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ORIGINAL ARTICLE

Long-term efficacy of radiofrequency ablation compared to surgical resection for the treatment of small hepatocellular carcinoma

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Summary

Purpose: *To compare the clinical efficacy of surgical resection (SR) and radiofrequency ablation (RFA) for the treatment of small hepatocellular carcinoma (SHC; ≤5 cm in diameter).*

Methods: *The clinical and follow-up data for 88 patients with SHC, including 42 cases of SR and 46 cases of RFA, were analyzed.*

Results: *The mean follow-up time was 34.36±16.93 (range 6-72) months. The 1-, 3- and 5-year tumor-free survival rates were 85.4, 40.9, and 29.2% for the SR group and 82.6, 27.7, and 16.4% for the RFA group (p=0.51). The mean tumor-free survival for the SR and RFA groups was 32.78 and 29.39 months (p=0.51), respectively. The cumulative survival rates were 100. 63.7, and 50.4% for the SR group and 100, 66.3 and 37.4% for the RFA group (p=0.67). The average survival time was 50.78 and 47.62 months (p=0.67) for the SR and RFA groups, respectively. We divided the tumors into a ≤3 cm diameter group and a 3-5 cm diameter group and found that the data for both groups were not statistically different. Cox multivariate analysis indicated that the number of tumors significantly affected overall survival (p=0.02) after the effects of various factors were excluded. The overall tumor-free survival and overall survival of the SR and RFA groups were not statistically different.*

Conclusions: *RFA is safe and effective for the treatment of SHC, with a long-term efficacy similar to that achieved by SR. Therefore, RFA is a preferred treatment method for SHC.*

Key words: *hepatocellular carcinoma, radiofrequency ablation, surgical resection*

Introduction

Primary liver cancer is one of the most frequent malignancies worldwide, and its incidence rate has increased in recent years [1,2]. Patients are typically diagnosed at an advanced stage due to the vague symptoms associated with the disease. Although SR has long been considered the preferred method for liver cancer treatment (because of the post-SR stability of the patient), some patients are either unable or not willing to undergo surgery for various reasons. Liver transplantation technology has advanced in recent years and the number of such cases has increased. Although this method has the potential to be curative, it cannot be performed on many patients because of the severe shortage of liver donors and the high costs associated with liver transplantation. Thus, there are multiple possible treatments for liver cancer and the current approach involves inte-

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Table 1. Comparison of general characteristics of the 2 groups

Characteristics	*SR group (42 cases) N (%)*	*RFA group (46 cases) N (%)*	*p value*
Age, years (mean±SD)	53.93±10.74	55.89±7.37	0.317
Gender (male/female)	36/6	40/6	0.856
Tumor lesions			0.278
1	38 (90.48)	38 (82.61)	
2	4 (9.52)	8 (17.39)	
Tumor size (cm)			0.328
<3	14 (33.33)	20 (43.48)	
3-5	28 (66.67)	26 (56.52)	
Accompanied with cirrhosis			0.417
Yes	38 (90.48)	39 (84.78)	
No	4 (9.52)	7 (15.22)	
Grade of liver function			0.001
A	36 (85.71)	25 (54.35)	
B	6 (14.29)	21 (45.65)	
Serum AFP (μg/L)			0.798
≤20	20 (47.62)	20 (43.49)	
20-400	16 (38.09)	17 (36.95)	
≥400	6 (14.29)	9 (19.56)	

grating the various therapies [3-6], which include interventional chemotherapy [7]. A variety of focal ablation therapies have been shown to be effective treatments for primary liver cancer, including dehydrated ethanol injection, microwave ablation and RFA [8-10]. RFA has been widely applied in recent years. There has been an increasing number of studies that have validated the clinical efficacy of RFA and demonstrated an improved prognosis for patients with SHC who are treated with RFA therapy. A comparison of SR and RFA for the treatment of SHC is of particular interest given the conflicting conclusions regarding the efficacy of these therapies. Additional studies are therefore required [11-17].

We performed a retrospective analysis of the clinical data and the prognosis of patients who were put under long-term follow-up after RFA or SR treatment for primary liver cancer. We aimed to compare the clinical efficacy of both methods and to provide a basis for the clinical diagnosis and treatment of primary liver cancer. Initially, we collected data for tumors with diameters ≤5 cm, but during the analysis, a diameter 3 cm was used as the boundary for a subgroup comparison. We hypothesized that an objective comparison of RFA and SR after large-scale, long-term studies would result in identification of the best treatment options for different patients.

Methods

General information

We selected 88 SHC patients who were treated in our center from June 2002-March 2010. In this study, we analyzed tumors with diameters ≤5 cm. We further analyzed the data by subdividing them into two groups: a <3 cm and a 3-5 cm group. Diagnosis of primary liver cancer was confirmed for all patients based on two or more radiographic or pathological findings. The whole group was followed for 6-72 months (mean 34.36±16.93). A comparison of the general information for the two study groups is shown in Table 1.

This study was conducted in accordance with the declaration of Helsinki and after approval from the Ethics Committee of Shandong University. Written informed consent was obtained from all participants.

Methods

An abdomen-opening surgery under general anesthesia was performed in the SR group. Within this group, a regular anatomic liver resection, segmentectomy, was performed in 25 cases, and an irregular non-anatomic liver resection, non-segmentectomy, or tumor resection alone was performed in 17 cases. Intraoperative hepatic inflow occlusion was performed depending on the circumstances, such as bleeding difficult to control.

A RITA®1500X RF Generator (RITA Medical Systems, Inc., Mountain View, CA, USA) was used for RFA.

Percutaneous punctures were performed in 45 cases. B-mode ultrasound guidance was used in 41 of these cases, computed tomography (CT) guidance was used in 2 cases, laparoscopic guidance was used in 2 cases, and RFA was performed under direct vision after laparotomy in 1 case. Percutaneous RFA was performed with local intravenous anesthesia. General anesthesia methods were used in the laparoscopic or laparotomic RFA groups.

General and intraoperative conditions for each individual patient were carefully recorded. Postoperative liver function, alpha-fetoprotein (AFP), B-mode ultrasound, and CT results were reviewed every 3 months. In terms of ultrasound and CT image assessment of patients in the RFA group, a complete ablation was defined as the presence of low-density residual lesions, without enhancement of the arterial phase and blood flow within the lesions as evidenced by a B-mode ultrasound. If no complete ablation was achieved, the treatment was repeated in order to achieve complete ablation.

Recurrences were defined as local or distant at the end of 1, 3, and 5 years. Liver cancer-related deaths were the endpoint during follow-up.

Statistics

Data were compared using chi-square test, and the initial tumor clearance was compared using Fisher's exact test. The tumor-free survival and the overall survival rates were estimated using Kaplan-Meier method with log-rank test. Multivariate Cox regression analysis was used to identify independent factors in the two treatment groups. A two-sided $p<0.05$ was considered statistically significant.

Results

Intraoperative and perioperative conditions in the SR group

No intraoperative anesthesia-related complications were observed in the 42 cases that comprised the SR group. The tumor clearance rate after surgical excision was 100% (42/42 cases). The pathology results confirmed the diagnosis of hepatocellular carcinoma and that the tumor tissue did not involve the cutting edge. There were no operation-related deaths. However, pain (42/42;100%) and fever of varying degrees (27/42;88.10%) were observed. The complication rate was 23.81% (10/42). Abdominal bleeding occurred in 1 (2.38%) case, small pleural effusion in 3 (7.14%), subphrenic effusion in 2 (4.76%), gastrointestinal bleeding (fecal occult blood) in 1 (2.38%), cardiac dysfunction and pulmonary congestion accompanied by sinus bradycardia in 1 (2.38%) and subcutaneous fat liquefaction was observed in 1 (2.38%) case.

Conditions in the RFA group

There were no intraoperative anesthesia-related complications in the 46 cases that comprised the RFA group. During the percutaneous puncture procedure, no bleeding occurred and thus no blood transfusions were needed. Similarly, no patient with laparoscopy and laparotomy needed blood transfusions. Complete ablation was achieved in 40 (86.96%) cases and incomplete ablation in 6 (13.04%). Residual lesions were promptly replenished and complete ablation was achieved. There was a significant difference in the initial tumor clearance between the two groups (Fisher's exact test, two-sided $p=0.03$). Puncture biopsies and pathological data confirmed the diagnosis of hepatocellular carcinoma in 33 (71.74%) cases, while preoperative diagnosis of primary liver cancer was confirmed in the other 13 (28.26%) cases. This was followed by interventional angiography or by the tumor malignant biological behavior such as recurrence or metastasis during the postoperative follow-up period. There were no procedure-related deaths. Fever occurred in 34 (73.91%) cases and moderate pain 1-7 days after the procedure occurred in 26 (56.52%) cases. The complication rate was 17.39% (8/46). Small amount of pleural effusion was observed in 4 (8.70%) cases and perihepatic effusion in 2 (4.35%) cases. Postoperative intra-abdominal hemorrhage was observed in 1 (2.17%) in which laparoscopic RFA was performed; the case was treated conservatively without blood transfusion. Also, one case developed mild burns at the sites of the electrode plates. There was no statistically significant difference in the incidence of complications between the two groups ($x^2=0.56$, $p=0.46$).

Long-term efficacy

The mean follow-up time for the SR group was 32.33 months (range 6-72), during which recurrence occurred in 22 (52.38%) cases. Local recurrence occurred in 4 cases (9.52%), while intrahepatic recurrence occurred in 18 (42.86%) cases. Within these 18 cases of intrahepatic recurrence, pulmonary metastasis occurred in 3 cases and bone metastasis in one.

The mean follow-up time for the RFA group was 36.22 months (range 9-67), during which 32 (69.57%) cases developed recurrence. Local recurrence occurred in 7 (15.22%) cases, while intrahepatic recurrence occurred in 25 (54.35%) cases. Of the 25 cases with intrahepatic recurrence lung metastasis occurred in 4 cases, while bone metas-

Table 2. Comparison of tumor-free survival rates according to tumor size and treatment method

Tumor size (cm)	*Treatment method*	*Patients N*	*Mean tumor-free survival (months)*	*Tumor-free survival (%)*			x^2	*p value*
				1-year	*3-year*	*5-year*		
0-5	SR	42	32.78±25.50	85.4	40.9	29.2	0.44	0.51
	RFA	46	29.39±21.20	82.6	27.7	16.4		
<3	SR	14	36.48±23.42	85.7	62.5	37.5	0.45	0.50
	RFA	20	33.64±23.73	85.0	37.4	29.9		
3-5	SR	28	31.45±25.24	85.7	30.6	30.0	0.31	0.58
	RFA	26	26.95±19.27	80.8	21.8	10.9		

SR: surgical resection, RFA: radiofrequency ablation

Table 3. Multivariate Cox regression analysis of different factors possibly influencing tumor-free survival

Factors	*B*	*df*	*Sig.*	*95% CI for Exp (B)*	
				Lower	*Upper*
Treatment method	0.053	1	0.867	0.567	1.961
Gender	-0.472	1	0.334	0.239	1.625
Age	-0.020	1	0.265	0.947	1.015
No of tumor lesions	0.391	1	0.360	0.640	3.416
Cirrhosis	-0.593	1	0.257	0.198	1.542
Liver function	0.411	1	0.222	0.780	2.917
AFP	0.096	1	0.641	0.735	1.648
Tumor diameter	0.243	1	0.106	0.950	1.712

tasis occurred in 1 case.

In the ≤ 3 cm subgroup, 14 cases belonged to the SR group, with 6 (42.86%) cases of recurrence, including one case of local recurrence and 5 cases of intrahepatic recurrence. Of the 20 cases in the RFA group 11 (55%) developed recurrence (2 local and 9 intrahepatic recurrences).

In the 3-5 cm subgroup, of the 28 cases in the SR group 16 (57.14%) developed recurrence. Local recurrence occurred in 3 cases and intrahepatic recurrence in 13. There were 26 cases in the RFA group and out of these, recurrence occurred in 21 (80.77%) cases. These included 5 cases of local recurrence and 16 cases of intrahepatic recurrence. No significant differences were noticed in the tumor-free survival rates for the two groups or in the overall tumor-free survival rates between the subgroups where 3 cm were used as the cut off point (Table 2).

Given the impact of multiple factors on the results multivariate Cox regression analysis was performed and showed that the impact of various factors on tumor-free survival was not statistically significant. The same was true for the comparison between the two groups (Table 3).

Long-term survival

Among the 42 cases in the SR group,14 (33.33%) died as a result of tumor recurrence. In the RFA group, 20/46 (43.48%) patients died of the same cause. In the subgroup with tumor ≤ 3 cm, 3/14 (21.43%) SR-patients died because of tumor recurrence and 5/20 (25%) patients in the RFA group died of the same cause. In the 3-5 cm subgroup, 11/28 SR (39.29%) patients died because of tumor recurrence and 15/26 (57.69%) RFA patients died of the same cause. There were no significant differences in the overall survival rates of the two groups or in the overall survival rates between the subgroups with < 3 cm and 3-5 cm tumors (Table 4).

Multivariate Cox regression analysis showed that the number of tumors significantly affected the overall survival (p=0.02) (the more the number of tumors, the worse the survival) (Table 5).

Discussion

RFA technology for the treatment of liver tumors has advanced significantly in recent years. In the clinic, RFA is not limited to lesions that are not suitable for SR after initial treatment modalities. Additionally, RFA can be used successfully in the treatment of patients who have high risks associated with SR. Therefore, clinicians must continually decide between RFA and SR [18,19]. The concept of a comparative study of RFA vs SR gradually developed as a result of the continuous clinical application of this therapeutic modality. We selected SHC patients, who should have better liver function, as the background for this comparative study, and predicted that the efficacy of both methods could be quantified.

Table 4. Comparison of overall survival rates of the 2 groups

Tumor size (cm)	*Treatment method*	*Patients N*	*Mean cumulative survival (months)*	*Overall survival rate (%)*			x^2	*p value*
				1-year	*3-year*	*5-year*		
0-5	SR	42	50.78±26.78	100	63.7	50.4	0.19	0.67
	RFA	46	47.62±19.52	100	66.3	37.4		
<3	SR	14	47.79±23.52	100	78.8	59.1	0.03	0.87
	RFA	20	51.36±18.45	100	78.8	51.7		
3-5	SR	28	49.06±25.27	100	56.8	45.4	0.68	0.41
	RFA	26	44.13±18.05	100	56.9	29.1		

For abbreviations see footnote of Table 2

Table 5. Multivariate Cox regression analysis of different factors, possibly affecting overall survival

Factors	*B*	*df*	*Sig.*	*95% CI for Exp(B)*	
				Lower	*Upper*
Treatment method	-0.078	1	0.850	0.409	2.090
Gender	0.031	1	0.955	0.354	3.006
Age	-0.029	1	0.263	0.923	1.022
No. of tumor lesions	1.165	1	0.019	1.215	8.464
Cirrhosis	0.472	1	0.334	0.225	1.648
Liver function	0.439	1	0.319	0.654	3.683
AFP	0.327	1	0.221	0.821	2.344
Tumor diameter	-0.150	1	0.474	0.570	1.299

In addition to considering the 100% SHC tumor clearance rate observed with SR treatment, we considered the risk of traumatic injuries (including intraoperative bleeding and hepatic inflow blockage) in the SR group. The advantages of simplicity and minimal invasion in the RFA group as well as the disadvantage of initial tumor clearance rate of 86.96% after ablation should be noted. Additionally, both finger touch/squeeze during surgery and needle punctures during RFA could cause tumor dissemination. Therefore, long-term comparisons of the two methods should be used to define long-term prognosis.

We initially assumed that RFA and SR were comparable for the treatment of SHC. Our results support this hypothesis and demonstrated that the 1-, 3- and 5-year tumor-free survival rates, as well as the overall survival rates for the SR and RFA groups, were similar. Division of the tumors into a < 3 cm and a 3-5 group resulted in no statistically significant differences between the SR and RFA groups. In addition, Cox multivariate analysis showed no statistically significant differences in the tumor-free survival and overall survival between the SR and RFA groups.

No treatment-related deaths or serious complications were observed in either the SR or RFA groups, with the exception of common complications such as fever, pain, and pleural effusion. The main problems in the SR group were post-traumatic bleeding, ascites, and subcutaneous fat liquefaction, while the main problems in the RFA group were perihepatic effusions and skin burns. All complications were improved after conservative treatments.

The number of reports that have compared of SR and RFA has gradually increased, however they have come to different conclusions. Huang et al. [11] reported that SR resulted in improved survival compared to RFA for the treatment of Child A cirrhotic patients with solitary hepatocellular carcinomas of 3-5 cm or with 2-3 lesions < 5 cm. Similar recurrence-free survival was achieved with SR and RFA for the treatment of Child A cirrhotic patients with solitary hepatocellular carcinoma (≤3 cm) but RFA is a less invasive therapy. Chen et al. [12] compared the efficacy of percutaneous RFA and SR for SHC (diameter ≤5 cm) and concluded that while the two methods were similar, RFA was advantageous in that it was less traumatic. Molinari et al. [13] used a Markov model to compare the efficacy of RFA and SR for the treatment of SHC patients with cirrhosis who were not candidates for liver transplantation. The

results demonstrated that SR resulted in better quality-of-life-adjusted survival, as RFA was associated with increased risk of local recurrence that required multiple sessions of therapy, and RFA appears to be the best therapeutic option for older individuals. Hong et al. [15] performed a comparison of non-randomized trials and demonstrated that despite the higher rate of local recurrence after RFA, there were no differences in the rates of distant metastasis and overall survival after RFA or SR therapy. Ikeda et al. [20] found that RFA was more cost-effective than SR for the treatment of SHC. In addition, post-RFA treatments like ethanol injection, and re-treatments could significantly reduce the recurrence rate. Vivarelli et al. [16] performed a 4-year comparison of SR and RFA for the treatment of SHC. Their results showed that the overall survival and tumor-free survival rates in the SR group were higher than in the RFA group, and that the advantages were more noticeable in patients with Child A grade liver function and single tumors with diameters <3 cm.

In this study, the relapse rate in the RFA group was higher than in the SR group, and the local recurrence rate in the RFA group was also slightly higher than in the SR group. The 1-, 3-, and 5-year tumor-free survival and the overall survival in the SR group were slightly higher than in the RFA group, but the differences were not statistically significant. Cox regression analysis also showed no differences between the two treatment groups. Tumor size, tumors' number, AFP levels, cirrhosis, and liver function also had no impact on recurrence. Mulier et al. [21] performed a meta-analysis of the local recurrence rate in 5224 cases of RFA for the treatment of liver tumors. Multivariate analysis indicated that tumor size as well as the therapeutic approach had a significant impact on tumor recurrence. The long-term survival rates in the RFA and SR groups were similar, which may be related to the multiple RFA treatments. Most patients in our study received multiple RFA treatments in order to control tumor progression during the follow-up period. There were 32 patients who received RFA more than once and one patient received 8 RFA treatments. Multivariate Cox regression analysis demonstrated that the number of tumors influences the overall survival rate, meaning the more the number of tumors, the worse the survival.

Percutaneous RFA treatment was primarily performed in this study. However, laparoscopic RFA was performed in 2 cases because of the tumor's geographical location. This approach was utilized to avoid adverse effects. In one case, a hepatic caudate lobe tumor was directly visualized by laparotomic RFA and no adverse effects were observed. Should this particular patient also had liver cirrhosis, SR may have significantly increased the risk of adverse events. Similarly, we believe SR would increase the risk of adverse events in patients who have deep-located tumors or near the hepatic hilar region, especially those with obvious cirrhosis. In both cases, our results suggest that RFA is the preferred treatment method.

In contrast, Mulier et al. [21] mentioned that under certain conditions, the laparoscopic RFA or SR treatment methods would exhibit more noticeable advantages than percutaneous RFA. We found that the equipment affected the rates of post-RFA residual tumors and recurrence. We expect that RFA could be improved if the single needle ablation range could be enhanced. This would likely result in further reduction of the residual tumor, which in turn would result in reduction in the local recurrence rate and improved long-term survival rate. Long-term studies will provide a more objective evaluation of the advantages of RFA and SR resulting in more appropriate treatment options.

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