J Gastrointest Surg (2015) 19:1466–1475
DOI 10.1007/s11605-015-2850-z

ORIGINAL ARTICLE

Local Recurrence after Radiofrequency Ablation of Hepatocellular Carcinoma: Treatment Choice and Outcome

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Received: 26 February 2015 / Accepted: 1 May 2015 / Published online: 27 May 2015

Abstract

Background/aims Radiofrequency ablation (RFA) has been proven effective for treating small hepatocellular carcinoma (HCC) nodules. However, post-RFA local recurrence is a major factor limiting prognosis. Up to now, there is no consensus on a standardized treatment strategy for these local recurrences. The aim of this study is to evaluate the outcomes of salvage treatments for RFA-related local recurrence.

Methods From May 2008 to June 2013, a total of 112 patients with HCC were detected with local recurrence after RFA. Among them, 94 patients received sequential treatments in our hospital, including salvage resection (SR) (n=24), salvage liver transplantation (n=2), repeated RFA (n=62), and transarterial chemoembolization (TACE) (n=6). We evaluated the treatment outcomes of patients by salvage surgery (SS), RFA, and TACE.

Results The median follow-up time was 32 months. After treatment, local recurrence was eradicated in 82 of 94 patients (87.2 %). The complete response (CR) rate in the RFA group was 90.3 % (56/62), while it was 100 % (26/26) in the SS group (P=0.175) and 0 % (0/6) in the TACE group. When analysis confined to patients with CR, the 1- and 3-year disease-free survival (DFS) rates were 57.7 and 20.2 % in the SS group, and 41.7 and 28.6 % in the RFA group, respectively (P=0.640). The 1- and 3-year overall survival (OS) rates were 93.3 and 69.1 % in the SS group, and 78.6 and 57.5 % in the RFA group, respectively (P=0.251).

Conclusion Repeated RFA is the first treatment choice for patients with post-RFA local recurrence. SS should be considered when RFA failed or is inapplicable.

Keywords Salvage surgery · Radiofrequency ablation · Transarterial chemoembolization · Local recurrence · Hepatocellular carcinoma

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Introduction

Hepatocellular carcinoma (HCC) is a global public health problem and is the third most common cause of death from cancer worldwide.[1] Surgical resection is regarded as the standard curative treatment of HCC. However, the majority of patients are not candidates for curative resection mainly because of tumor advances at the first diagnosis or inadequate liver function reserve.[2,3]

Tumor ablation such as radiofrequency ablation (RFA) is now recommended by the guidelines established by American Association for the Study of Liver Disease (AASLD) and

European Association for the Study of Liver (EASL) for small HCC in patients with preserved liver function reserve, showing a comparable long-term outcome to liver resection.[3–6] However, tumor recurrence especially local recurrence after RFA is more common, which seriously jeopardizes the chances of cure. The reported local recurrent rates after RFA ranged from 2 to 60 %.[7–9] Previous studies have shown that large tumor size, subcapsular tumors, incomplete ablation, and the physician's experience are all associated with local recurrence after percutaneous RFA.[8–11] Intrahepatic distal recurrence is usually nodular, capsulated, whereas local recurrence is irregular, with an indistinctive border. Re-treatment for local recurrence is often difficult and has a high risk of failure.[9] Although various treatment modalities, such as repeated ablation, transarterial chemoembolization (TACE), liver resection and liver transplantation, have been applied for local recurrence,[10,12–14] the optimal treatment strategies remain debatable. To our knowledge, few previous studies have compared the treatment efficacies and the survival outcomes of different treatment modalities for local recurrence after ablation.

The aim of this retrospective study is to evaluate and compare the efficacies of multidisciplinary treatments for post-RFA local recurrence and define a logical management algorithm.

Patients and Methods

Patient and Prior RFA

This study was performed according to the guidelines of the Helsinki Declaration. It was registered and approved by the ethics committee at The First Affiliated Hospital of Sun Yat-Sen University. All patients signed a written informed consent before treatment.

From May 2008 to June 2013, 244 consecutive patients with primary HCC and 764 patients with recurrent single HCC after initial liver resection underwent percutaneous RFA in our hospital. The indication of RFA for HCC is based on the AASLD guideline.[3] RFA was carried out with LeVeen electrodes (Boston Scientific, Natick, MA), Starburst XL electrodes (RITA Medical Systems, Mountain View, CA), or Cool-tip electrodes (Valleylab, Boulder, CO). The selection of device was based on the size and location of the tumor. With real-time ultrasound (US) guidance, the electrode was percutaneously introduced into the tumors through the guiding needle. RFA was performed with the intent to completely eradicate the tumor with an ablative margin of 0.5 cm. For the treatment of tumor larger than 3 cm, multiple overlapping ablations were performed. After RFA, the needle track was coagulated for reducing bleeding and tumor seeding.

All patients received contrast-enhanced computed tomography (CECT) scan and contrast-enhanced ultrasound (CEUS) 1 month after initial RFA to confirm complete tumor eradication. After that, subsequent CECT scan or/and CEUS with measurements of serum alpha-fetoprotein (AFP) and liver biochemistry were performed every 3–6 months to detect recurrence. If necessary, chest CT scan or 18F-fluorodeoxyglucose (18F-FDG) position emission tomography/CT was performed to assess distant metastases. Local recurrence was defined as reappearance of enhancement within or at the peripheral of the original ablated lesion less than 2.0 cm after complete tumor response. HCC tumors found in other segments or more than 2.0 cm from the ablated lesion were considered as intrahepatic distal recurrence. Extrahepatic metastases referred to any recurrences outsider the liver.

During the period of study, a total of 112 patients developed local recurrence after RFA. The baseline characteristics of patients with and without local recurrence were listed in Table 1. Ninety-four patients received subsequent treatments of local recurrence, including 62 who underwent repeated RFA (same criteria as abovementioned), 6 TACE, 24 salvage resection, and 2 liver transplantation. The remaining 18 patients underwent conservative treatment owing to extrahepatic metastases, refusal of treatment, etc. (Fig. 1). We evaluated the outcomes of patients treated by salvage surgery (SS) (Fig. 2), RFA (Fig. 3), and TACE.

Treatment Selection of Local Recurrence

A panel discussion with our multidisciplinary treatment team including surgeons, radiologists, oncologists, and pathologists was performed to make a decision regarding the optimal treatment modality for local recurrence. RFA was recommended as the first choice for favorable local recurrence. The favorable local recurrence was defined as tumor size ≤5 cm, focality around prior ablation site, absence of macrovascular invasion, and located >5 mm from important structures (such as the bowel, bile duct, and liver capsule). TACE was an alternative treatment for patients with concurrent multiple or large intrahepatic metastases. When local non-surgery treatment was deemed infeasible or failed, salvage liver resection was recommended when liver function reserve was enough and all radiology-found tumors were located within one lobe; salvage liver transplantation was selected when other treatments were inapplicable in cases with poor liver function and small tumors within the liver. Systemic chemotherapy or other conservative treatments were used if multiple extrahepatic metastases occurred accompanied with local recurrence.

Treatment Outcomes and Follow-up

One month after the treatment of local recurrence, CECT and CEUS were both performed to evaluate the local efficacy.

Table 1 The baseline characteristics of patients at initial RFA

	Patients with local recurrence (n=112)	Patients without local recurrence (n=896)	P value
Age (year)[a]	54±12	55±11	0.826
Gender			
Male	99	807	0.580
Female	13	89	
Etiology			
HBV related	91	792	0.089
HCV related	6	26	
Others	15	78	
Primary/recurrent HCC	53/59	189/707	0.000
Serum total bilirubin (mol/L)[a]	16±9	17±9	0.812
Serum albumin (g/L)[a]	42±4	42±5	0.873
Prothrombin time (s)[a]	12.7±1.6	12.4±1.5	0.901
Platelet count (10^9/L)[a]	152±70	166±65	0.795
Child-Pugh class			
Class A	102	825	0.712
Class B	10	71	
MELD score	4.9±2.7	5.1±2.4	0.613
Serum AFP level (μg/L)			
≤20	45	423	0.059
21–200	21	101	
>200	46	372	
Maximum tumor size (cm)			
≤2.0	42	493	0.000
2.1–3.0	26	209	
>3.0	44	194	
Number of tumors			
1	49	406	0.754
>1	63	490	

[a] Mean±standard deviation

Complete response (CR) was defined as complete disappearance of target tumor due to curative surgery or complete radiological necrosis of treated lesion on CECT and CEUS. Tumor assessed as CR enters follow-up, and serum AFP, liver function, CECT, and CEUS were performed every 3 months. Local treatment was defined failure if CR was not achieved after three consecutive times of re-treatments. SS was defined failure if CR was not accomplished after first SS.

Statistical Analysis

Continuous variables were expressed as mean±standard deviation and compared by the Mann-Whitney U test or ANOVA test. Categorical variables were compared using the chi-square test (or Fisher's exact probability test where appropriate). The disease-free survival (DFS) rates and overall survival (OS) rates were estimated by Kaplan-Meier method and compared by log-rank test. Analysis of DFS rates was available for patients with CR after re-treatment. All the statistical analyses were carried out using SPSS version 16.0 (Chicago, IL, USA). A P value<0.05 was considered as statistical significant difference.

Results

Patients and Tumor Profile

Among the 94 patients, previous liver resection had been performed for 44 patients (44/94, 46.8 %). The initial tumor size in these patients was 7.1±3.0 cm (range, 2.4–12.8 cm). After a follow-up of 1 to 84 months, intrahepatic new recurrent HCC (mean size, 2.3±0.9 cm; range, 0.9–5.0 cm) were detected, and then treated by RFA. The remaining 50 patients with primary HCC (mean size, 3.1±1.1 cm; range, 0.9–4.9 cm) were initially treated by RFA. There was a significant difference of tumor size between patients with primary HCC and recurrent HCC (P=0.001) (Table 2).

The median time to local recurrence was 5 months (range, 1 to 49 months). At the time of the treatments for local recurrence, there were no significant differences in the Child's grading, preoperative serum bilirubin, serum albumin, and platelet count among the SS, RFA, and TACE groups. The tumor sizes of local recurrence in the SS and TACE groups were significantly larger than those in the RFA group (4.6 versus 2.6 cm for SS versus RFA, respectively, P=0.000; 5.0 versus 2.6 cm for TACE versus RFA, respectively, P=0.000).

Tumor Response to Treatment

Complete response (CR) after treatment of local recurrence was achieved in 82 patients. The treatment effectiveness was 87.2 % (82/94). In the SS group, curative treatment was achieved in all the patients. Six patients did not achieve CR after three sessions of RFA, and they were resorted to salvage resection and got CR. All the six patients in the TACE group did not achieve CR and did not resort to other therapies due to unresectable distal metastases in two, unresectable intrahepatic multiple recurrences in three, and poor liver function in one. Therefore, the CR rate of RFA for local recurrence was 82.4 % (56/68) but only 48 patients achieved CR after the first session of RFA. For the 12 patients without CR after repeated RFA, the tumor size was 3.8±2.1 cm, which was significantly larger than the remaining 56 patients (2.2±1.0 cm, P=0.022) (Table 3). The CR rate in the SS and TACE groups was 100 % (26/26) and 0 % (0/6), respectively.

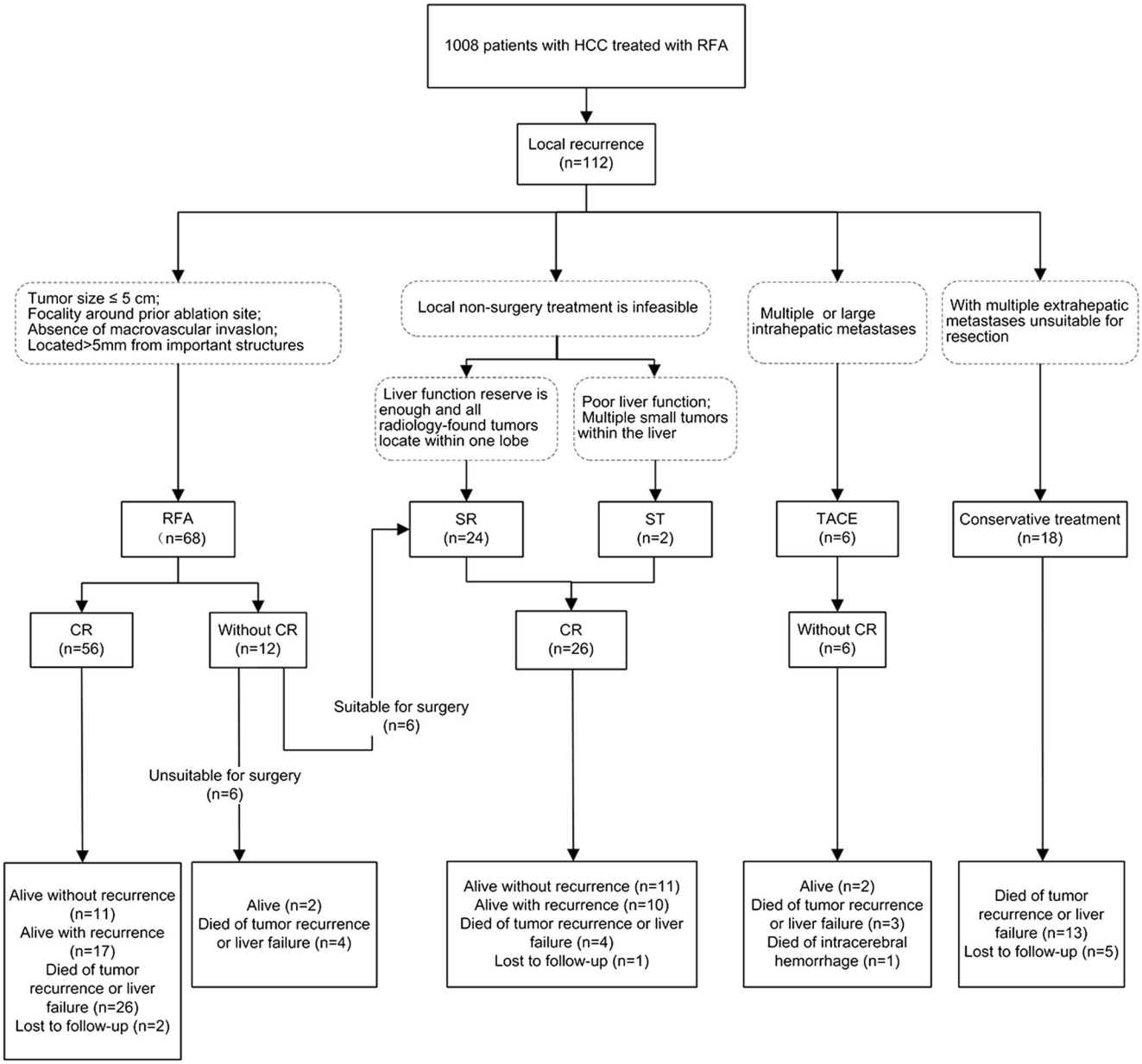

Fig. 1 Flow schematic for treatment of local recurrence after RFA

Follow-up

The median follow-up was 32 months. At the end of the follow-up, among the 82 patients with CR, 49 were still alive, including 22 who survived without recurrence, 30 patients died of tumor recurrence or liver failure, and 3 patients were lost to follow-up. Four of 12 patients without CR remained alive. Eight patients died of tumor recurrence (n=4), liver failure (n=3), and intracerebral hemorrhage (n=1), respectively.

During the follow-up, 60 out of 82 patients with CR after salvage treatment were detected with new recurrences. In the SS group, tumor recurrence was found in 15 of 26 patients, including 7 liver alone, 3 liver plus lymph node, 2 liver plus bone, 2 liver plus adrenal gland, and1 liver plus abdominal wall. In the RFA group, tumor recurrence was found in 45 of 56 patients, including 25 liver alone, 2 adrenal gland, 1 diaphragm plus adrenal gland, 1 bone, 5 liver plus lymph node, 2 liver plus lung, 3 liver plus lung plus lymph node, 2 liver plus abdominal wall, 3 liver plus bone, and 1 liver plus brain.

Survival Analysis After Salvage Treatment of Local Recurrence

After treatment, the 1- and 3-year OS rates were 85.2 and 58.6 % in all patients with CR (n=82), and 25.5 and 12.7 % in those without CR (n=12), respectively (P=0.000) (Fig. 4). When analysis was confined to patients with CR, the 1- and 3-

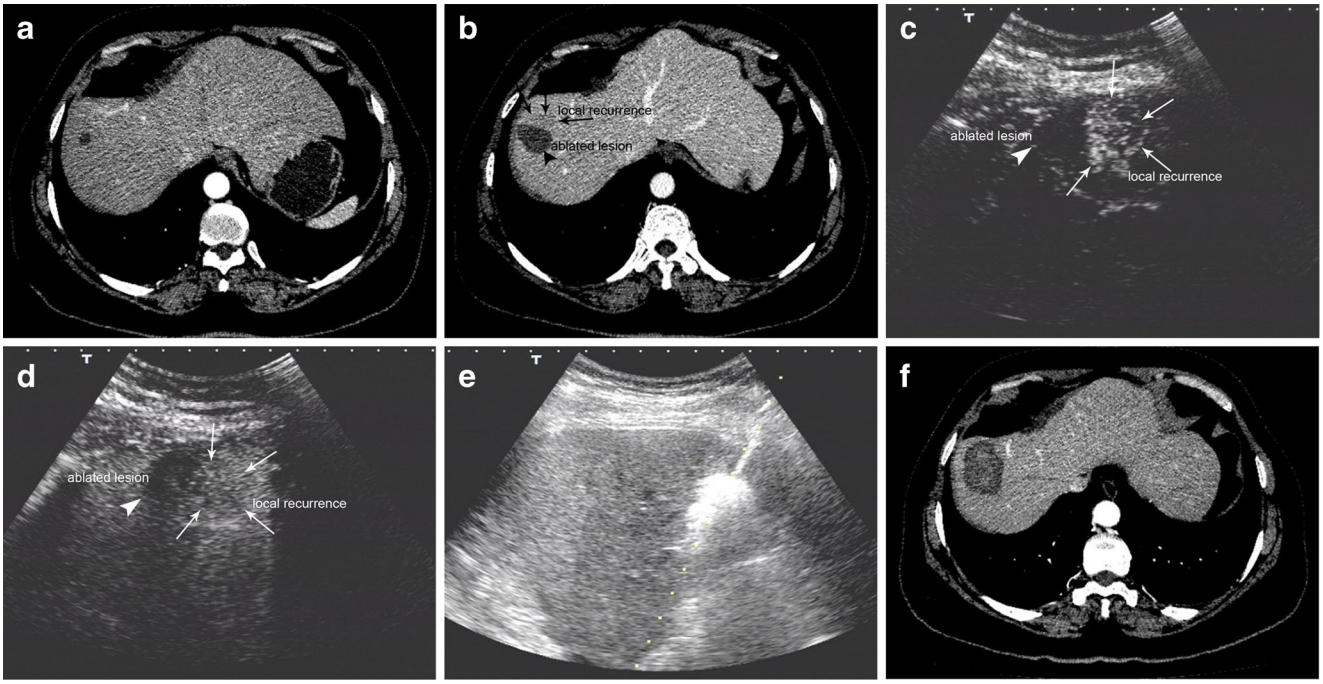

Fig. 2 A 55-year-old female patient with HCC who underwent repeated RFA for local recurrence at 6 months after initial RFA. **a** Transverse CT imaging before initial RFA showed the intrahepatic lesion. **b** Transverse CT imagings showed this ablated lesion (*black arrowhead*) and local recurrence (*black arrow*). **c** and **d** CEUS imagings showed this ablated lesion (*white arrowhead*) and local recurrence (*white arrow*) in arterial phase (**c**) and delayed phase (**d**). **e** RFA was performed for the local recurrence. **f** transverse CT imaging showed complete ablation after repeated RFA

year DFS rates were 57.7 and 20.2 % in the SS group, and 41.7 and 28.6 % in the RFA group, respectively (P=0.640) (Fig. 5a). The 1- and 3-year OS rates were 93.3 and 69.1 % in the SS group, and 78.6 and 57.5 % in the RFA group,

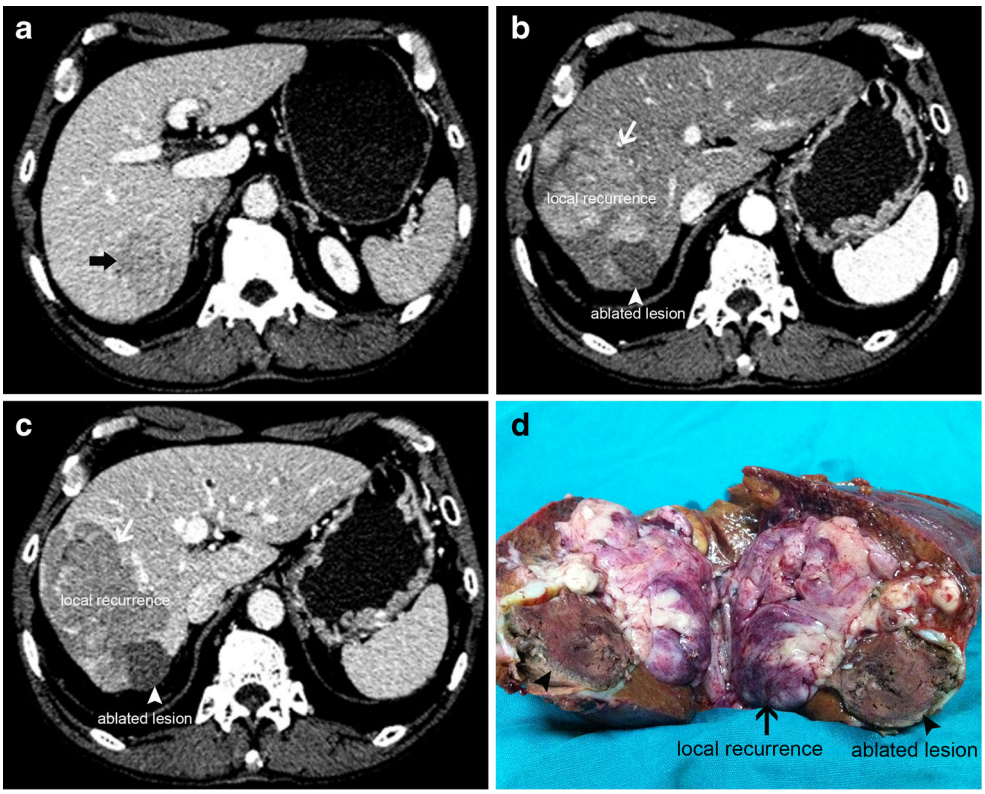

Fig. 3 A 62-year-old male patient with HCC who underwent salvage resection for the RFA-related local recurrence at 35 months after initial RFA. **a** Transverse CT imaging before initial RFA showed the intrahepatic lesion in right posterior section (*black arrow*). **b** and **c** Transverse CT imagings before salvage resection showed this ablated lesion (*white arrowhead*) and huge corresponding local recurrence (*white arrow*). **d** Dissected specimen showed the huge local recurrence (*black arrow*) at the periphery of the original ablated lesion (*black arrowhead*)

Table 2 Patient characteristics and tumor profile in patients who received subsequent treatments of local recurrence

	SS (n=26)	RFA (n=62)	TACE (n=6)	P value
Age (year)[a]	55±11	53±11	55±11	0.750
Gender				0.643
Male	23	54	6	
Female	3	8	0	
Initial treatment modality				0.006
Liver resection	6	35	3	
RFA	20	27	3	
Time to recurrence after initial treatment (month)[a]	15.4±15.9	10.7±14.7	7.7±9.2	0.309
Serum AFP level (μg/L)				0.243
≤20	12	23	0	
21–200	5	12	1	
>200	9	27	5	
HBV positive/negative	21/5	56/6	6/0	0.291
Serum total bilirubin (mol/L)[a]	15±5	16±8	21±5	0.539
Serum albumin (g/L)[a]	42±4	42±5	41±3	0.976
Prothrombin time (s)[a]	12.5±1.3	12.8±1.9	13.0±0.5	0.927
Platelet count (10^9/L)[a]	166±65	147±71	137±7	0.568
Child-Pugh class				0.979
Class A	25	59	6	
Class B	1	3	0	
Time to local recurrence				0.148
≤12mons	17	52	5	
>12mons	9	10	1	
Maximum tumor size (cm)[a]	4.3±2.1	2.3±1.1	5.0±2.7	0.000
Concurrent distal intrahepatic recurrence				0.073
Yes	10	12	3	
No	16	50	3	
Concurrent extrahepatic recurrences				0.012
Yes	7	3	1	
No	19	59	5	

SS salvage surgery, *RFA* radiofrequency ablation, *TACE* transarterial chemoembolization, *AFP* alpha-fetoprotein, *HBV* hepatic B virus

[a] Mean±standard deviation

respectively (P=0.251) (Fig. 5b). In the RFA group, there were no significant differences of OS rates between patients undergoing one single RFA and multiple ablation sessions for local recurrence (69.2 versus 81.3 % at 1 year, 49.5 versus 55.6 % at 3 years, P=0.443).

Subgroup Analysis in Patients Initially Treated by RFA

Among the 50 patients that were initially treated by RFA, 27 underwent repeated RFA for local recurrence, 20 underwent SS, and 3 underwent TACE. The OS rates were 85.2 and 52.6 % at 1 and 3 years, respectively, for patients after RFA, and 91.7 and 78.6 %, respectively, for patients after SS (P=0.374) (Fig. 6). The OS rates after TACE were not assessed due to insufficient patients.

Multivariate Analysis

We used multivariate analysis to evaluate the predictors for recurrence after initial or repeat RFA, and for failure RFA after repeat RFA. For patients after initial RFA, by univariate analysis, prothrombin time (P=0.002), serum albumin (P<0.001), platelet count (P=0.002), serum albumin (P<0.002), number of tumors (P<0.001), maximum tumor size (P<0.001), and AFP level (P<0.001) were associated with recurrence. Multivariate Cox proportional hazards regression analysis showed that serum albumin (HR=1.320; 95 % CI, 1.029–1.693; P=

Table 3 Patient characteristics and tumor profile for patients with failure RFA after repeat RFA

	Patients with failure RFA (n=12)
Age (year)	54±9
Gender	
Male	9
Female	3
Etiology	
HBV related	12
HCV related	0
Others	0
Primary/recurrent HCC	7/5
Serum total bilirubin (mol/L)	14±7
Serum albumin (g/L)	40±3
Prothrombin time (s)	12.5±1.5
Platelet count (10^9/L)	149±64
Child-Pugh class	
Class A	10
Class B	2
MELD score	4.5±2.3
Serum AFP level (μg/L)	
≤20	3
21–200	2
>200	7
Maximum tumor size (cm)	
≤2.0	1
2.1–3.0	2
>3.0	9
Number of tumors	
1	3
>1	9
Adjacent to vessels (≤0.5 cm)	
Yes	8
No	4

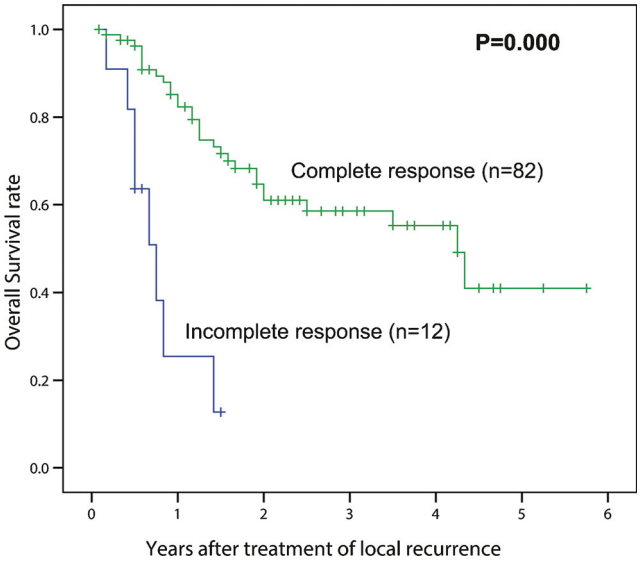

Fig. 4 Overall survivals in all the patients with and without complete response after salvage treatment of RFA-related local recurrence

0.029), number of tumors (HR=1.312; 95 % CI, 1.044–1.649; P=0.020), maximum tumor size (HR=1.449; 95 % CI, 1.125–1.866; P=0.004), and serum AFP level (HR=1.336; 95 % CI, 1.223–1.527; P<0.004) were significant prognostic factors recurrence after initial RFA (Table 4). For recurrence after repeat RFA, by univariate analysis, the number of tumors (P=0.037), maximum tumor size (P=0.045), and AFP level (P=0.044) were associated with recurrence. Multivariate Cox proportional hazards regression analysis showed number of tumors (HR=2.934; 95 % CI, 1.012–8.521; P=0.048) was the only significant prognostic factor for recurrence after repeat RFA (Table 5). For patients with failure RFA, number of tumors (P<0.001), maximum tumor size (P=0.01), and adjacent to vessels (P=0.003) were associated with failure RFA after repeat RFA. However, there was no predictor determined for failure RFA after repeat RFA by multivariate analysis (Table 6).

Discussion

The present study showed our experiences in treating local recurrence after RFA of HCC. Repeated RFA and SS showed comparable short-term and long-term treatment efficiency for RFA-related local recurrence. SS was still useful when RFA failed or was inapplicable. Response to treatment was the independent prognostic factor associated with the cumulative OS of patients with RFA-related local recurrence, as well as concurrent extrahepatic recurrence. The observed results provide useful evidence to select optimal treatment strategies for local recurrence after RFA.

RFA is safe and effective for managing small HCC, and its easy repeatability makes it particularly valuable for controlling intrahepatic recurrences after initial curative treatment.[15,16] However, the efficacy of repeated RFA for local recurrence has received little attention. Re-ablation of local recurrence after RFA is more difficult than that of initial HCC nodule, given that initial untreated tumor is usually oval in shape whereas local recurrence is mostly irregular. Therefore, multiple sessions and overlapping technique are usually required to treat local recurrence. Our study showed that in the majority of patients, the tumors were eradicated after repeated sessions, and the survival outcomes were similar to those achieved by SS. Besides, considering the risk and cost advantages, repeated RFA may be a more acceptable first-line treatment than surgery in patients with post-RFA local recurrence at favorable location.

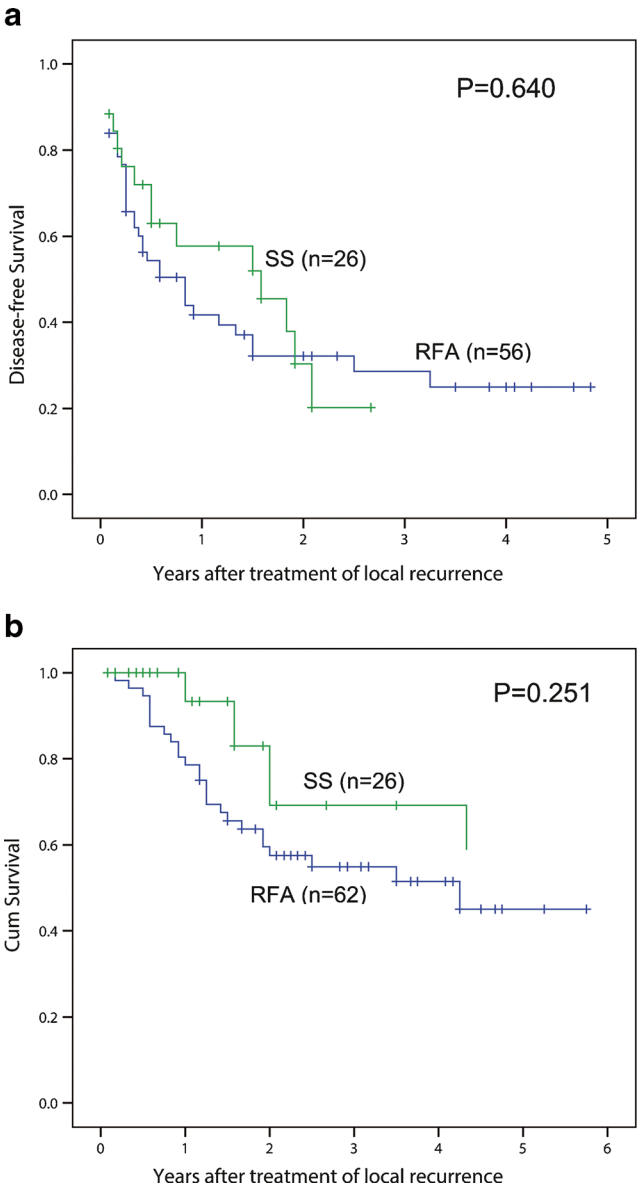

Fig. 5 Disease-free survivals (**a**) and overall survivals (**b**) in patients with complete response after RFA and SS for local recurrence

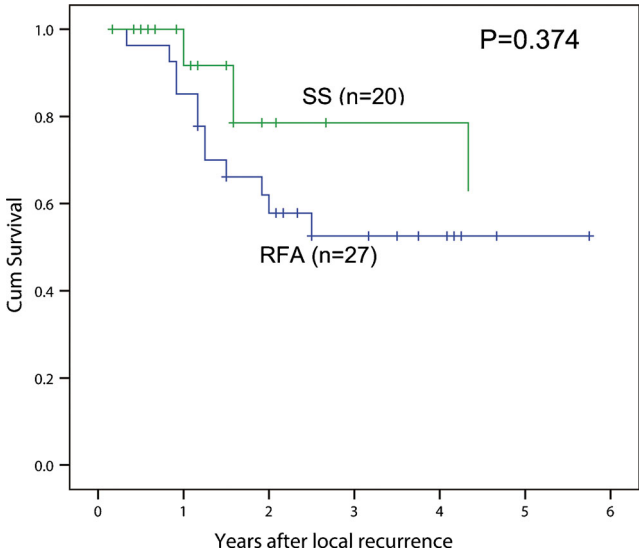

Fig. 6 Overall survivals in patients initially treated by RFA after repeated RFA and SS for local recurrence

Salvage liver resection for post-RFA recurrence is technically feasible.[7,12,17,18] Recently, Sugo et al.[7] reported that among the patients with local recurrence prior to undergoing RFA, the overall survival rates after salvage liver resection were 91, 91, and 67 % at 1, 3, and 5 years, which did not significantly differ from those after primary liver resection. Our study showed that the survival outcomes of patients that underwent salvage surgery seem better than those that underwent RFA treatments. Partial liver resection removes at least 1 cm of normal liver parenchyma together with the original tumor and thus eradicates both any locally recurrent tumor and venous tumor thrombi, and liver transplantation removes both tumor and cirrhotic liver. Moreover, surgery has benefits in treatment of concurrent resectable tumors, especially those unseen on preoperative images, which was found by laparotomy in nine cases in this study and eradicated by surgery. Therefore, SS is the most radical treatment for local recurrence. Another advantage of SS is that it is an effective salvage treatment option in cases where local ablation fails. In this study, initial RFA failed to eradicate local

Table 4 Univariate and multivariate analysis of predictors of recurrence after initial RFA

Factors	Univariate	Multivariate		
	P value	HR	95 % CI	*P* value
Gender (M/F)	0.062			
Age (years)	0.052			
Etiology (HBV/HCV/other)	0.087			
Child-Pugh (A/B)	0.562			
Platelet count (109/L)	0.004			
Prothrombin time (s)	0.002			
Serum albumin (g/L)	<0.001	1.320	1.029–1.693	0.029
ALT (IU/L)	0.550			
Serum total bilirubin (mol/L)	0.489			
Number of tumors (n)	<0.001	1.312	1.044–1.649	0.020
Maximum tumor size (cm)	<0.001	1.449	1.125–1.866	0.004
MELD score	0.220			
Serum AFP level (ng/mL)	<0.001	1.336	1.223–1.527	<0.001
Primary/recurrent HCC	0.054			

Table 5 Univariate and multivariate analysis of predictors of recurrence after repeat RFA

Factors	Univariate	Multivariate		
	P value	HR	95 % CI	*P* value
Gender (M/F)	0.406			
Age (years)	0.775			
Etiology (HBV/HCV/other)	0.266			
Child-Pugh (A/B)	0.177			
Platelet count (109/L)	0.862			
Prothrombin time (s)	0.879			
Serum albumin (g/L)	0.216			
ALT (IU/L)	0.490			
Serum total bilirubin (mol/L)	0.421			
Number of tumors (n)	0.037	2.934	1.012–8.521	0.048
Maximum tumor size (cm)	0.045			
MELD score	0.675			
Serum AFP level (ng/mL)	0.044			
Primary/recurrent HCC	0.09			

Table 6 Univariate and multivariate analysis of predictors for failure RFA after repeat RFA

Factors	Univariate	Multivariate		
	P value	HR	95 % CI	*P* value
Gender (M/F)	0.320			
Age (years)	0.451			
Etiology (HBV/HCV/other)	0.980			
Child-Pugh (A/B)	0.538			
Platelet count (109/L)	0.746			
Prothrombin time (s)	0.294			
Serum albumin (g/L)	0.876			
ALT (IU/L)	0.500			
Serum total bilirubin (mol/L)	0.756			
Number of tumors (n)	<0.001	–	–	–
Maximum tumor size (cm)	0.01	–	–	–
MELD score	0.356			
Serum AFP level (ng/mL)	0.056			
Primary/recurrent HCC	0.082			
Adjacent to vessels (≤0.5 cm)	0.003	–	–	–

recurrence in six patients, which were solved by the subsequent SS. Therefore, appropriate selection of SS in HCC patients with post-RFA local recurrence may help improve the whole prognosis.

Up to now, there was only one study comparing different treatment strategies for local recurrence after prior ablation.[19] It was reported that there was no significant difference of DFS rates and OS rates between the salvage resection group (n=23) and the RFA group (n=27) in the study. Therefore, they concluded that salvage hepatectomy for local recurrent HCC is recommended for selected patients in terms of its good local control effect, and salvage RFA is acceptable because it is less invasive and also has a reasonable long-term outcome. However, 24 of 50 patients in the study (24/50, 48 %) received prior ablation in the other institutions, which might make the indication for initial ablation treatment unclear. The present study showed similar results between the SS group and RFA group performed by the same medical group.

Theoretically, liver transplantation probably produces the best survival outcome because it simultaneously cures the tumor and the underlying cirrhosis. It is deemed that salvage liver transplantation is an efficacious treatment for patients with recurrent HCC, with a comparable survival to repeated resection.[20,21] Two patients underwent salvage liver transplantation for post-RFA local recurrence in the present study and both were alive without recurrence at the end of follow-up. Salvage liver transplantation seems to be a potential treatment option when salvage liver resection is not feasible. However, the number of patients was too small in this study and more cases are required to provide a whole picture.

Although TACE is a common interventional treatment for unresectable HCC, the clinical effectiveness for post-RFA local recurrence is unclear. In the current study, the treatment outcome of TACE alone for RFA-related local recurrence was unsatisfied. None of the patients could achieve CR after TACE. Some possible explanations are as follows: First, TACE is effective for hypervascular HCC supplied by arterial blood. However, most RFA-related local recurrences are hypovascular due to destruction of intra- and peri-tumor vessels by prior ablation. Second, tumor size in the TACE group was much larger than those in other groups, which may influence the results because of selection bias. Third, the number of TACE cases was too small. We suggested that TACE alone as a palliative treatment may not be suitable for post-RFA local recurrence but more cases are required to draw a solid conclusion.

As demonstrated by our results, patients with complete response after salvage treatment showed significantly better overall survival than those with incomplete response. Tumor response is a prognostic factor associated with cumulative OS after treatments of local recurrence. Such a view has been recently supported by results of Lam et al.[10] obtained from a small series of patients. Therefore, in order to increase long-term survival, subsequent treatment for local recurrence should achieve a really complete response.

There are several limitations in the present study. First is the bias of patients' selections and choices of treatment. There is a mix of patients with primary HCC and recurrent HCC after liver resection in our study. Moreover, the patients in the RFA group were characterized primarily by their impaired liver function reserve in comparison with the SS group. The patients in the SS group and TACE group had more advanced and aggressive tumors. These differences might have affected treatment outcome of the patients with RFA-related local recurrence. Secondly, this is a retrospective data analysis from one single institution. Thirdly, the number of patients in the TACE group was relatively small.

In conclusion, we demonstrated that re-treatments with complete response improve the survival of patients with RFA-related local recurrence. Repeated RFA is the first choice for patients with favorable local recurrence. Salvage surgery should be considered when RFA fails or is inapplicable. TACE has poor treatment efficacy and should not be applied alone.

Conflicts of Interest The authors have no conflict of interest to declare in connection with this study.

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