

Original Article

Radiofrequency ablation versus surgical resection for the treatment of hepatocellular carcinoma conforming to the Milan criteria: systemic review and meta-analysis

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Abstract: Radiofrequency ablation (RFA) is a promising ablation technique and has become one of the best alternatives for hepatocellular carcinoma (HCC) patients. But whether RFA or surgical resection (SR) is the better treatment for HCC conforming to the Milan criteria has long been debated. A meta-analysis of trials that compared RFA versus SR was conducted regarding the survival rate and recurrence rate. Pooled odds ratios (OR) with 95% confidence intervals (95% CI) were calculated using fixed or random effects models. Nineteen studies, comprising 2 randomized controlled trials and 17 non-randomized controlled trials, were included with a total of 2895 patients. The 5 years overall survival rate for SR group was significantly higher than that for RFA group. In the SR group, the local recurrence rate was significantly lower when compared with the RFA group. This meta-analysis yielded no significant differences between laparoscopic RFA and SR in 5-year overall survival rate. In conclusion, surgical resection remains the better choice of treatment for HCC conforming to the Milan criteria, whereas RFA should be considered as an effective alternative treatment when surgery is not feasible. As for RFA technique, laparoscopic approach may be more effective than percutaneous approach for HCC conforming to Milan criteria.

Keywords: Meta-analysis, hepatocellular carcinoma, radiofrequency ablation, surgical resection, Milan criteria

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third most common cause of cancer-related death in the world [1]. It is prevalent in Asia and Africa, and increasing in the United States and Europe [2]. Advances in diagnostic imaging and widespread application of screening programs in high risk populations have allowed detection of small HCC, which can be cured by partial hepatic resection, liver transplantation, or local ablation therapies [3].

Surgical resection (SR) has generally been accepted as the first choice of treatment for HCC within the Milan criteria (solitary tumor ≤ 5 cm in diameter and up to three nodules ≤ 3 cm in diameter) in many centers [1]. Nevertheless, only 9% to 29% of patients with HCC are candidates for surgery owing to either poor hepatic reserve resulting from underlying chronic liver disease or a multifocal distribution of tumor nodules [4].

Therefore, many nonsurgical ablation methods have been developed. Among these therapies, radiofrequency ablation (RFA) is a promising and recently developed ablation technique. Favorable survival outcomes have been reported for patients with small HCC following RFA [5, 6]. Basically, RFA is recommended for HCC with three or fewer nodules ≤ 3 cm in diameter [7]. For these small tumors, reliable local tumor control can be achieved with a single application of RFA in most cases [6]. However, whether RFA or SR is the better treatment for HCC eligible for SR has long been debated [8]. Some researchers reported that SR had more advantages in terms of survival and recurrence rates regardless of tumor size larger or smaller than 3 cm in diameter [9-11]. Conversely, other studies showed that RFA was as effective as SR in the treatment of solitary and small HCC and suggested that RFA can be considered as the choice of treatment for patients with single and small HCC even when SR is possible [12-14]. Two prospective randomized trials compared

SR and RFA for HCC conforming to the Milan criteria and the results were still controversial [11, 13].

In the current study, by performing a meta-analysis, we attempted to compare the long-term outcomes of RFA and SR for the treatment of HCC conforming to the Milan criteria.

Methods

Search strategy

A systematic literature search was based on an electronic database search. Electric databases included PubMed, Medline and CNKI until March 2013, the last 1 of which is major Chinese database. The following Mesh search headings were used: (radiofrequency ablation) (surgical resection or hepatectomy or surgery) and (hepatocellular carcinoma or liver cancer) in English. This search was supplemented by manual search and a review of reference lists. In addition, we chose some Chinese articles, as there are many patients with HCC in China.

Criteria for inclusion

For inclusion in the meta-analysis, a study has to fulfill the following criteria: 1) to compare the initial therapy effects of RFA and SR for the primary treatment of HCC conforming to the Milan criteria without any invasion into the major portal/hepatic vein branches or extrahepatic metastasis regardless of the etiology of liver disease; 2) patients should be suitable for treatment with either SR or RFA; 3) In multiple studies reported by the same institution, the most recent publication was included in the analysis.

Criteria for exclusion

Abstracts, letters, editorials and expert opinions, reviews without original data, case reports and studies lacking control groups were excluded.

The following studies were also excluded: 1) those dealing with unresectable HCC or HCC recurrence after hepatectomy; 2) those with no clearly reported outcomes of interest; 3) those evaluating patients with cholangiocellular carcinomas or liver metastases.

Data synthesis

Two reviewers (WZ and HMY) independently extracted the following parameters from each

study: 1) first author and year of publication; 2) number of patients, patient characteristics, study design; and 3) treatment outcomes. All relevant texts, tables and figures were reviewed for data extraction. Discrepancies between the two reviewers were resolved by discussion and consensus.

Statistical analysis

Comparison of the overall survival rate, the disease-free survival rate, the local recurrence rate and the non-local recurrence rate between RFA with SR were performed in this study, in addition, two subgroup analyses including comparison of outcomes between the two groups for HCC ≤ 3 cm in Diameter as well as outcomes between laparoscopic RFA and SR for HCC conforming to Milan criteria were also conducted.

The meta-analysis was performed using the Review Manager (RevMan) software, version 5.00 (Cochrane Collaboration, Oxford, UK). Pooled odds ratios (OR) with 95% confidence intervals (95% CI) were calculated to assess treatment efficacy using either the fixed effects model or random effects model depending on the absence or presence of significant heterogeneity. Heterogeneity was evaluated by I^2 for the meta-analyses of randomized controlled trials. The fixed effects model was applied for the meta-analyses of the randomized controlled trials in the case of $I^2 < 40\%$. Besides, the random effects model was used for the meta-analyses of non-randomized controlled trials, irrespective of I^2 value because of a considerable clinical heterogeneity in different treatment procedures and study designs. In all analyses, a threshold of $P < 0.05$ for overall effect was considered statistically significant [15].

Quality scoring and risk of bias assessment

Risk of bias assessment in randomized controlled trials was performed according to Cochrane methodology under consideration of random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other bias [15]. Each category was scored as yes, unclear or no risk of bias. Inspection of funnel plots based on meta-analysis, including more than 10 studies, was also used for assessment of publication bias [16].

RFA versus SR for hepatocellular carcinoma treatment

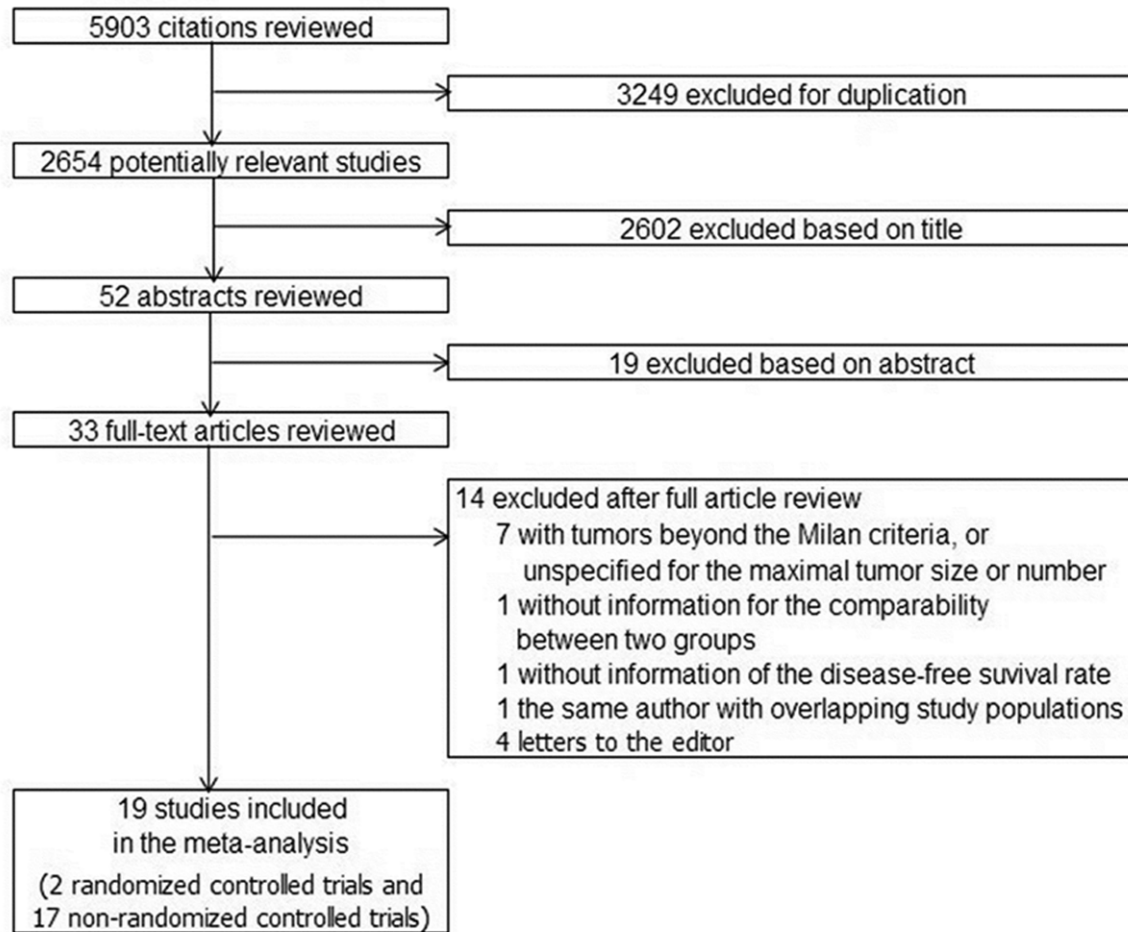


Figure 1. Flowchart of the literature search.

The Newcastle-Ottawa Quality Assessment Scale (NOS) was used for quality assessment of non-randomized controlled trials [17]. This was done by assessing patient's selection criteria, compatibility of the 2 study groups and of the outcome in the individual studies. A star rating of 0 to 9 was allocated to each study based on these parameters. Studies achieving 6 or more stars were considered as indicative for high quality [15].

Two reviewers (WZ and HMY) independently assessed the methodological quality of the considered studies. Any discrepancies were resolved by discussion among all authors.

Results

The flow of selecting studies for the meta-analysis is shown in **Figure 1**. Finally, a total of 19 studies including 2 randomized controlled trials

and 17 non-randomized controlled trials [11, 13, 14, 18-33] published until March 2013 matched the selection criteria and were therefore included. Of these studies, 15 (78.9%) used percutaneous RFA [11, 13, 14, 19-27, 29-31], 3 (15.8%) used laparoscopic RFA [18, 32, 33], and the remaining 1 used both percutaneous and laparoscopic RFA [28]. These studies included a total of 2895 patients including 1520 treated with RFA and 1375 treated with SR. The mean age ranged from 49.2 to 69.4 years. Male to female ratio in the pooled data was 2.67. Most patients had a single tumor (**Table 1**). Among the 19 studies selected, 2 (10.5%) Chinese articles were included [20, 22], corresponding to the high incidence of hepatitis B virus-associated HCC in China. The characteristics of the 19 clinical trials included and summary of results are shown in **Table 1**.

RFA versus SR for hepatocellular carcinoma treatment

Table 1. Characteristics of included studies and summary of the results in patients with hepatocellular carcinoma conforming to Milan criteria

Author & Year	Design (NOS) & Period	Treatments	Cases	Mean age (years)	Sex M/F (cases)	Tumor number (cases)		OS rate (%)			DFS rate (%)			Recurrence (cases)
						single/multiple	1-yr	3-yr	5-yr	1-yr	3-yr	5-yr	local/non-local	
Hong SN [14] 2005	NRCT (7)	RFA	55	59.1	41/14	55/0	100	72.7	nd	74.1	40.2	nd	10/22	
	1999-2001	SR	93	49.2	69/24	93/0	97.9	83.9	nd	75.9	54.7	nd	2/42	
Montorsi M [18] 2005	NRCT (6)	RFA*	58	67	43/15	58/0	85	61	nd	70	31	nd	11/20	
	1997-2003	SR	40	67	33/7	40/0	84	73	nd	80	59	nd	0/11	
Ogihara M [19] 2005	NRCT (7)	RFA	26	67	10/16	26/0	83	53	32	71	31	23	4/10	
	1995-2003	SR	18	61	12/6	18/0	64	64	21	64	37	37	1/13	
Chen MS [13] 2005	RCT (nd)	RFA	71	51.9	56/15	71/0	94.4	68.6	nd	90.8	59.8	nd	nd	
	1999-2004	SR	90	49.4	75/15	90/0	93.3	73.4	nd	86.6	69	nd	nd	
Gao W* [20] 2007	NRCT (7)	RFA	53	57.1	41/12	29/24	95.9	74.5	nd	82.8	57.5	nd	4/14	
	1999-2006	SR	34	51.5	28/6	32/2	94.1	75.3	nd	85.1	57.1	nd	1/10	
Zhou T* [22] 2007	NRCT (7)	RFA	47	57	37/10	40/7	91	69.7	nd	57.3	35.3	nd	11/17	
	2001-2006	SR	40	53	35/5	38/2	90	75.4	nd	71.1	30.9	nd	1/17	
Lupo L [21] 2007	NRCT (7)	RFA	60	68	47/13	60/0	96	53	32	68	18	0	nd	
	1999-2006	SR	42	67	33/9	42/0	91	57	43	74	35	14	nd	
Hiraoka A [24] 2008	NRCT (7)	RFA	105	69.4	76/29	105/0	95.1	87.8	59.3	87.5	58.7	24.6	nd	
	2000-2007	SR	59	62.4	44/15	59/0	98.1	91.4	59.4	91.4	64.3	22.4	nd	
Abu-Hila [23] 2008	NRCT (6)	RFA	34	65	27/7	34/0	83	nd	57	42	nd	21	10/10	
	1991-2003	SR	34	67	26/8	34/0	91	nd	56	77	nd	28	1/19	
Ueno S [25] 2009	NRCT (8)	RFA	155	66	100/55	101/54	98	92	63	78	36	20	35/59	
	2000-2005	SR	123	67	82/41	110/13	99	92	80	80	48	38	0/52	
Huang J [11] 2010	RCT (nd)	RFA	115	56.57	79/36	84/31	87	69.57	54.78	81.7	46.08	28.69	10/63	
	2003-2005	SR	115	55.91	85/30	89/26	98.3	92.17	75.65	85.2	60.87	51.3	5/43	
Nishikawa H [26] 2011	NRCT (7)	RFA	162	68.4	95/67	162/0	95.4	79.6	63.1	82	38.3	18	20/nd	
	2004-2010	SR	69	67.4	50/19	69/0	100	81.4	74.6	86	47.2	26	10/nd	
Yun WK [27] 2011	NRCT (6)	RFA	255	57	197/58	255/0	98	92	87	73	34	24	74/163	
	2000-2007	SR	215	51.7	171/44	215/0	100	98	94	86	72	66	9/67	
Peng ZW [29] 2012	NRCT (8)	RFA	71	53.1	63/8	71/0	98.5	87.7	71.9	76.4	65.2	59.8	0/24	
	2003-2008	SR	74	51.5	65/9	74/0	90.5	70.9	62.1	75.6	56.4	51.3	1/30	
Imai K [28] 2012	NRCT (7)	RFA	82	67.6	46/36	82/0	97.4	84.6	59.4	70.2	36.3	23.9	nd	
	2000-2011	SR	101	63.3	75/26	101/0	100	92.5	87.5	91.5	58.7	46.8	nd	
Wong KM [30] 2013	NRCT (7)	RFA	36	63.5	18/18	36/0	97.1	91	72.8	66.7	34.8	14.9	nd	
	2004-2009	SR	46	55.1	30/16	46/0	100	97	84.6	86.8	65.8	53.7	nd	
Lai EC [32] 2013	NRCT (7)	RFA*	31	63.1	19/12	nd	100	92	84	76	40	40	5/11	
	2006-2012	SR	80	60.8	55/25	nd	92	75	71	76	60	60	3/18	
Desiderio J [31] 2013	NRCT (7)	RFA	44	64.4	35/9	19/25	95.5	68.2	36.4	90.9	52.3	22.7	nd	
	2004-2012	SR	52	65.6	37/15	22/30	100	98	46.2	100	80.2	26.9	nd	
Tohme S [33] 2013	NRCT (8)	RFA*	60	65.6	38/22	47/13	86	50	35	68	42	28	4/23	
	2000-2011	SR	50	66.3	31/19	39/11	88	68	47	66	42	34	0/21	

SR, surgical resection; RFA, radiofrequency ablation; RFA, laparoscopic RFA; HCC, hepatocellular carcinoma; OS, overall survival; DFS, disease-free survival; M, male; F, female; yr, year; NRCT, non-randomized controlled trial; RCT, randomized controlled trial; nd, not detectable; NOS, The Newcastle-Ottawa Quality Assessment Scale (used for quality assessment of NRCTs); *Sindicates Chinese article.

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Table 2. Risk of bias in randomized controlled trials

Author & year	Cochrane Risk of Bias Criteria						
	Random Sequence Generation (selection bias)	Allocation Concealment (selection bias)	Blinding of Participants (performance bias)	Blinding of Outcome Assessment (detection bias)	Incomplete Outcome Data Addressed (attrition bias)	Free of Selective Outcome Reporting (reporting bias)	Free of Other Bias
Chen MS [13], 2005	Yes	No	No	Unclear	Yes	Yes	Yes
Huang J [11], 2010	Yes	No	No	Unclear	Yes	Yes	Yes

The level of bias was determined as: Yes, indicating a yes risk of bias; Unclear, indicating an uncertain risk of bias, and No, indicating a no risk bias.

Table 3. Summary of the outcomes in patients with hepatocellular carcinoma ≤ 3 cm

Author & year	Design & Period	Treatments	Cases	Tumor number (cases)	OS rate (%)			DFS rate (%)		
				single/multiple	1 yr	3 yr	5 yr	1 yr	3 yr	5 yr
Gao W* [20] 2007	NRCT 1999-2006	RFA	53	29/24	95.9	74.5	nd	82.8	57.5	nd
		SR	34	32/2	94.1	75.3	nd	85.1	57.1	nd
Hiraoka A [24] 2008	NRCT 2000-2007	RFA	105	105/0	95.1	87.8	59.3	87.5	58.7	24.6
		SR	59	59/0	98.1	91.4	59.4	91.4	64.3	22.4
Ueno S [25] 2009	NRCT 2000-2005	RFA	146	92/54	98.1	91.1	nd	78.9	36.3	nd
		SR	91	78/13	98.6	91	nd	82.9	52.1	nd
Huang J [11] 2010	RCT 2003-2005	RFA	88	57/31	86.4	70.5	55.7	nd	nd	nd
		SR	71	45/26	97.2	90.1	77.5	nd	nd	nd
Nishikawa H [26] 2011	NRCT 2004-2010	RFA	162	162/0	95.4	79.6	63.1	82	38.3	18
		SR	69	69/0	100	81.4	74.6	86	47.2	26
Yun WK [27] 2011	NRCT 2000-2007	RFA	255	255/0	98	92	87	73	34	24
		SR	215	215/0	100	98	94	86	72	66
Peng ZW [29] 2012	NRCT 2003-2008	RFA	71	71/0	98.5	87.7	71.9	76.4	65.2	59.8
		SR	74	74/0	90.5	70.9	62.1	75.6	56.4	51.3
Imai K [28] 2012	NRCT 2000-2011	RFA	82	82/0	97.4	84.6	59.4	70.2	36.3	23.9
		SR	101	101/0	100	92.5	87.5	91.5	58.7	46.8
Wong KM [30] 2013	NRCT 2004-2009	RFA	36	36/0	97.1	91	72.8	66.7	34.8	14.9
		SR	46	46/0	100	97	84.6	86.8	65.8	53.7
Desiderio J [31] 2013	NRCT 2004-2012	RFA	44	19/25	95.5	68.2	36.4	90.9	52.3	22.7
		SR	52	22/30	100	98	46.2	100	80.2	26.9

RFA, radiofrequency ablation; SR, surgical resection; HCC, hepatocellular carcinoma; OS, overall survival; DFS, disease-free survival; RCT, randomized controlled trial; NRCT, non-randomized controlled trial; nd, not detectable; yr, year; *indicates Chinese article.

RFA versus SR for hepatocellular carcinoma treatment

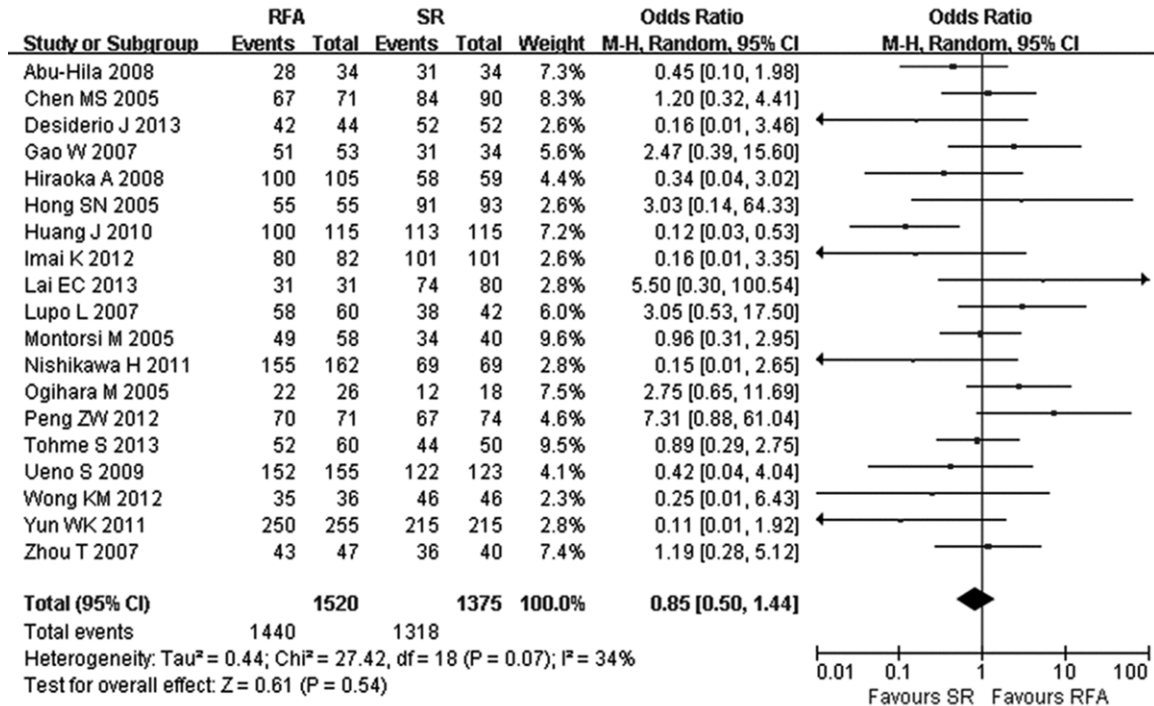


Figure 2. Forest plot for the 1-year overall survival rate for hepatocellular carcinoma conforming to Milan criteria. RFA, radiofrequency ablation; SR, surgical resection; M-H, Mantel-Haenszel.

Among 19 studies included, 17 (89.5%) are non-randomized controlled trials, so the random effects model was used for the meta-analyses in all analyses, irrespective of I² value because of a considerable clinical heterogeneity in different SR and RFA procedures and study designs.

Quality assessment

Blinding and Allocation Concealment were assessed as no in two randomized controlled trials, because it was impossible to completely blind assessors and patients in randomized controlled trials concerning SR or RFA procedures. Accordingly, both randomized controlled trials had risks of detection bias, performance bias and selection bias (**Table 2**).

The rest seventeen non-randomized controlled trials were retrospective and they all scored 6 or more stars on the Newcastle-Ottawa scoring system (**Table 1**).

Overall survival rate

One-year overall survival rate: All 19 studies reported the 1-year survival rate. There was no significant difference in the 1-year overall survival rate between the RFA group and the SR

group (OR: 0.85 [95% CI: 0.50-1.44], P=0.54) (**Figure 2**).

Three-year overall survival rate: Of 19 studies included, 18 reported the 3-year survival rate. The meta-analysis showed that the 3-year overall survival rate for SR group was higher than that for RFA group (OR: 0.64 [95% CI: 0.45-0.93], P=0.02).

Five-year overall survival rate: Among 19 studies, 14 reported the 5-year overall survival rate. The meta-analysis showed that the 5-year overall survival rate for SR group was higher than that for RFA group (OR: 0.64 [95% CI: 0.47-0.87], P=0.005) (**Figure 3**).

Disease-free survival (DFS) rate

One-year DFS rate: All 19 studies reported the 1-year DFS rate. The meta-analysis showed that statistically significant difference existed and the SR group was more favorable (OR: 0.67 [95% CI, 0.53-0.85], P=0.001).

Three-year DFS rate: 18 studies reported the 3-year DFS rate. The meta-analysis showed that statistically significant difference existed and the SR group was more favorable (OR: 0.55 [95% CI, 0.42-0.73], P < 0.00001).

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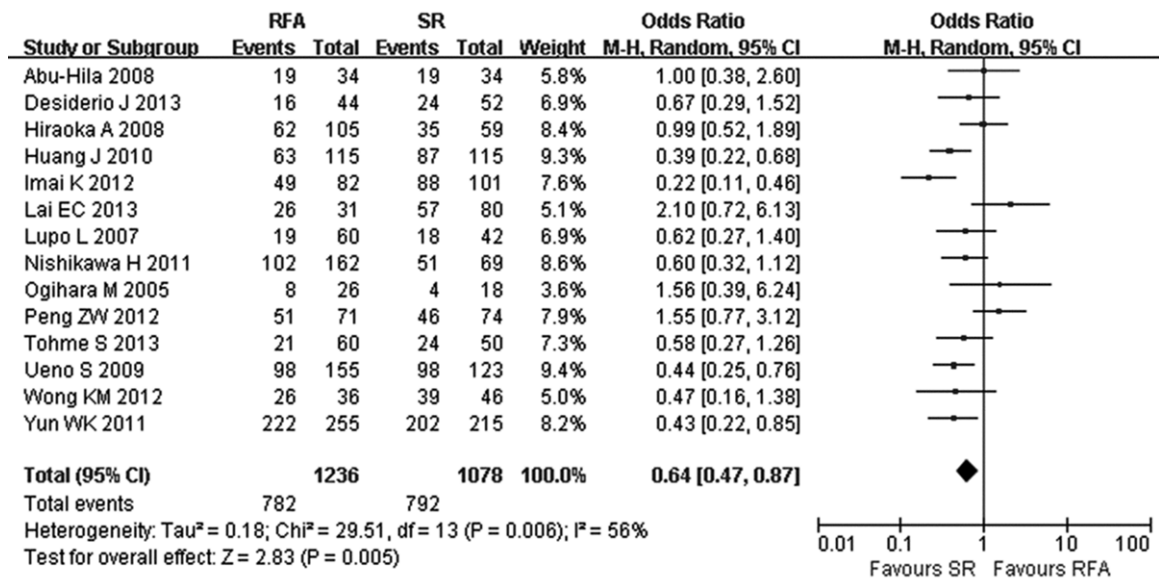


Figure 3. Forest plot for the 5-year overall survival rate for hepatocellular carcinoma conforming to Milan criteria. RFA, radiofrequency ablation; SR, surgical resection; M-H, Mantel-Haenszel.

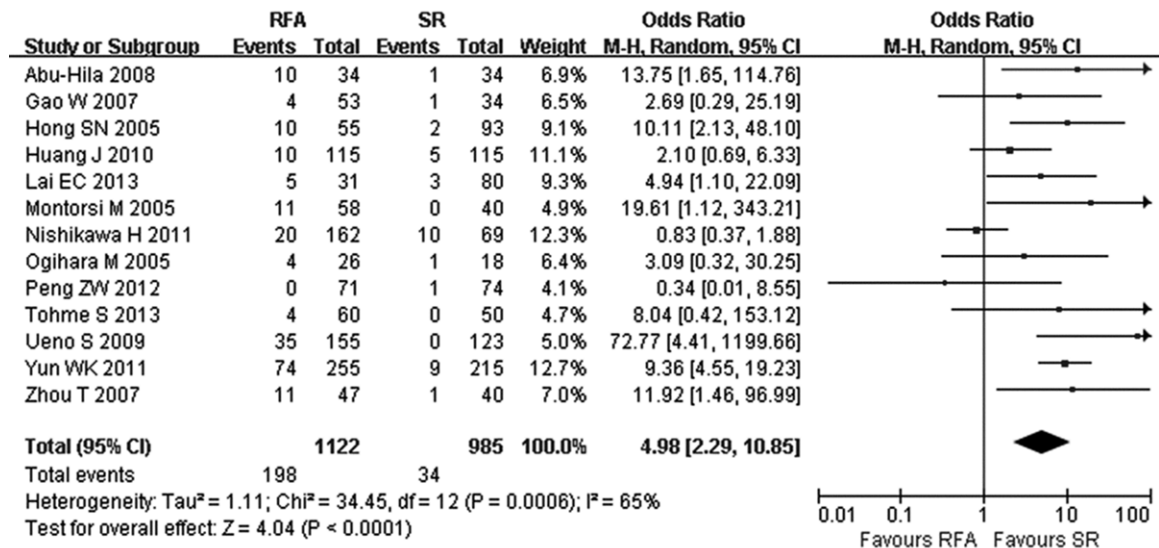


Figure 4. Forest plot for local recurrence rate for hepatocellular carcinoma conforming to Milan criteria. RFA, radiofrequency ablation; SR, surgical resection; M-H, Mantel-Haenszel.

Five-year DFS rate: 14 studies reported the 5-year DFS rate. The meta-analysis showed that statistically significant difference existed and the SR group was more favorable (OR: 0.47 [95% CI, 0.31-0.71], P=0.0003).

Local recurrence rate (local intrahepatic recurrence)

Among 19 studies included, 13 reported the local recurrence rate. This meta-analysis pro-

duced statistically significant difference and the SR group was superior to the RFA group (OR: 4.98 [95% CI, 2.29-10.85], P < 0.0001) (**Figure 4**).

Non-local recurrence rate (including the distant intrahepatic recurrence and the extrahepatic metastasis)

Of 19 studies, 12 reported non-local recurrence rate. This meta-analysis yielded no sig-

RFA versus SR for hepatocellular carcinoma treatment

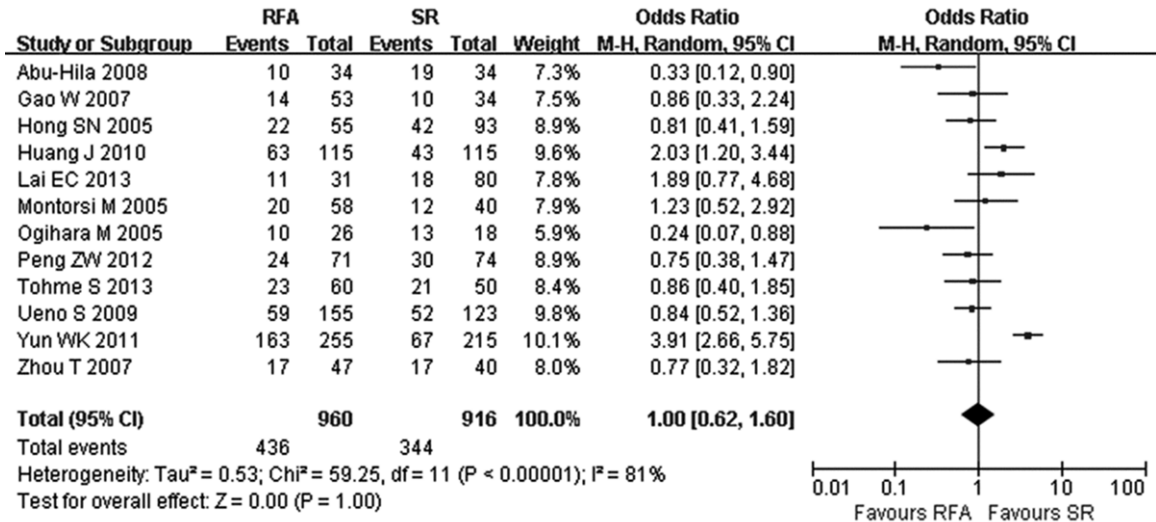


Figure 5. Forest plot for non-local recurrence rate for hepatocellular carcinoma conforming to Milan criteria. RFA, radiofrequency ablation; SR, surgical resection; M-H, Mantel-Haenszel.

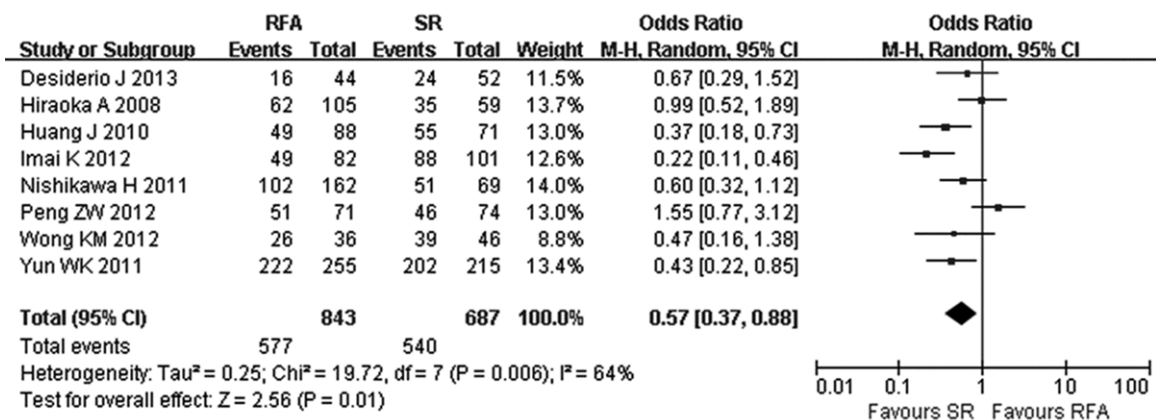


Figure 6. Forest plot for the 5-year overall survival rate for hepatocellular carcinoma ≤ 3 cm in diameter. RFA, radiofrequency ablation; SR, surgical resection; M-H, Mantel-Haenszel.

nificant difference between the RFA group and the SR group (OR: 1.00 [95% CI, 0.62-1.60], P=1.00) (Figure 5).

Comparison of outcomes between two groups for HCC ≤ 3 cm in diameter

Ten studies compared the outcomes of the RFA group and the SR group for HCC ≤ 3 cm in diameter (Table 3).

One-year overall survival rate: The meta-analysis including 10 trials yielded no significant difference between the two groups for HCC ≤ 3 cm (OR: 0.46 [95% CI, 0.18-1.16], P=0.10).

Three-year overall survival rate: The meta-analysis including 10 trials yielded no significant difference between the two groups for HCC ≤ 3 cm (OR: 0.56 [95% CI, 0.31-1.02], P=0.06).

5-year overall survival rate: The meta-analysis including 8 trials showed that significant difference existed and the SR group was more favorable for HCC ≤ 3 cm in diameter (OR: 0.57 [95% CI, 0.37-0.88], P=0.01) (Figure 6).

Local recurrence rate: The meta-analysis including 3 trials showed that there was no significant difference between the two groups for

RFA versus SR for hepatocellular carcinoma treatment

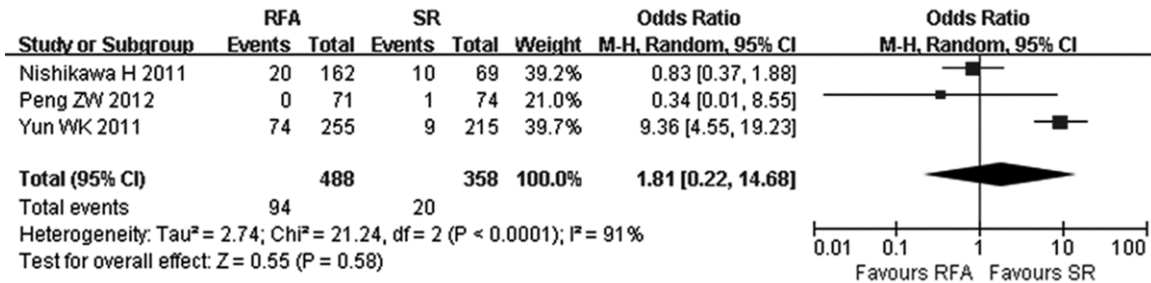


Figure 7. Forest plot for local recurrence rate for hepatocellular carcinoma ≤ 3 cm in diameter. RFA, radiofrequency ablation; SR, surgical resection; M-H, Mantel-Haenszel.

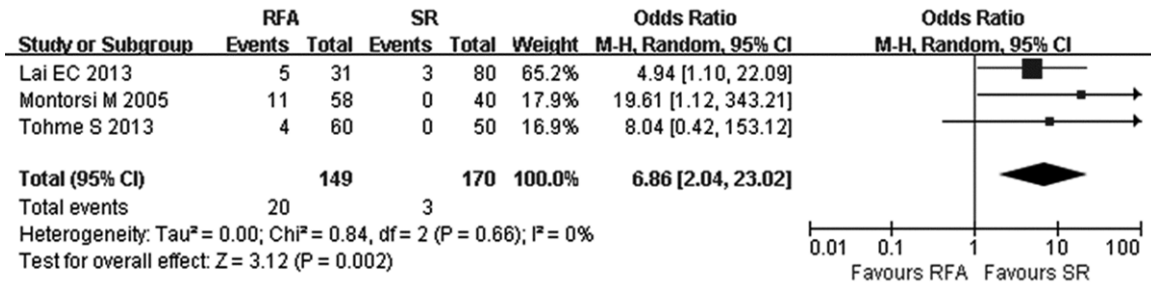


Figure 8. Forest plot for local recurrence rate between laparoscopic radiofrequency ablation and surgical resection for hepatocellular carcinoma conforming to Milan criteria. RFA, radiofrequency ablation; SR, surgical resection; M-H, Mantel-Haenszel.

HCC ≤ 3 cm in diameter (OR: 1.81 [95% CI, 0.22-14.68], $P=0.58$) (Figure 7).

Comparison of outcomes between laparoscopic RFA and SR for HCC conforming to Milan criteria

Three studies compared the outcomes of laparoscopic RFA and SR for HCC conforming to Milan criteria (Table 1) [18, 32, 33].

This meta-analysis showed that there were no significant differences between laparoscopic RFA and SR for HCC conforming to Milan criteria in terms of 1, 3 and 5-year overall survival rates (OR: 1.05 [95% CI, 0.48-2.26], $P=0.91$; OR: 0.92 [95% CI, 0.29-2.85], $P=0.88$; OR: 1.05 [95% CI, 0.30-3.66], $P=0.94$, respectively). In addition, there were also no significant differences in terms of 1, 3 and 5-year disease-free survival rates (OR: 0.92 [95% CI, 0.54-1.55], $P = 0.75$; OR: 0.51 [95% CI, 0.25-1.04], $P=0.06$; OR: 0.58 [95% CI, 0.32-1.04], $P=0.07$, respectively). As for recurrence after both treatments, compared with laparoscopic RFA, the SR group still got a lower local recurrence rate (OR, 6.86 [95% CI, 2.04-23.02]; $P=0.002$) (Figure 8) and no significant difference existed

in terms of non-local recurrence (OR, 1.21 [95% CI, 0.74-1.94]; $P=0.45$).

Assessment of publication bias

Funnel plots of all analyses including more than 10 studies were symmetrical and thereby no publication bias was presented.

Discussion

This meta study showed that SR was superior to RFA in the treatment of patients with HCC conforming to the Milan criteria in terms of 3 and 5-year survival rates and local recurrence rate, suggesting that SR remains the better choice of treatment for small HCC, whereas RFA should be considered as an effective alternative treatment when surgery is not feasible.

Only 2 randomized controlled trials with risks of detection bias, performance bias and selection bias were available and included in this meta-analysis. The main reason for this is that it remains a challenge to conduct clinical trials with randomization and double blind for choice of treatment in patients with HCC, both of which are effective means of preventing bias and

improving the objectivity of clinical evidence for both the efficacy and the safety of any approved medical product or procedure or device. Although meta-analysis is best confined to randomized controlled trials, meta-analytical techniques using non-randomized controlled trials might be a valid method in some clinical settings in which either the number or the sample size of randomized controlled trials is insufficient [34].

According to the American Association for the Study of Liver Diseases (AASLD) practice guidelines, SR is the standard treatment option for compensated cirrhotic patients with HCC conforming to the Milan criteria. However, according to the same guideline, SR is not recommended for the treatment of HCC when the expected operative mortality rate is greater than 3%. In this situation, other nonsurgical treatment options, such as local ablation therapies, may be considered as a primary treatment for HCC [35].

RFA is a minimally invasive, target-selective local ablation technique that has been applied in clinical studies since 1990s [36]. Only 1 needle is placed through the skin or laparoscope into the tumor guided by imaging modalities. It induces deep thermal injury in hepatic tissue while sparing the normal parenchyma. This procedure could be performed under conscious sedation and the hospital stay is then shortened. RFA has become one of the best alternatives in treating HCC patients who are not candidates for curative hepatectomy, because it results in large coagulated necrosis of the tumor, requires fewer treatment sessions, and achieves higher survival rates [37, 38]. Compared with surgery, RFA did not cause significant liver function damage, had a lower rate of complications and was more affordable in terms of treatment costs [39]. With newer and larger multiple probes, larger tumors can be ablated predictably. At the same time, RFA can be performed not only percutaneously but also by laparoscopic or laparotomy approach that is simpler than hepatectomy [19].

But the indications of RFA for HCC and the long-term survival are still matter of debate. There is some dispute whether survival benefits of RFA exist for patients with HCC conforming to the Milan criteria compared with SR. This meta-analysis demonstrated that SR had significantly better survival rates in terms of overall sur-

vival rates at 5 years, whereas overall survival rate at 1 year between the two groups did not reach statistical significance in patients with HCC conforming to the Milan criteria as well as patients with HCC ≤ 3 cm, and the overall disease-free survival rates were all significantly lower in the group of RFA, indicating that treatment of HCC by SR could increase the long-term survival rates, and may lower the overall recurrence of HCC when compared with RFA. This could be partly explained by the increased understanding of liver segmental anatomy, and the advances in surgical and radiological techniques and perioperative care, which have led to a dramatic decrease in operative mortality and an improvement in surgical outcome [40].

A high rate of recurrence after treatment is the main factor affecting overall survival and late death of patients with HCC [41]. The risk factors for tumor recurrence after treatment include tumor location, tumor size, multinodular tumors, and an insufficient safety margin [42-44]. Recurrences may also arise because of pre-existing microscopic tumor foci that are undetected by imaging modalities or malignant cells that have been disseminated during manipulation [45, 46].

Many investigators have reported that local recurrence rates are largely dependent on minimal safety margin [47, 48]. In the current study, SR is preferable to RFA in terms of local recurrence, which means that RFA is still less reliable than SR in terms of local tumor control, in patients with HCC conforming to Milan criteria. This may be a result of the safety margin of RFA being narrower than that of SR, as SR usually removes the entire Couinaud segment containing tumors, so the clearance of tumors and any potential sites of microscopic disease will be more complete in these patients. Local recurrences after RFA may be attributable to insufficient ablation of the primary tumor and/or the presence of undetected tumor venous invasion in the adjacent liver [49]. Besides, recent research demonstrated that insufficient RFA caused by low temperature at the target sites could be an important cause of rapid progression of residual hepatic carcinoma [50]. But the situation changes regarding to patients with HCC ≤ 3 cm in diameter as demonstrated by the meta-analysis that there was no significant difference between the RFA group and the SR group in terms of local recurrence rate, indicating that RFA could reach a sufficient safety mar-

gin for HCC ≤ 3 cm in diameter more successfully.

As regards the non-local recurrence, no differences were found between the two groups. This finding is reasonable because the occurrence of distant recurrence is correlated with the host factors and initial tumor factors [51], and the treatment does not affect this outcome.

RFA can be performed by percutaneous, laparoscopic and open approaches. This meta study shows no significant difference between laparoscopic RFA and SR in terms of both overall survival rate and disease-free survival rate at 1, 3 and 5-year, which indicates that laparoscopic RFA could reach more effective outcomes although with a higher local recurrence rate compared with SR, probably because laparoscopic and open approaches increase the chance of detection of unknown intrahepatic and extrahepatic tumors owing to complete abdominal exploration and intraoperative ultrasound assessment. The additional advantages of open and laparoscopic approaches are the accurate placement of electrodes and the possibly sufficient treatment of tumors in close proximity to the adjacent organs, which are inaccessible areas for percutaneous RFA [52].

This study has several limitations. First, the number of studies included in this meta-analysis is limited especially in subgroup analyses and the majority of data in the present study come from non-randomized controlled trials, therefore the overall level of clinical evidence is low and several bias may exist [53]. Furthermore, unequal constitution of patients due to heterogeneity between two groups in terms of patient demographics and tumor characteristics may affect these findings. Second, several different RFA systems were used in the treatment centers, such as RITA Medical System (Mountain View, CA, USA), Radionics (Burlington, MA, USA) and Valleylab (Boulder, CO, USA). Different RFA systems would also impact on the pooling of data and interpretation of results. Unfortunately, we failed to find any study that compared the outcomes of different RFA systems on therapy efficacy of HCC. Thus, we were not able to assess the influence of these factors. Third, various therapies were used in the tumor recurrences in both RFA and

SR groups, including repeat RFA, transarterial chemoembolization (TACE), second resection, systemic chemotherapy, and supportive treatment. Different therapeutic schedules for tumor recurrences could affect these findings absolutely. Fourth, the search language was limited to English. The integrity of the data was affected to a certain extent. Fifth, funnel plots can be suggestive of publication bias. However, a firm conclusion about bias is difficult to reach as the asymmetry of the funnel plot is minimal. In addition, funnel plots can show asymmetry for reasons other than publication bias. Therefore, our pooled OR might be an overestimate of the true effect. Due to data constraints, this meta-analysis could not carry out stratified analyses of other possible confounding factors such as outcomes of HCC > 3 cm in diameter, different Child-Pugh grading, different pathogens and different surgery procedures depending on different tumor locations.

Thus, the findings have to be carefully interpreted due to the lower level of evidence and other limitations. Further prospective and multi-center RCTs with longer follow-up are required to provide clinically useful data and clarify the exact value of SR and RFA for HCC conforming to the Milan criteria.

In conclusion, surgical resection was superior to RFA in the treatment of patients with HCC conforming to the Milan criteria in terms of long-term survival rates due to more reliable local tumor control, but there is no significant difference in short-term survival rate between the two treatments. Surgical resection remains the better choice of treatment for HCC conforming to the Milan criteria, whereas RFA should be considered as an effective alternative treatment when surgery is not feasible. As for RFA technique, laparoscopic approach may be more effective than percutaneous approach for HCC conforming to Milan criteria.

Disclosure of conflict of interest

None.

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