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ORIGINAL ARTICLE

Is radiofrequency ablation equal to surgical re-resection for recurrent hepatocellular carcinoma meeting the Milan criteria? A meta-analysis

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Summary

Purpose: *To evaluate the clinical efficacy and safety of radiofrequency ablation (RFA) with surgical re-resection (SRR) in patients with postoperative recurrent hepatocellular carcinoma (RHCC) meeting the Milan criteria.*

Methods: *A literature search was performed to identify comparative studies addressing outcomes of both RFA and SRR for RHCC meeting the Milan criteria. Pooled odds ratios (OR) with 95% confidence intervals (95% CI) were calculated using either the fixed effects model or the random effects model.*

Results: *Five nonrandomized controlled trials were included in the analysis. These studies included a total of 543 patients: 243 treated with RFA and 300 treated with SRR. The SRR group had a better 3-year recurrence-free survival rate compared with RFA group (OR 0.44, 95%CI 0.25-0.77, p=0.004). However, there were no obvious differences between RFA and SRR group in overall survival (OS) rates, re-recurrence rate and OS rates with tumors ≤ 3cm. What's more, the RFA group had a safety advantage with less complications of Clavien classification grade II or higher compared with SRR group (OR 0.21, 95%CI 0.05-0.94, p=0.04).*

Conclusions: *RFA seemed to be superior to SRR in the treatment of patients with RHCC meeting the Milan criteria on account of clinical safety. However, these findings have to be carefully interpreted due to the lower level of evidence.*

Key words: *efficacy, meta-analysis, radiofrequency ablation, recurrent hepatocellular carcinoma, surgical re-resection*

Introduction

It has been reported that HCC is the fifth most common carcinoma in the world, causing nearly 500,000 deaths per year [1]. With advances in surgical techniques and perioperative care, results of hepatic resection for HCC have greatly improved. Nonetheless, the long-term survival after hepatectomy remains unsatisfactory, due to recurrence and metastasis of primary HCC which has always been a critical problem for surgeons. Intrahepatic recurrence of HCC after primary hepatectomy is frequent and is reported to be nearly 45.5-64.3% within 5 years after surgery [2-7]. Thus, effective therapeutic strategy of intrahepatic recurrence is decisive in prolonging survival after resection of primary HCC.

SRR is an effective treatment for intrahepatic HCC recurrence, with 5-year survival ranging from 35.5 to 56.1% [8,9], which is comparable to the survival after initial hepatectomy for HCC. Currently, many centers use the repeat hepatectomy as the first choice of treatment for RHCC and have claimed that it is preferable [10]. Unfortunately, repeat hepatectomy can be carried out only in a small proportion of patients with RHCC, which is

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within 13.4-22.9%, due to either poor function of liver reserve or the widespread intrahepatic recurrence [11]. Ablative therapies, such as percutaneous ethanol injection (PEI), microwave coagulation therapy (MCT) and RFA, are also considered effective in improving survival after recurrence [12]. In the past two decades, RFA has emerged as a new treatment modality and has attracted great interest because of its effectiveness and safety for small HCC (diameter ≤ 5 cm) [13]. Studies using RFA to treat RHCC after primary hepatectomy report a 5-year survival rate of 29.1-83.0 % [14], which is comparable to rates achieved by surgery. RFA is particularly suitable to treat RHCC after primary hepatectomy because these tumors are usually detected when they are small and RFA causes the least deterioration of liver function [12]. Besides, transarterial chemoembolization (TACE) has been performed in most cases of intrahepatic recurrence with multiple tumors, unfavorable tumor location, and poor liver function, with relatively poor 5-year survival rates ranging from 0 to 56% [14]. In addition, salvage liver transplantation might be the ideal treatment for both recurrent tumors and deteriorated liver function in patients with intrahepatic recurrence. The severe inconformity between the demand for transplantation and the supply of organs from deceased donors has limited an expansion of the selection criteria of patients with HCC [15,16].

Therefore, controversies are seen in clinical studies concerning the best therapeutic strategy of RHCC meeting the Milan criteria. Dong et al. [17] and Luo et al. [18] had demonstrated that there is a tendency for SRR, on account of benefits in survival and recurrent rates. Increasing data [19-23] considered that RFA was as effective as SRR in the treatment of RHCC. However, two trials [3,20] proposed that RFA should be the first-line treatment of RHCC.

As it is well-known, meta-analysis can be used to evaluate the existing literature from both a qualitative and quantitative aspect by comparing and integrating the results of different studies and taking into account variations in characteristics that can influence the overall estimate of the outcome of interest [24]. To the best of our knowledge, there has been no report published in the medical literature comparing the efficacy and safety of RFA with SRR for RHCC in a meta-analysis. Therefore, we evaluated the available evidence comparing the clinical long-term results of RFA with SRR for the best therapeutic modality of RHCC meeting the Milan criteria.

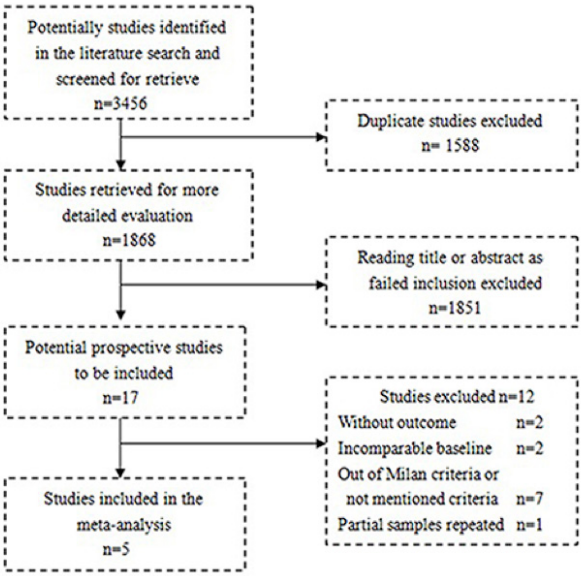

Figure 1. Flow chart showing the selection of articles for this meta-analysis.

Methods

Study selection methodology

A Medline, Pubmed, Ovid, Cochrane Library, CNKI, VIP, WANFANG databases search was performed on all studies between January 2000 and February 2013 to compare RFA and SRR for RHCC meeting the Milan criteria. The following English keywords were used: "recurrent, or recurrence, or relapse, or recurring", "liver neoplasms, or hepatocellular carcinoma, or hepatic carcinoma, or liver cancer, or HCC", "radiofrequency ablation, or radiofrequency, or ablation, or radio frequency, or radio-frequency, or RFA, or PRFA" and "resection, or hepatectomy". Only studies on humans and in English and Chinese were considered for inclusion. This search was supplemented by manual research and a review of the reference lists. We were not blind to authors, institutions, journals while selecting trials or extracted the data (Figure 1).

Inclusion and exclusion criteria

For inclusion in the meta-analysis, a study had to meet the following criteria: (1) the patient baseline characteristics should be similar; (2) the recurrence of HCC should be definite, the surgery of primary HCC and the consequent treatment of RHCC should be radical; (3) the RHCC had to fulfill the Milan criteria: solitary liver nodule ≤ 5cm in maximum diameter or 2-3 nodules ≤ 3cm in diameter without vascular invasion or extrahepatic metastases; (4) good liver function with Child-Pugh Class A or B, with no history of encephalopathy, ascites refractory to diuretics or variceal bleeding and patients should be suitable for treatment with ei-

ther RFA or SRR; (5) comparison of the therapeutic effect of RFA and SRR for RHCC and report on at least one of the outcomes mentioned below (OS rates, rates of re-recurrence and Clavien classification complications of grade II or higher).

Abstracts, letters, editorials and experts opinions, reviews without original data, case reports and studies lacking control groups were excluded. The following studies were also excluded: (1) those assessing patients with primary HCC or cholangiocarcinoma; (2) those out of the Milan standard; (3) those treating patients with combined or other therapies; (4) those with no clearly reported outcomes of interest.

Data extraction and quality assessment

Data were extracted by two independent reviewers (Zhou and Li) using standard forms. The recorded data included first author, year of publication, country or district, number of patients, patients' characteristics, the size and the number of tumors, the follow-up time, overall survival rates and re-recurrence-free survival rate, rates of re-recurrence and complications of Clavien classification grade II or higher [30]. All relevant texts, Tables and Figures were reviewed for data extraction. Discrepancies between the two reviewers were resolved by discussion and consensus. The quality of all selected studies was ranked in accordance with the score of the non-randomized controlled clinical trial quality evaluation standard.

Statistics

Related-data from the comparative groups was compared using x^2 test for categorical data. All statistical analyses were performed using SPSS 13.0 statistical software and a difference was considered significant with $p<0.05$. The meta-analysis was performed using the Review Manager (RevMan) software, version 5.2. We analyzed dichotomous variables using estimation of OR with 95% CI. Pooled effect was calculated using either the fixed effects model or the random effects model. Heterogeneity was evaluated by x^2 and I^2. We considered heterogeneity to be present if the I^2 statistics was >50%. A p value <0.05 was considered significant.

Results

Description of study

We were able to identify 17 related studies comparing RFA with SRR as treatment of RHCC meeting the Milan criteria. However, in 7 retrospective comparative studies [3,7-9,14,25,26] the included articles did not satisfy the Milan criteria or the maximal tumor size or tumor lesion numbers were not specified. Outcomes of interest were not reported in 2 retrospective comparative studies [23,27], 2 studies were confounded with combined or other therapies [18,28] and 1 study [20] was excluded because partial samples were repeated with an inclusive study from the same research center [20]. All these 12 studies were excluded from analysis. Ultimately we identified 5 studies where cases of RHCC met the criteria (Figure 1). Of 543 patients in 5 studies, 243 were classified to the RFA group, and 300 to the SRR group and were evaluated for their therapeutic efficacy in RHCC. Baseline characteristics of studies included in the meta-analysis are shown in Table 1. Four studies were performed in China mainland, one in Hong Kong, and one in Japan. The sample size of each study varied from 15 to 213 patients. The age of the patients (460 men and 68 women; one study did not report the age) ranged from 23 to 78 years. The follow-up period ranged from 12 to 61 months.

Overall survival

1-year OS: 2 studies that reported this data showed no statistical difference between the RFA and SRR groups (OR 2.63; 95%CI 0.93-7.48; p=0.07), with no evidence of significant heterogeneity (Table 2).

3-year OS: 2 studies that reported this data showed no statistical difference between the RFA and SRR groups (OR 1.42; 95%CI 0.89-2.25; p=0.14), with no evidence of significant heterogeneity.

5-year OS: 3 studies that reported this data showed no statistical significance between RFA group and SRR group (OR 1.12; 95%CI 0.73-1.71; p=0.60), with no evidence of significant heterogeneity (Figure 2).

3-year re-recurrence-free survival

Two studies reported this data and showed significant difference favoring the SRR group (OR 0.44; 95%CI 0.25-0.77; p=0.004), with no evidence of significant heterogeneity.

Re-recurrence rate

Four studies reported this data and showed no statistical difference between the RFA and the re-resection group (OR 1.40; 95%CI 0.57-3.43; p=0.46), with no evidence of significant heterogeneity (Figure 3).

Treatment-related complications of Clavien classification grade II or higher

Three studies reported this data and showed

Table 1. Baseline characteristics of studies included in the meta-analysis

First author [ref. no.] and year	*Country/District*	*Group*	*N*	*M/F*	*Mean tumor size (cm)*	*Mean lesions number*	*Follow-up (mo) (range)*
Ng [19] 2008	Hong Kong	RFA	3	-	≤5	≤3	61
		SRR	12	-	≤5	≤3	61
Ren [21] 2008	China Mainland	RFA	68	64/4	≤3	≤3	23 (3-88)
		SRR	145	127/18	≤3	≤3	23 (3-88)
Ueno [22] 2009	Japan	RFA	10	10/0	1.8 (1.0-2.5)	1	30 (16-60)
		SRR	9	4/5	1.8 (1.0-2.4)	1	34 (13-60)
Liang [24] 2011	China Mainland	RFA	79	69/10	≤3 (2.46±0.09)	1	32 ± 21
		SRR	72	65/7	≤3 (2.16±0.10)	1	36 ± 25
Dong [17] 2011	China Mainland	RFA	17	28/7	≤5	≤3	12 - 36
		SRR	18		≤5	≤3	12 - 36

RFA: radiofrequency ablation, SRR: surgical re-resection; M: male; F: female, mo: months

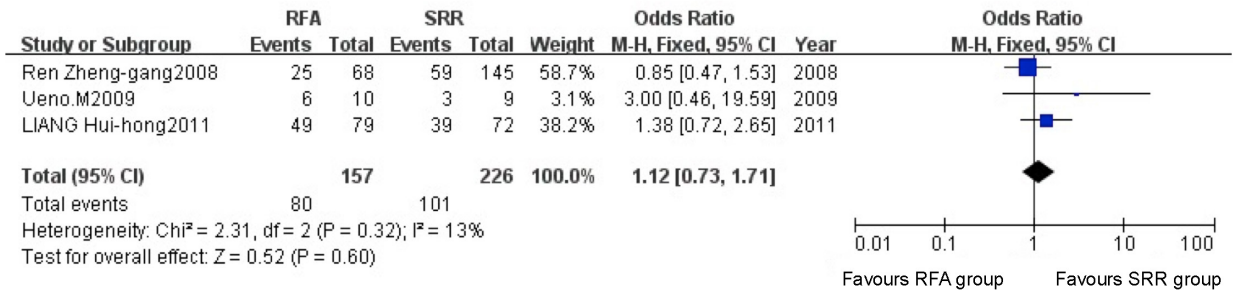

Figure 2. Results of meta-analysis on 5-year overall survival

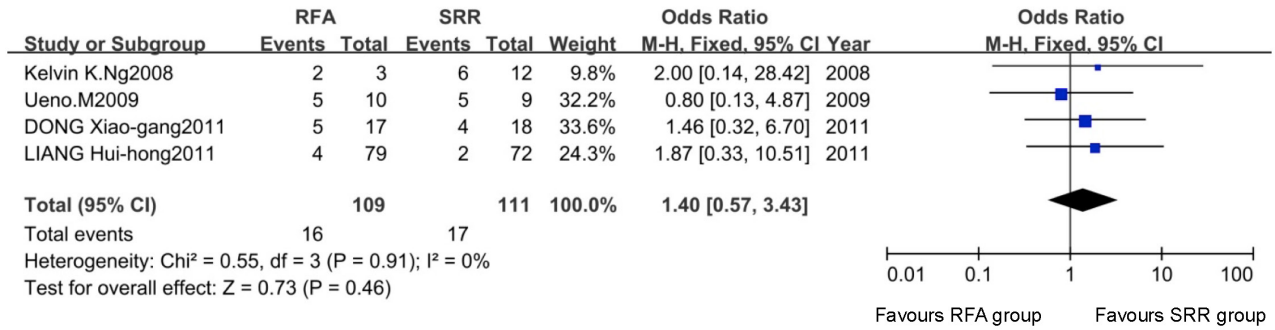

Figure 3. Results of meta-analysis on recurrence rate.

significant difference favoring the RFA group (OR 0.21; 95%CI 0.05-0.94; p=0.04), with no evidence of significant heterogeneity (Figure 4).

Comparison between the two groups with RHCC ≤ 3cm

Four studies compared RFA vs SRR in patients with tumors ≤ 3 cm. Of these studies, 2 contained patients with a single tumor [20,22]. Significant difference was noticed at 3-year survival between the RFA and SRR groups (p=0.035). Further analysis, showed that patient survival with single or multiple lesions was similar in the treatment groups of Dong and Ren [17,21] (Table 3).

No significant difference in OS in RHCC ≤ 3cm

Table 2. Summary of the results on the efficacy and safety between RFA and SRR in management of RHCC meeting the Milan criteria

Variables	*No. of studies providing data [ref.no.]*	*Results*		*OR (95%CI)*	*p value*	*I^2 (%)*
		RFA (%)	*SRR (%)*			
Overall survival						
1-year	2 [21,24]	96.60	90.78	2.63 (0.93-7.48)	0.07	0
3-year	2 [21,24]	72.79	63.59	1.42 (0.89-2.25)	0.14	46
5-year	3 [21,22,24]	50.96	44.69	1.12 (0.73-1.71)	0.60	13
Re-recurrence-free survival						
3-year	2 [17,21]	31.76	49.69	0.44 (0.25-0.77)	0.004	0
Overall survival in RHCC≤3cm						
1-year	2 [21, 24]	97.28	90.48	2.63 (0.93-7.48)	0.07	0
3-year	3 [17, 21, 24]	71.07	62.88	1.38 (0.88-2.15)	0.16	0
5-year	3 [21, 22, 24]	50.96	44.69	1.12 (0.73-1.71)	0.60	13
Re-recurrence	4 [17, 19, 22, 24]	14.68	15.32	1.40 (0.57-3.43)	0.46	0
Treatment related complications	3 [19,21, 24]	8.00	24.02	0.21 (0.05-0.94)	0.04	52

RFA: radiofrequency ablation, SRR: surgical re-resection, RHCC: recurrent hepatocellular carcinoma, OR: odds ratio, CI: confidence interval

Table 3. Studies comparing RFA versus SRR for RHCC ≤3cm meeting the Milan criteria

First author [ref. no.] year	*Treatment*	*Patients, N*	*Survival*		
			1-year N (%)	*3-year N (%)*	*5-year N (%)*
Ren [21] 2008	RFA	68	64 (94.70)	44 (65.10)	25 (37.30)
	SRR	145	128 (88.10)*	91 (62.60p)*	59 (41)*
Ueno [22] 2009	RFA	10	-	-	6 (57)
	SRR	9	-	-	3 (29%)*
Liang [24] 2011	RFA	79	79 (100)	63 (79.40)	49 (62.10)
	SRR	72	69 (95.30)*	47 (65.70)**	39 (54.50)*
Dong [17] 2011	RFA	12	-	6 (50)	-
	SRR	12	-	6 (50)*	-

*: not significant;**: significant at p<0.05.
RFA: radiofrequency ablation, SRR: surgical re-resection, RHCC: recurrent hepatocellular carcinoma

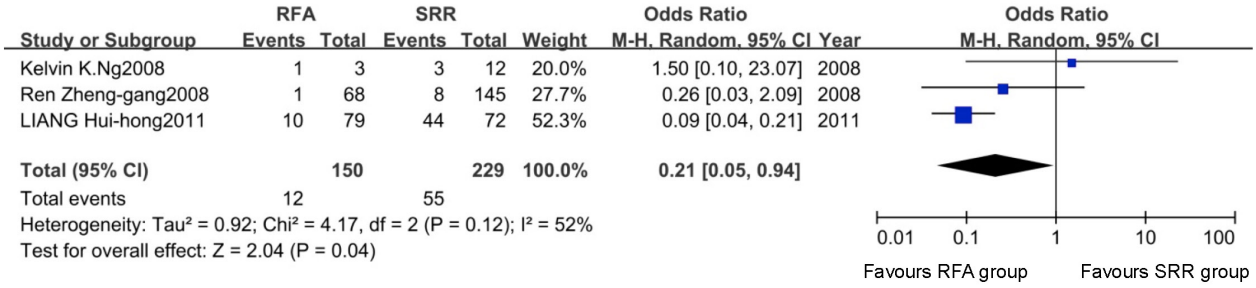

Figure 4. Results of meta-analysis on complications of Clavien classification grade II or higher.

was registered between the two groups at 1 year (2 trials reported this data with OR 2.63; 95%CI 0.93-7.48; p=0.07), 3 years (3 trials reported this data with OR 1.38; 95%CI 0.88-2.15; p=0.16), and

at 5 years (3 trials reported this data with OR 1.12; 95%CI 0.73-1.71; p=0.60) and without no evidence of significant heterogeneity (Table 2).

Discussion

Meta-analysis, a qualitative and quantitative technique for therapeutic evaluation, is widely used when controversy persists after several trials. Unfortunately, we did not search for randomized clinical trials (RCT) literature and merely retrieved 5 suitable studies that compared RFA and SSR in RHCC meeting the Milan criteria. As far as we are concerned, the main reason maybe that few people are trending to research the treatment modalities of RHCC and compare them with the therapeutic method of primary HCC. Carrying out a clinical randomized controlled trial without sufficient preparation may cause ethical dispute to the people's plans concerning the comparison between RFA and SRR for RHCC. Although meta-analysis has traditionally been applied and is best confined by RCT, meta-analytical techniques using non-randomized controlled trials (NRCT) might be a valid method in some clinical settings in which either the number or the sample size of RCT is insufficient [29,30].

Although this meta-analysis showed SRR increased the 3-year re-recurrence-free survival in patients with RHCC meeting the Milan criteria, the comprehensive effect of treatment with RFA was superior to treatment with SRR. First, RFA had a similar efficacy with SRR in OS and re-recurrence rate. Second, RFA was safe with low complications of Clavien classification grade II or higher. We even found RFA was significantly better than SRR concerning 3-year survival in the report of Liang et al. [20], however, it didn't show obvious difference between RFA and SRR in RHCC ≤ 3cm in OS from the subgroup analysis.

In comparison with a previous report of RFA and surgical resection for primary small HCC in our center [31], we noticed a decline of 3-year re-recurrence-free survival in both RFA and SRR groups of RHCC. Next, we found a similarity in OS, treatment related complications and re-recurrence between the two RFA groups, but a remarkable reduction of OS and increase of re-recurrence was observed in the SRR group of RHCC compared with surgical resection in primary HCC. In addition, the incidence of treatment related complication of RFA and surgical resection were similar between the primary and RHCC and clinical safety of RFA was obviously superior to surgical re-resection.

In primary HCC, surgeons usually remove the entire Couinaud segment containing tumor lesions, so the clearence of tumor and any potential sites of microscopic disease will be more complete in these patients [32]. However, in case of HCC recurrence, it is difficult to differentiate the recurrent lesion that is a clinically local recurrence or a new primary HCC after previous HCC resection. Recurrence is reported to be attributed to micrometastases within the liver [33] which caused the decline of 3-year re-recurrence-free survival in both RFA and SRR groups of RHCC.

Among 13 clinicopathologic variables assessed by univariate analysis, the therapeutic modality was the only significant prognostic factor for survival after single nodular intrahepatic recurrence, with RFA being superior to SRR and TACE in relative risk ratios [14,22]. It has also been reported that intraoperative blood transfusion is an independent risk factor for poor cancer-related survival after intrahepatic recurrence [3]. Comparing with SRR, RFA practically abolishes the likelihood of bleeding and blood transfusion, which has been reported to be associated with potentially devastating complications such as transmission of human immunodeficiency virus and hepatitis, transfusion reactions, increased postoperative infection rate and increased incidence of recurrences for certain cancers [34]. Tralhão et al. reported that prevention of intraoperative bleeding or blood transfusion should improve the disease-free and OS in HCC patients [35]. As the hypothesis that recurrence is accompanied with micrometastases, the transfusion caused by the surgery of recurrence may aggravate the metastasis and recurrence. Therefore, transfusional re-resection may play a key role in the dramatic decrease of OS and increase of re-recurrence of RHCC with the use of SRR.

SRR has limited application because of the low rate of resectability in patients with intrahepatic recurrence due of poor hepatic functional reserve and/or unresectable tumor dissemination in the remnant liver [36]. It is also limited owing to significant adhesions from a previous operation and proximity of the tumor to major vascular or biliary structures. This results in an unplanned increase in the level of medical care, prolonged hospitalization, permanent adverse sequelae or death [20]. In contrast, RFA has an obvious superi-

ority in terms of hospitalization and expenditure compared with SRR in a previous study of ours [23]. RFA is particularly suitable for the management of RHCC, because RHCC lesions after liver resection are usually detected when small-sized and can be destroyed with ablation. However, RFA is sometimes inadequate for lesions on the liver surface or near large vessels. Primary postoperative adhesions between the remnant liver and the gastrointestinal tract may prevent patients with RHCC after hepatectomy from undergoing percutaneous RFA.

Conclusion

This study showed no remarkable differences in OS and re-recurrence between RFA and SRR in the treatment of patients with RHCC meeting the Milan criteria. However, RFA seems to be superior to SRR on account of clinical safety. This conclusion has to be carefully interpreted due to the lower level of relevant evidence. More NRCTs and further RCTs are warranted to find out the explicit value of RFA and SRR for RHCC meeting the Milan criteria.

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