Journal of Gastrointestinal Surgery (2019) 23:1549–1558
https://doi.org/10.1007/s11605-019-04229-6

Safety and Efficacy of Radiofrequency Ablation for Solitary Hepatocellular Carcinoma (3–5 cm): a Propensity Score Matching Cohort Study

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Received: 12 December 2018 / Accepted: 10 April 2019 / Published online: 13 June 2019

Abstract

Background We aim to investigate the safety and efficacy of radiofrequency ablation in the treatment of solitary hepatocellular carcinoma (3–5 cm) in comparison with surgical resection.

Methods Included in this study were 388 patients with primary and solitary hepatocellular carcinoma, of whom 196 patients underwent surgical resection and the other 192 patients received radiofrequency ablation. Clinicopathological characteristics, prognosis, post-treatment complications, hospital stay, and financial expenditures between the two groups were compared retrospectively.

Results The result of propensity score matching and subgroup analysis showed that the 1-, 3-, and 5-year overall survival and disease-free survival were comparable in patients with tumors of 3–4 cm in diameter between surgical resection and radiofrequency ablation groups. However, when the tumor size exceeded 4 cm in diameter, surgical resection exhibited a superior long-term prognosis compared with radiofrequency ablation. Nevertheless, hepatectomy was associated with high occurrences of postoperative complications, long hospital stay, and high hospitalization cost as compared with radiofrequency ablation. Further analysis of the relationship between tumor size and pathological features of hepatocellular carcinoma showed that tumors larger than 4 cm were positively correlated with a high rate of microvascular invasion and satellite nodule formation.

Conclusion For solitary hepatocellular carcinoma of 3–4 cm in diameter, radiofrequency ablation could achieve a comparable prognosis with a low incidence of post-treatment complications and low hospitalization costs, while surgical resection is recommended for solitary hepatocellular carcinoma tumors of 4–5 cm in diameter when long-term prognosis is considered.

Keywords Hepatocellular carcinoma · Radiofrequency ablation · Prognosis · Hepatectomy

Introduction

Hepatocellular carcinoma (HCC) ranks as the fifth most common cancer and the third leading cause of cancer-related death worldwide.[1] It is a major health problem worldwide, especially in China,[1–4] because China not only has a high annual incidence of HCC but also has a large population of chronic hepatitis B patients about 20 millions who may be prone to progress to HCC.[4–6] So, prevention and treatment of HCC remain a great medical challenge in China.

The Barcelona Clinical Liver Cancer (BCLC) staging system is the most widely used guideline to classify and treat HCC in the world. According to the BCLC staging system, HCC can be treated effectively at an early stage.[7] Surgical resection, liver transplantation (LT), and radiofrequency ablation (RFA) have been recommended as the curative treatments for HCC at an early stage.[7, 8] These three therapeutic measures have their respective advantages and indications. For HCC

Qing-wang Ye, Shu-jie Pang and Ning Yang contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11605-019-04229-6) contains supplementary material, which is available to authorized users.

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patients diagnosed at stage 0 and A (BCLC), surgical resection, LT, and RFA can obtain comparable prognostic benefits.[2, 8] However, whether RFA is suitable for solitary HCC of 3–5 cm in diameter remains controversial. They are not recommended in the latest updated guidelines of HCC.[2] But some recent studies reported conflicting results with regard to this issue.[9, 10] For instance, a latest study by Lee et al.[9] suggested that RFA could provide comparable prognosis for patients with 3–5-cm solitary HCC tumors compared with surgery. But a meta-analysis by Xu et al.[10] reported an inferior prognosis of RFA for HCC at an early stage compared with surgical resection (RES). These inconsistent results may be ascribed to insufficient samples and patient heterogeneity in the related studies. Compared with RES, RFA may present less invasive and cheaper treatment for HCC and therefore its clinical value remains significant when RFA can be confirmed to achieve comparable long-term prognosis compared with RES in the treatment of 3–5-cm solitary HCC tumors.

In this study, we collected the clinicopathological and prognostic data from patients with 3–5-cm solitary HCC tumors to investigate the prognostic benefits of RFA in comparison with surgical resection by employing propensity score matching (PSM) analysis and subgroup analysis.

Material and Methods

Patients

Enrolled in this study were 388 patients with 3–5-cm solitary HCC tumors who underwent hepatectomy or RFA in our hospital between January 2007 and December 2011. The diagnosis for patients in the RFA group was based on the preoperative contrast-enhanced CT or MRI findings and serological tumor markers alpha-fetoprotein (AFP), carbohydrate antigen 19-9 (CA19-9), and carcinoembryonic antigen (CEA), while the diagnosis for patients in the hepatectomy group was confirmed by postoperative pathology. The inclusion criteria for patients in this study were as follows: (1) solitary tumor; (2) tumor with a diameter between 3 and 5 cm; (3) primary liver tumor without any history of associated therapies; (4) no evidence of macrovascular metastasis or distant metastasis; (5) HCC patients with complete data in terms of clinicopathology and survival. Curative hepatectomy was defined as complete resection of the tumor with a negative microscopic margin and no residual lesions as detected by CT or MRI scan 1 month post-operation and was conducted in patients in the surgical resection group.

Analysis of Variables

Clinicopathologic data were consisted of host-related data, serum markers, tumor-associated data, and post-treatment complications. In the host-related group, gender, age, history of viral hepatitis, and liver function based on Child-Pugh staging system (Child A or B) were included. Hepatitis B virus (HBV) infection was defined as HBsAg(+) or hepatitis B virus deoxyribonucleic acid (HBV DNA) $> 10^3$ IU/mL. Hepatitis C virus (HCV) infection was defined as a positive status of serum RNA of HCV. With regard to serum markers, we assessed total bilirubin (TBIL) (≤ 17.1 or > 17.1 μmol/L), alanine aminotransferase (ALT) (≤ 40 or > 40 U/L), serum albumin (ALB) (≤ 37or > 37 g/L), gamma-glutamyl transpeptidase (GGT) (≤ 64 or > 64 U/L), CA19-9 (≤ 37 or > 37 U/L), AFP (≤ 20 or > 20 μg/L), and the status of preoperative HBV DNA ($\leq 10^3$ or $> 10^3$ IU/mL). The tumor-associated data, including tumor size (≥ 3 cm and < 4 cm, ≥ 4 cm and < 5 cm), microvascular invasion (yes or no), integrity of the tumor capsule (yes or no), satellite nodule (yes or no), surgical margin (≤ 1 cm or > 1 cm), anatomic RES (yes or no), and tumor location, were collected. Among these factors, special location was defined as tumor location being close to the gallbladder or hepatic vessels that may affect the efficacy of RFA. Post-treatment complications included post-treatment liver failure, post-treatment abdominal hemorrhage, biliary fistula, massive ascites, hydrothorax, and hypoalbuminemia. According to Clavien-Dindo staging system, these complications were divided into I–V stages.[11] The length of hospital stay and medical costs of these patients were also compared between the two groups. In addition, medical cost data of each patient during duration in our hospital were tracked and collected from our electronic medical record management system. We intended to investigate the burden of medical care by comparing the different costs between RFA and RES for patients with HCC. Thus, we want to help patients find a less invasive and lower cost therapy with equal survival benefit from the individual perspective.

Hepatectomy

All hepatectomy procedures were carried out by three groups of HPB surgeons, and each group was equipped with experienced professors of hepatobiliary surgery to maintain the homogeneity of operation quality. Anatomic resection was defined as intact resection of the hepatic segment or lobe (Couinaud I–VII), which was involved by tumor. Only 54 patients received anatomic resection and the rest of 142 patients undergone non-anatomic hepatectomy (Table 5). Intraoperative ultrasound was routinely used to confirm the location of tumor. Concerning the aggressive nature of HCC, R0 resection with a clear margin of more than 1 cm was the goal. Thus, R0 goal was achieved in 157 patients, which is shown in Table 5.

RFA

In the present study, none patients underwent microwave ablation. RFA procedures were all carried out by intervention radiologists. RFA was administered with the RF 2000 generator system (Boston Scientific Corp., Natick, MA) under the guidance of real-time USG (EUB-2000, HITACHI Medical Systems).[12] RF 2000 system is consisted of a generator supplying up to 100 W of power, a LeVeen monopolar array needle electrode, and two indifferent dispersive grounding electrode pads adhered to the patient's skin.[12] The LeVeen electrode is a 15-gauge, 15–25-cm-long insulated cannula, which contains ten independent hook-shaped electrode arms to be deployed in situ. RFA was applied according to the instruction manual of the manufacturer. Our strategy of RFA was to involve a peripheral margin of 0.5 to 1.0 cm of normal liver tissue surrounding the tumor, as well as the entire tumor itself, regardless of the tumor size. Radiofrequency energy was delivered for 8–12 min for each application. For large tumors, the electrode was repeatedly inserted into different sites, such that the entire tumor could be enveloped by assumed necrotic volumes. Each prong was equipped with a thermocouple, which could monitor real-time temperature during treatment. Tissue impedance was also monitored by circuitry equipped in the generator. Hooks were deployed and the generator was set to reach an average temperature of the hooks of 100 °C. Treatment continued until complete ablation features were achieved in real-time USG. An overnight hospital stay was mandatory under close medical observations after RFA procedure. An enhanced CT scan was regularly performed to evaluate the efficacy of RFA 1 month later. Hypoattenuation of the entire tumor without intensification would be defined as complete ablation. If residual tumor was found by CT scan, RFA would be repeated. None patients involved in this study underwent repeated RFA.

Follow-ups

After hospital discharge, the patients were followed up regularly in the outpatient clinic by a standard protocol: every 3 months during the first 2 years and twice a year afterwards. Follow-up observations included serum levels of AFP, CEA, and CA19-9; abdominal ultrasonography; and enhanced CT or MRI. Chest CT scan was done when X-ray showed abnormalities. Bone metastases were diagnosed by scintigraphy or positron emission tomography (PET). Only 6 and 8 patients in the RFA and RES groups were lost to follow-up, and they were excluded in the present study. The rest of 388 patients were followed up consecutively until January 2016.

Propensity Matching Score Analysis

To investigate the differences of survival benefits and safety between the RES and RFA groups for the treatment of solitary HCC (3–5 cm) in an observational study rather than in a randomized, controlled trial, a propensity score matching analysis was employed to reduce biases in patients' selections. PSM was performed via binary logistic regression to generate a propensity score for each patient. The co-variables entered into the model included age, gender, status of infection with hepatitis virus, Child-Pugh score, tumor size, AFP, GGT, and tumor location. Subsequently, a one-to-one match between the RES group and the RFA group was obtained by use of the nearest-neighborhood matching using a caliper width of 0.15 without replacement. To screen the proper caliper for PSM employing in this study, we tested multiple caliper widths. The rationality of matching was assessed by comparing the differences in covariate means for dichotomous variables for the matched and unmatched samples. Small absolute values in standardized differences (< 20%) were assumed to support the assumption of balance between the treatment groups. We defined the caliper in 0.2, 0.15, 0.05, 0.02, 0.01, 0.005, 0.002, or 0.001 of standard deviation of the logit of the estimated propensity score, which meant the maximum distance that two units could be apart from each other was 0.2, 0.15, 0.05, 0.02, 0.01, 0.005, 0.002, or 0.001 of standard deviations of the logit of the estimated propensity score. Finally, we found that the caliper of 0.15 met the requirements of both preferable homogeneity and minor loss of sample size.

Statistical Analysis

Continuous variables were compared by Mann–Whitney *U* test, while categorical variables were compared by the Pearson chi-squared test or Fisher's exact test. For some continuous variables, clinically applicable cutoffs were chosen to transform them into categorical variables. Cox's proportional hazards regression model was used to identify independent risk factors of overall survival (OS) for HCC patients in the RFA group. The cumulative survival time was calculated by using the Kaplan–Meier method and compared by log-rank test between the RES and RFA groups. Statistical significance was defined as $P < 0.05$. All statistical analyses in this study were performed with SPSS software version 20 (IBM Corp., Armonk, NY).

Results

Clinicopathological Characteristics

The 388 HCC patients meeting the inclusion criteria who underwent treatment at our hospital between January 2007 and December 2011 were divided into two groups: RFA group ($n = 192$, 49.5%) and RES group ($n = 198$, 50.5%). A flow diagram for screening of patients enrolled in this study is shown in Fig supplement 1. Comparisons of the patients' clinicopathological characteristics between the two groups are illustrated in Table 1. As shown in Table 1, the clinicopathological characteristics analyzed in the current study were comparable between the two groups, exclusive of age and infection of hepatitis virus. To chase the balanced baseline information between the two groups, PSM was employed. After PSM, the two groups included 154 and 154 patients, respectively. There were no significant differences in the clinicopathological characteristics between the two groups after PSM (Table 2).

Comparison of OS and Disease-Free Survival

The OS and disease-free survival (DFS) curves of the two groups are shown in Fig. 1a and b. In RFA and the RES, the 1-, 3-, and 5-year OS was 95%, 58%, and 34% vs. 93%, 63%, and 40% for OS and 72%, 30%, and 10% vs. 76%, 30%, and 15% for DFS, respectively. These curves demonstrated that the RES group tended to achieve better survival benefits in

Table 1 Comparison of the patients' clinicopathological characteristics

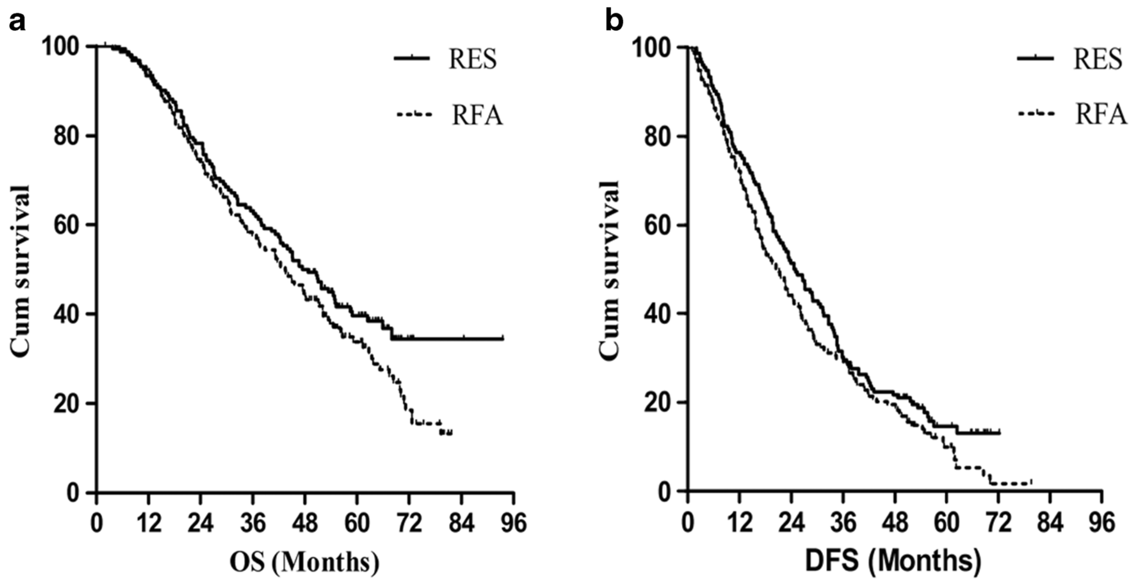
Characteristic	RFA ($n = 192$)	RES ($n = 196$)	t/χ^2	P value
Gender			0.05	0.81
Male	167	172		
Female	25	24		
Age			9.96	0.002
≤ 60	113	145		
> 60	79	51		
Hepatitis virus infection			6.649	0.036
Hepatitis B	161	172		
Hepatitis C	20	22		
Negative	11	2		
Child-Pugh score			0.185	0.667
Class A	175	181		
Class B	17	15		
Tumor size (cm)			0.284	0.594
3 ≤ diameter < 4	137	135		
4 ≤ diameter < 5	55	61		
ALT (U/L)			1.98	0.159
> 40	88	76		
≤ 40	104	120		
TBIL (μmol/L)			0.465	0.495
> 20	67	62		
≤ 20	125	134		
GGT (U/L)			0.168	0.681
> 50	92	98		
≤ 50	100	98		
ALB (g/L)			2.515	0.113
≥ 37	144	160		
< 37	48	36		
AFP (ng/mL)			2.949	0.229
< 20	94	87		
20 ≤ AFP < 400	62	58		
≥ 400	36	51		
CA19-9 (U/L)			0.331	0.565
< 40	130	138		
≥ 40	62	58		
HBV DNA (copies/mL)			0.326	0.568
≤ 1000	144	142		
> 1000	48	54		
Special location			0.64	0.424
Yes	60	54		
No	132	142		

RFA, radiofrequency ablation; *RES*, surgical resection; *HBV DNA*, hepatitis B virus deoxyribonucleic acid; *HBV*, hepatitis B virus; *ALT*, alanine aminotransferase; *GGT*, gamma-glutamyl transpeptidase; *TBIL*, total bilirubin; *ALB*, albumin; *AFP*, alpha-fetoprotein; *CEA*, carcinoembryonic antigen; *CA19-9*, carbohydrate antigen 19-9

Table 2 Comparison of the patients' characteristics after propensity score matching

Characteristic	RFA ($n = 154$)	RES ($n = 154$)	t/χ^2	P value
Gender			1.663	0.197
Male	134	141		
Female	20	13		
Age			0.000	1.000
≤ 60	103	103		
> 60	51	51		
Hepatitis virus infection			1.414	0.493
Hepatitis B	134	135		
Hepatitis C	5	2		
Negative	15	17		
Child-Pugh score			1.088	0.297
Class A	144	139		
Class B	10	15		
Tumor size (cm)			0.065	0.798
3 ≤ diameter < 4	111	113		
4 ≤ diameter < 5	43	41		
ALT (U/L)			1.596	0.207
> 40	73	62		
≤ 40	81	92		
TBIL (μmol/L)			0.130	0.718
> 20	54	51		
≤ 20	100	103		
GGT (U/L)			0.832	0.362
> 50	79	83		
≤ 50	75	71		
ALB (g/L)			0.487	0.485
≥ 37	119	124		
< 37	35	30		
AFP (ng/mL)			0.171	0.918
< 20	77	78		
20 ≤ AFP < 400	50	47		
≥ 400	27	29		
CA19-9 (U/L)			0.251	0.616
< 40	107	111		
≥ 40	47	43		
HBV DNA (copies/mL)			0.071	0.790
≤ 1000	116	118		
> 1000	38	36		
Special location			0.565	0.452
Yes	42	48		
No	112	106		

RFA, radiofrequency ablation; *RES*, surgical resection; *HBV DNA*, hepatitis B virus deoxyribonucleic acid; *HBV*, hepatitis B virus; *ALT*, alanine aminotransferase; *GGT*, gamma-glutamyl transpeptidase; *TBIL*, total bilirubin; *ALB*, albumin; *AFP*, alpha-fetoprotein; *CEA*, carcinoembryonic antigen; *CA19-9*, carbohydrate antigen 19-9.



Number at risk after treatmen(Months)	0	12	36	60
RFA	154	146	88	31
RES	154	142	96	38

Number at risk after treatmen(Months)	0	12	36	60
RFA	154	111	46	9
RES	154	116	46	11

Fig. 1 **a**, **b** Cumulative overall survival and disease-free survival after propensity score matching by different treatments

comparison with the RFA group, although there were no significant differences ($P = 0.103$ for OS, $P = 0.087$ for DFS).

Subgroup Analysis of OS and DFS Differences Between the Two Groups

Both univariate and multivariate analyses showed that tumor size (4 cm < diameter ≤ 5 cm) was an independent risk factor of dismal OS for patients undergoing RFA (Table 3). Thus, we proceeded further subgroup analysis to compare prognostic differences between the RFA and RES groups in patients with varying tumor sizes. And, there were 111 and 113 patients in the RFA and RES groups with tumors between 3 and 4 cm respectively. As shown in Fig. 2a and b, OS and DFS in patients with tumors between 3 and 4 cm were comparable between the two groups ($P = 0.961$ for OS, $P = 0.459$ for DFS). However, in patients with tumors larger than 4 cm, there were 43 and 41 patients in the respective groups. And, RES offered better OS and DFS than RFA ($P = 0.001$ for OS, $P = 0.037$ for DFS) (Fig. 3a, b).

Comparison of Post-treatment Complications, Hospital Stay, and Costs

With regard to the Clavien-Dindo staging system, post-treatment complications ranked as I to V stages. Post-treatment complications were compared between the two groups (Table 4). The length of hospital stay in the RFA group was shorter than that in the RES group (2.38 ± 0.89 vs. 8.90 ± 3.33 days, $P < 0.001$). In addition, the cost for hospitalization in the RFA group was lower than that in the RES group (2517.7 ± 14.6 vs. 4872.6 ± 58.5 *dollars*, $P < 0.001$).

Discussion

Based on the BCLC strategy for staging and treatment, LT and RES have been regarded as the curative therapies for HCC patients at an early stage.[2, 8, 13] However, in view of donor organ shortage, RES remains the mainstay of treatment for HCC patients at an early stage.[13, 14] RFA has been recommended as the treatment with curative intent for HCC patients at BCLC stages 0–A.[2, 8] But whether RFA is suitable for HCC patients within BCLC A stage remains controversial, especially for solitary HCC nodules ranging from 3 to 5 cm.[9, 10, 15–17] Some recent studies even reported opposing results concerning this issue. A meta-analysis conducted by Xu et al. reported that RES could obtain more satisfied OS and DFS than RFA.[10] While Lee et al.[9] maintained that RFA could get comparable OS and DFS with RES therapy. A latest study[15] suggested that RFA plus ethanol injection was superior to RES in terms of 1-, 3-, and 5-year OS and DFS. Insufficient samples and patient heterogeneity between different treatment groups may contribute to the conflicting results.

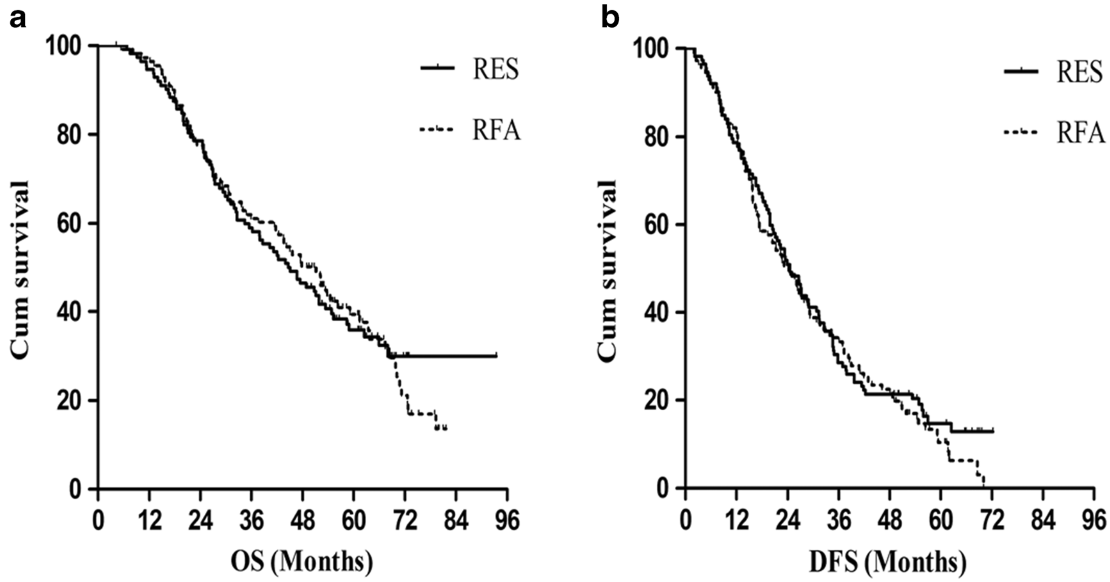
Table 3 Univariate and multivariate analyses of risk factors for poor OS in RFA group

Variable	*N*	Median OS ± SD	UV *P* value	MV HR (95% CI)	MV *P* value
Gender			0.469		
Male	134	45.0 ± 4.1			
Female	20	30.5 ± 8.1			
Age			0.600		
≤ 60	103	45.0 ± 4.9			
> 60	51	41.0 ± 4.3			
Hepatitis virus infection			0.757		
Hepatitis B	134	43.5 ± 4.0			
Hepatitis C	5	30.3 ± 6.2			
Negative	15	54.5 ± 10.4			
Child-Pugh score			0.011	1.172 (0.536–2.563)	0.691
Class A	144	45.0 ± 3.9			
Class B	10	22.2 ± 4.3			
Tumor size (cm)			0.013	1.608 (1.076–2.403)	0.020
3 ≤ diameter < 4	111	51.1 ± 4.3			
4 ≤ diameter < 5	43	34.6 ± 4.1			
ALT (U/L)			0.209		
> 40	73	41.7 ± 3.7			
≤ 40	81	45.6 ± 5.7			
TBIL (μmol/L)			0.196		
> 20	54	36.9 ± 6.5			
≤ 20	100	47.5 ± 4.6			
GGT (U/L)			< 0.001	1.711 (1.147–2.552)	0.008
> 50	79	31.0 ± 3.7			
≤ 50	75	59.1 ± 3.9			
ALB (g/L)			< 0.001	0.535 (0.333–0.859)	0.010
≥ 37	119	51.1 ± 3.9			
< 37	35	27.0 ± 3.7			
AFP (ng/mL)					
<20	77	41.4 ± 3.4	0.365		
20 ≤ AFP < 400	50	48.1 ± 4.4			
≥ 400	27	34.8 ± 8.7			
CA19-9 (U/L)			0.104		
< 40	107	47.8 ± 3.3			
≥ 40	47	33.0 ± 3.7			
HBV DNA (copies/mL)			0.332		
≤ 1000	116	41.1 ± 5.3			
> 1000	38	45.0 ± 5.1			
Special location			0.678		
Yes	42	41.1 ± 6.9			
No	112	43.6 ± 4.1			

RFA, radiofrequency ablation; *RES*, surgical resection; *HBV DNA*, hepatitis B virus deoxyribonucleic acid; *HBV*, hepatitis B virus; *ALT*, alanine aminotransferase; *GGT*, gamma-glutamyl transpeptidase; *TBIL*, total bilirubin; *ALB*, albumin; *AFP*, alpha-fetoprotein; *CEA*, carcinoembryonic antigen; *CA19-9*, carbohydrate antigen 19-9; *OS*, overall survival; *SD*, standard deviation; *UV*, univariate; *MV*, multivariate; *HR*, hazard ratio; *CI*, confidence interval

Thus, the current study intended to explore this issue by employing a relatively large sample and PSM method.

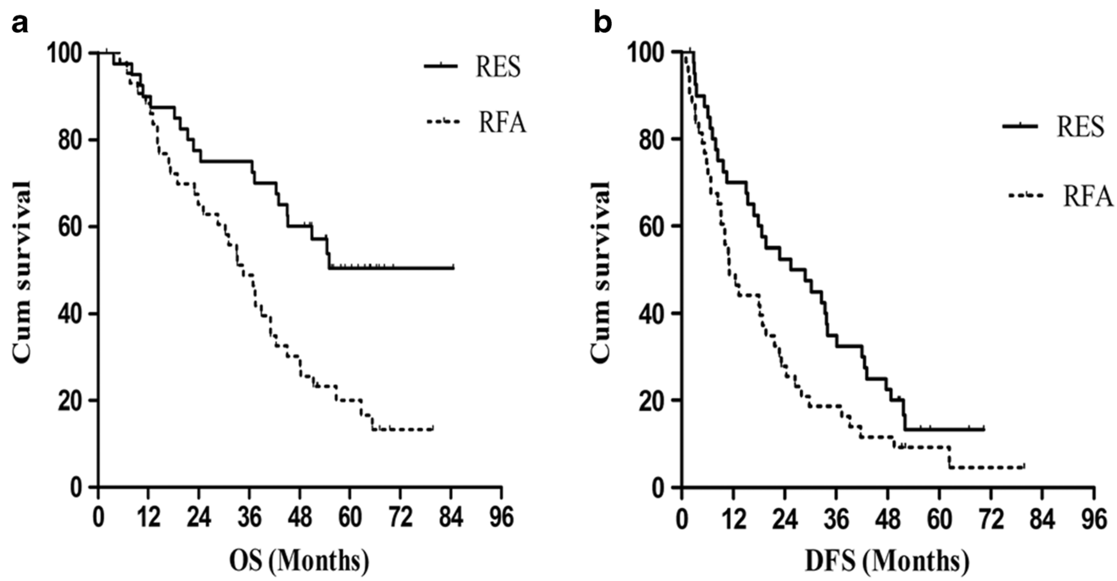
PSM showed that the baseline information between the patients of the two groups was comparable. However, our



	Number at risk after treatmen(Months)			
	0	12	36	60
RFA	111	108	67	25
RES	113	106	66	27

	Number at risk after treatmen(Months)			
	0	12	36	60
RFA	111	90	38	7
RES	113	88	32	9

Fig. 2 **a**, **b** Difference in overall survival and disease-free survival of patients with 3–4-cm HCC tumors between RES and RFA groups



	Number at risk after treatmen(Months)			
	0	12	36	60
RFA	43	38	21	6
RES	41	36	30	11

	Number at risk after treatmen(Months)			
	0	12	36	60
RFA	43	21	8	2
RES	41	28	14	2

Fig. 3 **a**, **b** Difference in overall survival and disease-free survival of patients with 4–5-cm HCC tumors between RES and RFA groups

Table 4 Comparison of post-treatment complications, hospital stay, and cost

Variable	RFA ($n = 154$)	RES ($n = 154$)	t/χ^2	P value
Hospital stay ($x \pm S$, days)	2.38 ± 0.89	8.90 ± 3.33		< 0.001
Complications			4.278	0.039
Yes	21	35		
No	133	119		
Clavien-Dindo stage			14.068	0.007
0 stage	133	119		
I stage	17	14		
II stage	4	12		
III stage	0	8		
IV stage	0	1		
Hospitalization costs (dollars)	2517.7 ± 14.6	4872.6 ± 58.5		< 0.001

RFA, radiofrequency ablation; *RES*, surgical resection

study showed that RES could obtain better OS and DFS compared with RFA for solitary HCC tumors ranging from 3 to 5 cm in diameter. Our univariate and multivariate analyses suggested that tumors larger than 4 cm in diameter were an independent risk factor of dismal OS for patients undergoing RFA. Then, we conducted subgroup analysis to investigate the prognostic differences of the patients with tumors of varying sizes between the two groups and found that the 1-, 3-, and 5-year OS and DFS rates were comparable in patients with HCC tumors of 3–4 cm in diameter between the two methods without showing significant difference. However, when tumors exceeded 4 cm in diameter, RES presented a superior long-term prognosis compared with RFA in terms of OS and DFS. Then, we tried to explore factors contributing to this discrepancy by uncovering the relationship between the tumor size and the pathological characteristics of HCC in the RES group and found that tumors larger than 4 cm in diameter were positively correlated with a higher risk of microvascular invasion (MVI) and the occurrence of satellite nodules (Table 5).

The positive status of MVI may reflect a progressive biological characteristic of HCC and predict a mean long-term prognosis even after curative therapy.[17–19] Previous studies[18, 19] reported that MVI was an independent risk factor leading to early recurrence of HCC undergoing treatment. The incidence of MVI in solitary HCC tumors less than 3 cm in diameter remains as high as 40.6%.[19] Anatomic hepatectomy and partial liver resection with a wide tumor margin are recommended to eradicate MVI of HCC.[2, 8, 20] But it is usually difficult to confirm MVI preoperatively based on the current imaging procedures because of the histopathological nature of HCC. Several models[21–23] have been constructed to evaluate the existence of MVI before hepatectomy for HCC using tumor size as the most important risk factor. But there are controversies over the precise tumor size cutoff point.[24, 25] It was found in our study that the incidence of MVI in HCC tumors of 4–5 cm was 29.5% vs. 13.3% in tumors of 3–4 cm, showing a significant difference ($P = 0.009$).

Like MVI, satellite nodule formation is another risk factor leading to poor prognosis of HCC after treatment.[24–26] Increasing evidence shows that tumor diameter affects the incidence of satellite nodule formation in HCC.[24, 25] Compared with RES, RFA is unable to manage HCC-associated MVI or satellite nodule formation effectively. Thus, MVI or satellite nodule formation may contribute to the survival differences between two groups with varying tumor sizes. For 3–4-cm HCC tumors, RFA can achieve comparable prognosis with RES. However, in patients with 4–5-cm HCC tumors, the prognosis with RFA was inferior to that with RES.

Given post-treatment complications and hospitalization cost, RES is by no mean less invasive and less costly than RFA in terms of hospitalization, seemingly suggesting that RFA is more

Table 5 Analysis of relationship between tumor size and patients' pathologic characteristics in RES group

Variable	Diameter (3–4 cm)	Diameter (4–5 cm)	t/χ^2	P value
MVI			7.331	0.009
Positive	18	18		
Negative	117	43		
Satellite nodule			7.842	0.008
Yes	10	13		
No	125	48		
Surgical margin			3.53	0.081
≤ 1 cm	22	17		
> 1 cm	113	44		
Integrity of capsule			0.006	1
Yes	15	7		
No	120	54		
Anatomic Res				
Yes	39	15	0.389	0.606
No	96	46		

MVI, microvascular invasion

suitable than RES for solitary HCC tumors between 3 and 4 cm in diameter in terms of safety and economic efficiency.

The current study has several limitations. First, the retrospective nature of this study had its intrinsic disadvantages, and therefore randomized double-blind controlled trials with larger sample size are required to confirm the results and conclusion of the present study. In addition, this is a single-center cohort study and therefore the results may be not generalizable. Data from multi-center studies are necessary.

Conclusions

In conclusion, PSM and subgroup analysis of the present study showed no significant difference in 1-, 3-, and 5-year OS and DFS in patients with 3–4-cm HCC tumors between RES and RFA; when HCC tumors were larger than 4 cm in diameter, RES could provide better long-term prognosis than RFA in terms of OS and DFS. However, hepatectomy was associated with a higher incidence of postoperative complications, a longer hospital stay, and higher hospitalization costs than RFA.

Acknowledgements Thanks for Dr. Xu Lin's help (an intervention radiologist) in the description of RFA.

Contributions Guang-shun Yang, Qing-wang Ye, and Shu-jie Pang designed the project. Qing-wang Ye and Shu-jie Pang wrote the manuscript with Guang-shun Yang. Guang-shun Yang and Lin Bin provided revisions of the manuscript; Yang Ning, Hai-bin Zhang, Fu Yong, and Guang-shunYang collected and assembled the data; Qing-wang Ye, Shu-jie Pang, Lin Bin, and Guang-shun Yang analyzed the data and interpreted results; and all authors have given their final approval for the manuscript.

Financial Support This study was supported by the General Program of Shanghai Municipal Commission of Health and Family Planning (No. 201440445) and the National Nature Science Foundation of China (No. 81372355).

Compliance with Ethical Standards

Ethics Approval and Consent to Participate This study complied with the ethical guidelines of the Declaration of Helsinki and was approved by our Ethics Committee of the hospital. Informed consent was obtained from all patients before treatment for their data to be used in this study.

Conflict of Interest The authors declare that there are no competing interests.

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