

A clinical study on salvage hepatectomy for treating recurrent liver cancer after radiofrequency ablation

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Abstract

Objective We studied the efficacy of salvage hepatectomy for treating recurrent hepatic cancer after radiofrequency ablation (RFA).

Methods A retrospective analysis of 67 patients who had recurrent liver cancer after RFA treatment and received salvage hepatectomy in the Department of Hepatobiliary Surgery, Southwest Hospital, Third Military Medical University (China), from January 2006 to January 2014, was performed. The analysis included patient gender, age, hepatitis type, alpha-fetoprotein (AFP), and TNM stage prior to RFA and salvage hepatectomy, overall survival rates, and tumor-free survival rates after salvage hepatectomy.

Results Among the 67 patients, there were 57 cases of hepatitis B, two cases of hepatitis C, and eight cases did not have hepatitis. AFP levels in patients ranged from 3 to 4521 ng/mL (median 33 ng/mL). Before RFA, 54 cases were stage I tumors, and 13 were stage II tumors. Tumor sizes varied from 0.82 to 4.83 cm (median 3.0 cm). In 20 cases, one RFA was performed, and for 47 cases, RFA was repeated. RFA-ablated region diameters ranged from 3.8 to 5.2 cm (median 4.5 cm). The interval between the salvage surgical resection and RFA was 3–37 months. Before salvage hepatectomy, 23 stage I tumors, 12 stage II tumors, and 32 stage III tumors were present (size ranged 4.83–11.84 cm; median 6.3 cm). For salvage hepatectomy, laparotomy was performed for 56 cases, and laparoscopy was performed for 28 cases. Inflow clamping was performed for 39 cases (15–45 min). Surgery was 219–370 min and intraoperative blood loss was 100–2100 mL. For 13 cases, intraoperative blood transfusion was required. Tumor pathological data revealed 31, 35, and 1 poorly, moderately, and well differentiated tumors, respectively. No patients died due to operative complications, and hospital stays were 8–10 days. Overall and tumor-free survival rates were 85% and 79% for 1 year, 50% and 20% for 3 years, and 39% and 19% for 5 years, respectively. Kaplan-Meier analysis and Cox regression confirmed that tumor number and size prior to salvage liver cancer were risk factors affecting survival.

Conclusion Patients who received RFA to treat early-stage liver cancer with postoperative recurrent stage I tumors have satisfactory outcomes with salvage hepatectomy.

Key words: liver cancer; radiofrequency ablation (RFA); salvage hepatectomy

Received: 29 June 2015
Revised: 26 July 2015
Accepted: 25 October 2015

Primary liver cancer is one of the most common malignant tumors, and it is the third most common type of cancer in China [1]. With advances in diagnostic imaging technology and optimization of medical examinations for high-risk populations, small liver cancer is being diagnosed more efficiently than it was previously, and many treatments are available, such as liver transplantation, partial hepatectomy and transarterial chemoembolization (TACE), radiofrequency ablation (RFA), and percutaneous ethanol injection [2]. RFA is a common method for treating liver cancer and, compared with traditional surgery, is less traumatic, offers more effective and rapid re-

covery, and is a simple operation. For treating liver cancer with tumor diameters less than 3 cm, RFA has almost replaced traditional resection surgery [2–3]. However, the high tumor recurrence rate after RFA decreases its efficacy. Clinical studies in both China and other countries [4] have shown that for treatment of small liver cancer, the 3–5 years overall survival rate after RFA is not significantly different from that after surgical resection, but the tumor-free survival rate after RFA is still relatively low likely due to high rates of tumor recurrence (local recurrence rate within 1 year, 15%–36%). Tumor recurrence is associated with incomplete tumor necrosis, i.e.,

the resurgence of residual cancer.

Surgical resection has traditionally been the most common means for treating primary liver cancer. Radical resection can often improve patient quality of life and prolong lives, and the overall postoperative survival and tumor-free survival rates are higher compared to other forms of treatment (chemotherapy, TACE, etc.) [5]. Long-term clinical data and other studies have indicated that for some cases of small liver cancer, surgical treatment is curative [6]. However, in clinical practice, different criteria used by different physicians for surgical resection of small liver cancer give rise to differences in efficacy. Further, the large amount of tissue being removed during resection, along with patient intolerance to continuous postoperative treatment and a high likelihood of serious postoperative complications, all contribute to infrequent utilization of surgical resection. To address this issue, we studied patients with recurrent liver cancer after RFA treatment who received salvage hepatectomy to better understand how these interventions can be best used.

Materials and methods

Clinical information

A retrospective analysis was performed on 67 patients with recurrent liver cancer after RFA who received salvage hepatectomy in the Department of Hepatobiliary Surgery, Southwest Hospital, Third Military Medical University (China), from January 2006 to January 2014. In all cases, RFA was completed by an experienced RFA expert and an experienced ultrasound specialist. Preoperative alpha-fetoprotein (AFP) level, tumor size and number, number of RFAs, and the RFA-ablated lesion size were recorded. Salvage hepatectomy for treating recurrent tumor after RFA was performed by 1–2 experienced surgeons in the Department of Hepatobiliary Surgery. Prior to surgery, using enhanced CT or ultrasound imaging the number and size of the recurrent tumors and tumor stage (stage I: T1N0M0, stage II: T2N0M0, stage III: T3aN0M0, T3bN0M0 and T4N0M0; for stage IV, due to the presence of metastasis, palliative treatment was provided, and these patients were not included in the study), were determined. Laparotomy or a laparoscopic approach was used for the resection. According to location and size of the recurrent tumor, partial hepatectomy, right hemihepatectomy, left hemihepatectomy or extended hemihepatectomy was performed. Operation time, duration of inflow clamping, and the amount of intraoperative blood loss were recorded. The resected tumor tissue was sent for pathological examination, and the degree of tumor cell malignancy was recorded. After the hepatectomy was completed, the patient was observed in the intensive care unit of the Department of Hepatobiliary Surgery, and returned to the general ward after stabilization.

Follow-up after the salvage hepatectomy for RFA recurrent tumor

During the first 3 months after RFA, all patients underwent monthly follow-up examinations including ultrasonography or contrast-enhanced CT of the upper abdomen. Further, AFP and liver function were measured and routine blood tests were performed. All patients received monthly telephone follow-up interviews thereafter.

Results

Clinical information

Patient information was given in Table 1 in addition to tumor stages and the number of RFA procedures performed. Surgical resection was performed to treat recurrent tumors after RFA, and Table 1 depicted the interval between hepatectomy and RFA, tumor stages and sizes prior to salvage hepatectomy. Laparotomic and/or laparoscopic hepatectomy was performed and Table 1 showed the frequency and timing of these procedures as well as those for inflow clamping, surgical duration and intraoperative blood loss. For 13 cases, intraoperative blood transfusion was performed. Pathology data for tumor differentiation and details regarding the length of stay in the hospital were given in Table 1. No deaths were attributed to postoperative complications during hospitalization.

Factors influencing overall survival and tumor-free survival rates after salvage hepatectomy (Fig. 1 and Table 2)

Among the 67 patients who had local recurrences of liver cancer after RFA and underwent salvage hepatectomy, 56 survived after 1 year (overall survival rate 85%), and 52 had tumor-free 1-year survival (rate of 79%) and

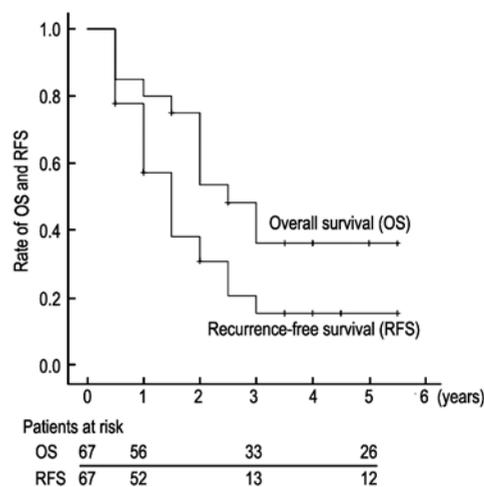


Fig. 1 Overall and recurrence-free survival rates from the time of salvage hepatic resection to recurrence of hepatocellular carcinoma after radiofrequency ablation

Table 1 Characteristics of patients after salvage hepatic resection for recurrence of hepatocellular carcinoma after radiofrequency ablation [*n* (%)]

Features	No.
Sex	
Male	56 (83.6%)
Female	11 (16.4%)
Age (years)*	56 (38–78)
Hepatitis-B	57 (85.1%)
Hepatitis-C	2 (3.0%)
Hepatitis non-B and non-C	8 (11.9%)
AFP (ng/mL)*	33 (< 100–4521)
TNM before RFA	
I	54 (80.6%)
II	13 (19.4%)
Maximum size of tumors before RFA (cm)*	3.0 (0.82–4.83)
RFA	
No. of RFA	
Single	20 (29.9%)
Multiple	47 (70.1%)
Maximum diameter of ablation (cm)*	4.5 (3.8–5.2)
The time to recurrence after RFA (month)*	17 (3–37)
TNM of tumors before salvage resection	
I	23 (34.3%)
II	12 (17.9%)
III	32 (47.8%)
Maximum size of tumors before salvage resection (cm)*	6.3 (4.83–11.84)
Salvage hepatic resection	
Operation	
Laparotomy	56 (83.6%)
Laparoscopic	11 (16.4%)
Inflow clamping	
Yes	39 (58.2%)
No	28 (41.8%)
Inflow clamping time (min)*	30 (15–45)
Hepatectomy	
Local	31 (46.3%)
Left	11 (16.4%)
Right	21 (31.3%)
Over half	4 (6.0%)
Duration of operation (min)*	312 (219–370)
Intraoperative blood loss (mL)*	780 (100–2100)
Blood transfusion	
Yes	13 (19.4%)
No	54 (80.6%)
Grade	
Poor	31 (46.3%)
Moderate	35 (52.2%)
Well	1 (1.5%)
Death	0 (0%)
Hospital stay (day)*	10 (8–14)

* Values were means (median, range). HCC: hepatocellular carcinoma; RFA: radiofrequency ablation; AFP: alpha-fetoprotein

33 survived after 3 years (overall survival rate 50%). For

13 patients, tumors did not recur (3-year tumor-free survival rate 21%). After 5 years, 26 survived (overall survival rate 39%). For 12 patients, no tumor recurred (5-year tumor-free survival rate 19%). Analysis of all patient data revealed that only TNM tumor stage prior to salvage hepatectomy had a significant effect on the overall survival rate ($P < 0.01$; Table 2).

Discussion

We present a clinical study on 67 patients who had recurrent liver cancer after RFA and received salvage hepatectomy. The efficacy of salvage hepatectomy for treating recurrent stage I liver cancer after RFA is relatively satisfactory. For patients with early-stage liver cancer, only radical treatments offer the best outcomes, and these methods include surgical resection, liver transplantation, and ablation [7]. Often, liver transplantation is limited due to severe donor shortage, but with surgical resection, a good prognosis can be achieved. However, few patients are suitable candidates for surgical treatment, and most patients cannot undergo resection owing to multiple tumors, concomitant cirrhosis, liver dysfunction, and other conditions [8]. Several clinical retrospective studies indicate that RFA is similar to surgical resection. For patients who temporarily cannot undergo hepatectomy owing to liver dysfunction, financial difficulty, or other reasons, RFA can be performed to prevent progression of liver cancer, and surgical resection can be performed when conditions are appropriate [9].

Few reports are available that depict salvage hepatectomy for treating recurrent small liver cancer after RFA. Torzilli's group [10] compared 21 cases of liver resection to treat recurrent liver cancer after percutaneous RFA and 116 cases of simple surgical resection to treat liver cancer. They reported that patients who underwent surgical resection after RFA had more tissues removed during surgery, a higher rate of tumor micrometastasis through blood vessels, and lower 1- and 2-year survival rates. In addition, after RFA treatment of liver cancer, tumor invasion was more aggressive than that they had not RFA treatment.

Here we report factors that influence 1-, 3-, and 5-year overall and tumor-free survival rates according to Kaplan-Meier and Cox regression analysis. Other studies have reported that patients were hepatitis C or hepatitis free. However, most of our patients had a hepatitis B background. N'kontchou and colleagues [11] conducted a retrospective cohort study in which 67 liver cancer patients who met the Milan criteria underwent percutaneous RFA as a first treatment, and then salvage liver transplantation was performed if recurrence or liver failure occurred during the follow-up. They reported that for Child stage A hepatocellular carcinoma patients who met

Table 2 Univariate and multivariate analyses of overall survival after salvage hepatic resection for recurrence of hepatocellular carcinoma after radiofrequency ablation (n)

	n	Survival (%)*		Univariate**		Multivariate***	
		3 years	5 years	Hazard ratio	P	Relative risk (95% CI)	P
All patients	67	50	39				
Sex							
Male	56	57	32		0.84		
Female	11	55	29				
Age (years)							
≥ 50	39	52	36		0.08		
< 50	28	58	38				
Hepatitis							
B	57	51	35		0.11		
C	2	45	21				
Non-B, non-C	8	60	41				
AFP (ng/mL)							
≥ 400	46	56	21		0.34		
< 400	21	52	39				
TNM of tumors before RFA							
I	54	67	39		0.82		
II	13	44	24				
Maximum size of tumors before RFA (cm)							
≥ 3	21	42	21		0.57		
< 3	46	65	37				
TNM of tumors before salvage resection							
I	23	69	43	1.51 (1.12–2.67)	< 0.01	2.05 (1.12–3.75)	0.02
II	12	41	11				
III	32	21	9				
Maximum size of tumors before salvage resection (cm)							
≥ 5	45	40	12	1.22 (0.89–2.44)	0.02	1.78 (1.02–3.10)	0.04
< 5	22	70	45				
Operation method							
Laparotomy	56	51	30		1.00		
Laparoscopic	11	49	24				
Hepatectomy							
Local	31	60	38		0.68		
Right	21	45	21				
Left	11	58	41				
Over half	4	21	9				
Grade							
Poor	31	44	21		0.12		
Moderate	35	63	46				
Well	1	100	0				

*: Kaplan-Meier analysis; **: Log rank test; ***: Cox regression model; HCC: hepatocellular carcinoma; RFA: radiofrequency ablation; AFP: alpha-feto-protein

Milan criteria, the survival curve obtained with the two-step strategy was no worse than that obtained with liver transplantation as the first treatment. This two-step strategy also helps to alleviate the serious donor liver shortage. Another study documented use of TACE combined with percutaneous RFA for unresectable liver cancer, but because liver cancer is often complicated by cirrhosis and repeated TACE procedures can further damage liver function and aggravate cirrhosis, a considerable portion

of liver cancer patients who had tumors under control or had positive treatment effects eventually died of liver failure or gastrointestinal bleeding caused by cirrhosis [12]. Zhang's group [13] reported that in the treatment of liver cancer patients, the RFA and surgical re-resection groups had similar recurrence rates. They also emphasized that patients undergoing RFA did not require blood transfusion and had significantly shorter hospital stays compared with patients undergoing surgical re-resection, and that

RFA was minimally invasive and highly reproducible. Thus, RFA is more suitable for treating patients with recurrent liver cancer than surgical re-resection.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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DOI 10.1007/s10330-015-0111-y

Cite this article as: Xiong Q, Feng XB, Yan J, *et al.* A clinical study on salvage hepatectomy for treating recurrent liver cancer after radiofrequency ablation. *Oncol Transl Med*, 2015, 1: 256–260.