%)	21 (19.1%)	17 (23.3%)	22 (22.4%)

Table 3 The Characteristics of Patients in Segmentation Before and After Matching in this study

	S2 and S3						S4						S5 and S6						S7 and S8					
	Before Matching			After Matching			Before Matching			After Matching			Before Matching			After Matching			Before Matching			After Matching		
	CK-SBRT	RFA	p-value	CK-SBRT	RFA	p-value	CK-SBRT	RFA	p-value	CK-SBRT	RFA	p-value	CK-SBRT	RFA	p-value	CK-SBRT	RFA	p-value	CK-SBRT	RFA	p-value	CK-SBRT	RFA	p-value
	(N=81)	(N=60)		(N=52)	(N=52)		(N=73)	(N=40)		(N=39)	(N=39)		(N=180)	(N=175)		(N=127)	(N=127)		(N=167)	(N=204)		(N=138)	(N=138)	
Gender																								
Female	17 (21.0%)	18 (30.0%)	0.221	10 (19.2%)	14 (26.9%)	0.352	14 (19.2%)	10 (25.0%)	0.469	8 (20.5%)	10 (25.6%)	0.591	44 (24.4%)	43 (24.6%)	0.978	30 (23.6%)	31 (24.4%)	0.883	37 (22.2%)	55 (27.0%)	0.286	26 (18.8%)	35 (25.4%)	0.192
Male	64 (79.0%)	42 (70.0%)		42 (80.8%)	38 (73.1%)		59 (80.8%)	30 (75.0%)		31 (79.5%)	29 (74.4%)		136 (75.6%)	132 (75.4%)		97 (76.4%)	96 (75.6%)		130 (77.8%)	149 (73.0%)		112 (81.2%)	103 (74.6%)	
Age (years)																								
Mean (SD)	55.4 (10.8)	54.5 (10.4)	0.646	54.6 (10.8)	55.0 (10.9)	0.878	56.5 (10.5)	55.0 (9.32)	0.447	57.1 (9.48)	54.9 (9.40)	0.294	54.9 (9.86)	54.4 (9.09)	0.588	54.4 (10.1)	54.3 (9.35)	0.949	55.1 (9.20)	54.2 (9.81)	0.401	54.6 (9.03)	54.1 (10.1)	0.692
Median [Min, Max]	55.0 [30.0, 88.0]	55.5 [24.0, 73.0]		53.5 [30.0, 88.0]	56.0 [24.0, 73.0]		55.0 [28.0, 82.0]	54.5 [36.0, 76.0]		55.0 [39.0, 77.0]	54.0 [36.0, 76.0]		55.0 [26.0, 86.0]	54.0 [31.0, 87.0]		55.0 [26.0, 86.0]	54.0 [34.0, 87.0]		54.0 [32.0, 81.0]	54.0 [22.0, 82.0]		54.0 [32.0, 81.0]	54.0 [22.0, 82.0]	
Tumor Diameter (cm)																								
Mean (SD)	2.46 (1.05)	1.76 (0.652)	<0.001	1.87 (0.564)	1.84 (0.648)	0.482	2.49 (1.09)	1.90 (0.972)	0.004	1.95 (0.841)	1.93 (0.974)	0.693	2.54 (1.08)	1.72 (0.698)	<0.001	1.99 (0.684)	1.96 (0.660)	0.61	2.32 (1.02)	1.71 (0.760)	<0.001	1.98 (0.722)	1.95 (0.762)	0.484
Median [Min, Max]	2.20 [0.600, 5.00]	1.60 [0.500, 3.40]		1.85 [0.600, 3.20]	1.65 [0.600, 3.40]		2.20 [0.900, 4.90]	1.60 [0.600, 4.70]		1.80 [0.900, 4.50]	1.60 [0.600, 4.70]		2.50 [0.700, 5.00]	1.60 [0.500, 3.60]		2.00 [0.700, 3.30]	1.80 [0.800, 3.60]		2.00 [0.500, 5.00]	1.60 [0.400, 4.70]		1.90 [0.500, 3.80]	1.80 [0.900, 4.70]	
Type of background disease																								
None	1 (1.2%)	2 (3.3%)	0.477	1 (1.9%)	2 (3.8%)	0.546	1 (1.4%)	0 (0%)	0.408	0 (0%)	0 (0%)	0.78	1 (0.6%)	4 (2.3%)	0.084	1 (0.8%)	4 (3.1%)	0.097	9 (5.4%)	5 (2.5%)	0.02	4 (2.9%)	4 (2.9%)	0.685
PBC	0 (0%)	1 (1.7%)		0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	1 (0.6%)		0 (0%)	1 (0.8%)		1 (0.6%)	3 (1.5%)		1 (0.7%)	2 (1.4%)	
HBV	74 (91.4%)	51 (85.0%)		47 (90.4%)	44 (84.6%)		61 (83.6%)	30 (75.0%)		31 (79.5%)	30 (76.9%)		168 (93.3%)	148 (84.6%)		119 (93.7%)	109 (85.8%)		149 (89.2%)	168 (82.4%)		126 (91.3%)	121 (87.7%)	
HCV	5 (6.2%)	6 (10.0%)		3 (5.8%)	6 (11.5%)		10 (13.7%)	10 (25.0%)		7 (17.9%)	9 (23.1%)		9 (5.0%)	18 (10.3%)		7 (5.5%)	9 (7.1%)		8 (4.8%)	24 (11.8%)		7 (5.1%)	11 (8.0%)	
ALD	1 (1.2%)	0 (0%)		1 (1.9%)	0 (0%)		1 (1.4%)	0 (0%)		1 (2.6%)	0 (0%)		2 (1.1%)	4 (2.3%)		0 (0%)	4 (3.1%)		0 (0%)	4 (2.0%)		0 (0%)	0 (0%)	
Platelet count (10^9/L)																								
Mean (SD)	114 (49.6)	115 (68.8)	0.649	105 (49.1)	118 (61.7)	0.307	121 (53.6)	121 (54.1)	0.99	116 (51.5)	120 (54.5)	0.726	128 (65.0)	109 (60.4)	0.003	126 (63.9)	117 (60.1)	0.273	123 (61.9)	106 (64.8)	0.002	122 (61.1)	114 (62.4)	0.29
Median [Min, Max]	111 [36.0, 242]	109 [16.0, 343]		94.5 [36.0, 233]	117 [16.0, 276]		116 [29.0, 269]	124 [22.0, 286]		106 [29.0, 207]	124 [22.0, 286]		119 [30.0, 331]	90.0 [28.0, 327]		119 [30.0, 331]	105 [30.0, 327]		118 [24.0, 294]	86.5 [14.0, 391]		118 [24.0, 294]	98.5 [14.0, 330]	

(*Continued*)

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Table 3 (Continued).

	S2 and S3						S4						S5 and S6						S7 and S8					
	Before Matching			After Matching			Before Matching			After Matching			Before Matching			After Matching			Before Matching			After Matching		
	CK-SBRT	RFA	p-value	CK-SBRT	RFA	p-value	CK-SBRT	RFA	p-value	CK-SBRT	RFA	p-value	CK-SBRT	RFA	p-value	CK-SBRT	RFA	p-value	CK-SBRT	RFA	p-value	CK-SBRT	RFA	p-value
	(N=81)	(N=60)		(N=52)	(N=52)		(N=73)	(N=40)		(N=39)	(N=39)		(N=180)	(N=175)		(N=127)	(N=127)		(N=167)	(N=204)		(N=138)	(N=138)	
ALBI Grade																								
1	22 (27.2%)	11 (18.3%)	0.073	11 (21.2%)	11 (21.2%)	0.841	28 (38.4%)	6 (15.0%)	0.035	6 (15.4%)	6 (15.4%)	1	53 (29.4%)	37 (21.1%)	0.006	34 (26.8%)	35 (27.6%)	0.415	48 (28.7%)	45 (22.1%)	<0.001	38 (27.5%)	41 (29.7%)	0.344
2	58 (71.6%)	44 (73.3%)		40 (76.9%)	39 (75.0%)		41 (56.2%)	31 (77.5%)		30 (76.9%)	30 (76.9%)		122 (67.8%)	120 (68.6%)		90 (70.9%)	85 (66.9%)		113 (67.7%)	128 (62.7%)		95 (68.8%)	87 (63.0%)	
3	1 (1.2%)	5 (8.3%)		1 (1.9%)	2 (3.8%)		4 (5.5%)	3 (7.5%)		3 (7.7%)	3 (7.7%)		5 (2.8%)	18 (10.3%)		3 (2.4%)	7 (5.5%)		6 (3.6%)	31 (15.2%)		5 (3.6%)	10 (7.2%)	
Alpha fetoprotein (ng/mL)																								
Mean (SD)	261 (620)	120 (252)	0.199	102 (250)	103 (216)	0.977	299 (1000)	156 (303)	0.222	142 (333)	156 (307)	0.487	258 (1240)	101 (372)	0.133	138 (319)	120 (429)	0.312	324 (881)	124 (312)	0.003	170 (363)	169 (368)	0.496
Median [Min, Max]	32.7 [0.823, 4480]	9.70 [0.610, 1210]		11.2 [1.40, 1530]	8.51 [0.610, 1210]		13.8 [1.82, 7900]	8.71 [0.893, 1210]		7.64 [1.99, 1500]	7.41 [0.893, 1210]		10.4 [0.850, 14500]	8.86 [0.772, 3810]		9.89 [0.850, 2150]	9.00 [0.772, 3810]		17.3 [1.18, 6860]	8.40 [1.01, 2310]		14.7 [1.18, 2010]	11.1 [1.51, 2310]	
Child-Pugh score																								
5	69 (85.2%)	38 (63.3%)	0.006	40 (76.9%)	38 (73.1%)	0.936	61 (83.6%)	31 (77.5%)	0.502	31 (79.5%)	30 (76.9%)	0.914	148 (82.2%)	129 (73.7%)	0.09	104 (81.9%)	105 (82.7%)	0.199	140 (83.8%)	133 (65.2%)	<0.001	113 (81.9%)	111 (80.4%)	0.901
6	9 (11.1%)	11 (18.3%)		9 (17.3%)	11 (21.2%)		7 (9.6%)	6 (15.0%)		4 (10.3%)	6 (15.4%)		21 (11.7%)	22 (12.6%)		16 (12.6%)	13 (10.2%)		20 (12.0%)	35 (17.2%)		18 (13.0%)	17 (12.3%)	
7	3 (3.7%)	6 (10.0%)		3 (5.8%)	3 (5.8%)		3 (4.1%)	3 (7.5%)		3 (7.7%)	3 (7.7%)		9 (5.0%)	17 (9.7%)		7 (5.5%)	5 (3.9%)		5 (3.0%)	27 (13.2%)		5 (3.6%)	7 (5.1%)	
8	0 (0%)	5 (8.3%)		0 (0%)	0 (0%)		2 (2.7%)	0 (0%)		1 (2.6%)	0 (0%)		2 (1.1%)	7 (4.0%)		0 (0%)	4 (3.1%)		2 (1.2%)	9 (4.4%)		2 (1.4%)	3 (2.2%)	
ECOG PS score																								
0	57 (70.4%)	40 (66.7%)	0.117	42 (80.8%)	35 (67.3%)	0.17	51 (69.9%)	34 (85.0%)	0.184	26 (66.7%)	34 (87.2%)	0.098	132 (73.3%)	135 (77.1%)	0.326	99 (78.0%)	97 (76.4%)	0.534	133 (79.6%)	164 (80.4%)	0.957	110 (79.7%)	108 (78.3%)	0.849
1	22 (27.2%)	13 (21.7%)		9 (17.3%)	11 (21.2%)		17 (23.3%)	4 (10.0%)		10 (25.6%)	4 (10.3%)		37 (20.6%)	26 (14.9%)		23 (18.1%)	21 (16.5%)		29 (17.4%)	34 (16.7%)		25 (18.1%)	28 (20.3%)	
2	2 (2.5%)	6 (10.0%)		1 (1.9%)	5 (9.6%)		5 (6.8%)	2 (5.0%)		3 (7.7%)	1 (2.6%)		11 (6.1%)	14 (8.0%)		5 (3.9%)	9 (7.1%)		5 (3.0%)	5 (2.5%)		3 (2.2%)	2 (1.4%)	
3	0 (0%)	1 (1.7%)		0 (0%)	1 (1.9%)		0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)		0 (0%)	0 (0%)	

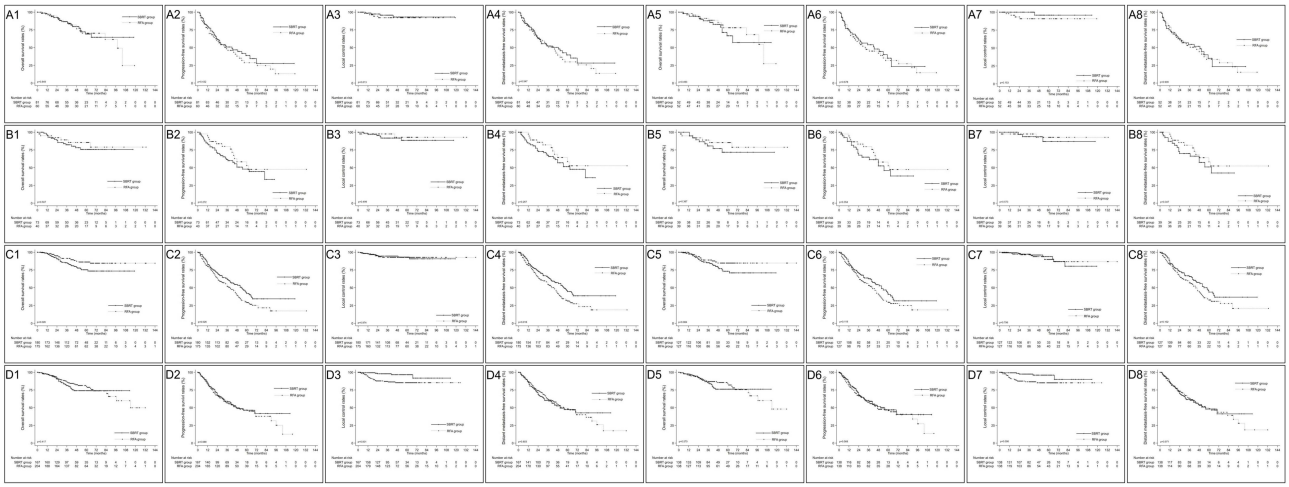

Figure 2 The survival rates before and after matching for different Couinaud's segmentation. (A1) to (A4): survival curves in the S2/S3 before matching; (A5) to (A8): survival curves in the S2/S3 after matching; (B1) to (B4): survival curves in the S4 before matching; (B5) to (B8): survival curves in the S4 after matching; (C1) to (C4): survival curves in the S5/S6 before matching; (C5) to (C8): survival curves in the S5/S6 after matching; (D1) to (D4): survival curves in the S7/S8 before matching; (D5) to (D8): survival curves in the S7/S8 after matching.

Nalee Kim and others[14] retrospectively analyzed and compared the efficacy of SBRT and RFA in 313 paired HCC patients with a maximum tumor diameter <6 cm for a single tumor or a sum of diameters <6 cm for up to 3 lesions. Their results showed that SBRT provided better local control than RFA among patients with HCC, especially for those with larger tumors (>3 cm) in a subphrenic location (especially segment 8). This high-quality article explored HCC populations that were more suitable for SBRT treatment, and some of the results were similar to ours. Our analysis results also showed that tumor diameter was an important influencing factor of LC rates in the RFA group. Moreover, there are several advantages in our research. First, the upper limit for tumor diameter in our study was 5 cm, rather than 6 cm in their study, which is not only consistent with the indications for RFA but also aligns with the range in which SBRT can exert its therapeutic advantages. Second, the patients received SBRT delivered using CyberKnife SBRT, tomotherapy, volumetric modulated arc therapy (VMAT) or three-dimensional conformal radiotherapy (3D-CRT), and the patients received RFA delivered using ultrasound guidance in their study. The patients who received SBRT in our study were all treated using CyberKnife, while the patients in the RFA group were treated under CT guidance, which was different from their study. Third, their study included tumors that were treated by other modalities, such as RFA, transcatheter arterial chemoembolization (TACE), surgery, and sorafenib, whereas none of the patients in our study received previous treatment. They also noted that SBRT had advantages over RFA in specific tumor locations, such as S8. Our analyses also showed that the location of the lesion was an important influencing factor of LC rate in the RFA group. Based on Couinaud's classification, we further studied and found that the LC rates in the SBRT group were better than that in the RFA group when the lesion was located in the S7/S8 of the liver. The main reason was that the tumors located in these two segments were close to the subphrenic region, large blood vessels, bile ducts or liver capsule, which made RFA more difficult. The operating doctors need to have more experience with the procedure; otherwise, the injury risk of RFA treatment will increase, and these injuries mainly manifest as diaphragm perforation, lung injury, hydrothorax, bleeding, bile duct fistula, etc. In addition, during the RFA procedure, sufficient outward expansion of the boundary was needed to reduce the rates of incomplete ablation after treatment. A previous study suggested that treatment targeting a 10 mm margin could reduce the risk of tumor recurrence in cirrhotic patients with a single small HCC.[15]

It is worth noting that the OS rates in the SBRT group were higher than those in RFA group when the lesions were located in S5/S6. We further reviewed the cases in this group and found that when the disease progressed two years later, the irradiated field area shrinkage occurred in SBRT group, resulting in patients with insufficient effective volume combined with/without liver function abnormalities, which may affect treatment choices when tumor recurrence occurs (Figure 3A–D). We considered the main reason was that the left liver, the left and lower intestine and the side right upper

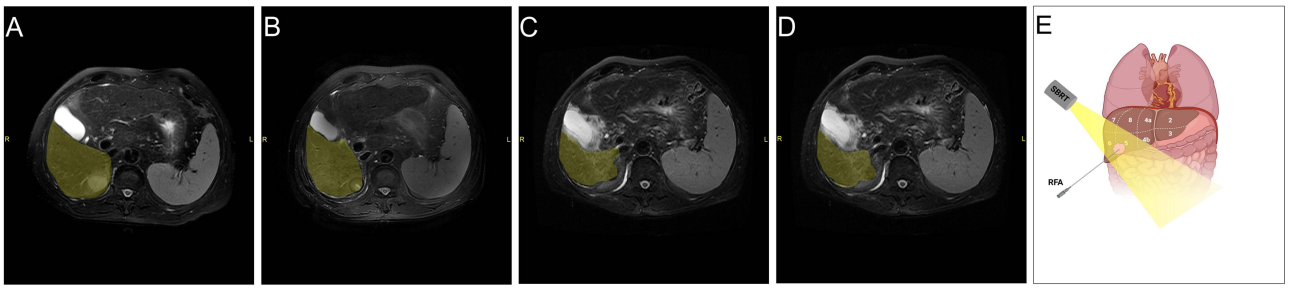

Figure 3 The classic patient with tumor located in S5/S6 treated by SBRT. April 2016: The primary upper-abdominal MRI scan with lesions (**A**). Then the patient received CK-SBRT with 54Gy/6fx. MRI scan in July 2016 (**B**), July 2017 (**C**) and October 2019(d) after SBRT. The lower right lobe of the liver volume was shrinkage (**D**). The tumor is located in S5/S6 segment. RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy(**E**).

limb needs to be protected during the planning design of S5/S6, which limited the irradiation field angle and induced more dose passing through local normal liver (Figure 3E). We have already conducted an ongoing study to optimize the SBRT planning by switching to prone position therapy to reduce liver injury, and the results are promising. When the tumor was located in other liver segmentations, we were able to minimize the volume of normal liver radiation exposure by assuming that there was a pseudo-organ acting as a shield to protect the right liver and the surrounding normal tissues (including the lungs and the gastrointestinal tract, etc.) that shared the radiation dose.

In addition, RFA treatment was more reproducible than SBRT when the patients had short periods of recurrence. Since liver repeated radiotherapy is complex and requires consideration of previous exposure doses to the OARs, the overlapping of repeated radiation doses may cause damage to normal organs. Our previous study has shown that repeated SBRT is relatively safe when the interval between first-course CK-SBRT and second-course CK-SBRT is longer than 6 months,[16] but the location of the maximum point of OARs should still be considered, and pseudo-organ as a shield should be added to the planning to protect the functional parts of the organ as much as possible.

In our study, the S1 group had the smallest number of patients, which is consistent with S1 having the lowest incidence of tumors mentioned in Matteo Renzulli's result.[17] Due to its deep anatomical location and proximity to large blood vessels, this segment has increased difficulty for invasive manipulation. Moreover, tumors in S1 are also located with small arteries that are difficult to catheterize selectively, which may affect the efficacy of TACE.[18] The reasons above indicate that treatment options for S1 segment tumors are limited. There were twenty-one patients in the S1 group. Among them, nineteen patients (90.48%) underwent SBRT treatment, and only two patients had local lesion progression after radiotherapy. SBRT is not restricted by blood vessels and bile ducts, so it is more advantageous as a treatment for lesions in S1.

There were some differences between RFA and SBRT in evaluating toxicity and effect. Different from RFA, the effect of SBRT on liver function is evaluated for a longer time, so there were more interfering factors. In our study, twenty patients died within one year after SBRT, during which radio-induced gastrointestinal injury and liver injuries often occur. Among them, ten patients' tumors progressed. Both the esophagus and stomach are early response tissues, and radiation-induced ulcers or bleeding usually occur within 6 months of radiation treatment. Six patients experienced upper gastrointestinal bleeding, diagnosed by gastroscopy (including two patients with stable tumor conditions). Eight patients died of liver failure after SBRT, but their tumor progression occurred before that. Both events could affect liver function. As a result, it was difficult to distinguish the immediate causes of liver injury. Moreover, unlike for local ablation, we tend to review images (including contrast-enhanced MRI, contrast-enhanced CT, etc.) more than 3 months after SBRT to evaluate its effect rather than immediately after treatment. Our result showed that SBRT is not necessarily associated with a higher risk of metastases, which is reflected by distant-free survival rates, than local ablation treatment.

The study has two shortcomings. First, S4 group can be subdivided into segment 4a and segment 4b, and the adjacent dangerous organs in the two sub-segments were also different. However, considering the small number of cases, no further sub-population analysis was performed. Second, this study is mainly a retrospective study on the efficacy of CyberKnife SBRT and CT-guided RFA. At present, there are many devices that can realize SBRT, and there are more

hospitals that use ultrasound to complete RFA of liver tumors. It is necessary to conduct multi-center prospective studies and reduce the restrictions on machine types when comparing SBRT and RFA.

Conclusions

According to Couinaud's classification of liver segments, for tumors localized in S7/S8, the LC rates were better in the SBRT group than in the RFA group. Moreover, there are limited therapeutic options for lesions in S1, but SBRT was safe and effective for this group of patients. Moreover, patients with tumors located in S5/S6 were better candidates for RFA treatment than SBRT.

Data Sharing Statement

To protect patient confidentiality, raw data are not publicly accessible. However, they can be requested from Jing Sun at sunjing0801@foxmail.com for legitimate inquiries.

Ethics Statement

The Ethics Committee Board of the Fifth Medical Center of PLA General Hospital approved this retrospective study and waived the requirement for patient consent for this retrospective review. This study was complied with the Declaration of Helsinki. We solemnly promised that this study strictly abided by relevant laws and regulations and did not disclose patient personal information and related information to any other personnel and organizations to ensure the security and confidentiality of patient information.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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