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Correspondence and requests for materials should be addressed to X.M. (xia.meng@biomerieux.com)

* These authors contributed equally to this work.

Comparison of Hepatic Resection and Radiofrequency Ablation for Small Hepatocellular Carcinoma: A Meta-Analysis of 16,103 Patients

Qinghua Xu[1,2]*, Seijin Kobayashi[3]*, Xun Ye[1,2] & Xia Meng[1,2]

[1]Fudan University Shanghai Cancer Center – Institut Mérieux Laboratory, Fudan University Shanghai Cancer Center, Shanghai, China, [2]bioMérieux (Shanghai) Co. Ltd., Shanghai, China, [3]École Polytechnique ParisTech, Paris, France.

We performed a meta-analysis to evaluate the therapeutic effects of radiofrequency ablation (RFA) and surgical hepatic resection (HR) in the treatment of small hepatocellular carcinoma (HCC). Thirty-one studies were included in the analysis. A total of 16,103 patients were involved: 8,252 treated with RFA and 7,851 with HR. Compared to the RFA group, the 3, 5-year overall and disease-free survival rates in the HR group were significantly higher. On the other hand, complications were significantly fewer and hospital-stay was significantly shorter in the RFA group than in the HR group. In subgroup analyses, the overall and disease-free survival in the HR group were also significantly higher than those in the RFA group for HCCs $\leq$ 3 cm, whereas there were no significant differences between the two groups for HCCs $\leq$ 2 cm. Our analysis showed that although HR was associated with higher complication rate and longer hospital-stay, HR is proposed as the first-line treatment rather than RFA for patients with HCCs larger than 2 cm. For patients with HCCs of 2 cm or less, RFA may be an alternative to HR because of their comparable long-term efficacy.

Hepatocellular carcinoma (HCC) is the fifth most common malignant tumor and the second leading cause of cancer-related deaths worldwide[1]. Hepatic resection (HR) represents the most common first-line therapy for patients with HCC; however, the majority of primary liver cancers are not suitable for curative resection at the time of diagnosis[2]. Factors precluding surgery include extrahepatic metastases, vascular invasion, high-risk anatomical location, excessive size or number of lesions, insufficient remnant liver to support life and co-morbid conditions[3]. Therefore, several nonsurgical alternative techniques have been developed, such as acetic acid injection, percutaneous ethanol injection (PEI), radiofrequency ablation (RFA) and microwave ablation (MWA). Among these, RFA has been the most widely investigated therapeutic option for unresectable HCCs. Numerous large series have shown that RFA is safe, with minimal morbidity and mortality[4]. General consensus guidelines from North America and Japan recommend that RFA be used for three or fewer HCCs with a diameter of 3 cm at most[5].

Nowadays, RFA has been commonly used as an alternative for patients with small HCCs who are not suitable for HR. However, whether it can compete with surgery as the first-line treatment still remains highly controversial. The results from published studies that examined the efficacy of RFA and HR for small HCC have been inconsistent. Huang *et al.*[6] and Yun *et al.*[7] reported that HR were more favorable regardless of tumor size. Elsewhere, Chen *et al.*[8] and Feng *et al.*[9] concluded that RFA was as effective as HR in the treatment of small HCCs. Additionally, Nashikawa *et al.*[10] and Peng *et al.*[11] recommended RFA as the first-line treatment for small HCCs.

Meta-analysis is a useful tool for revealing trends that might not be apparent in a single study. Pooling of independent but similar studies increases precision and therefore increases the confidence level of the findings[12]. The aim of this study is to evaluate the evidence from previous studies that directly compare the efficacy of RFA and HR in the treatment of small HCCs by summarizing it quantitatively with a meta-analysis approach.

Results

Literature Search. A flow diagram of our literature search was shown in Figure 1. Total searches yielded 1210 entries. After screening based on titles and abstracts, 72 articles appeared to be potentially relevant. Meta-analysis

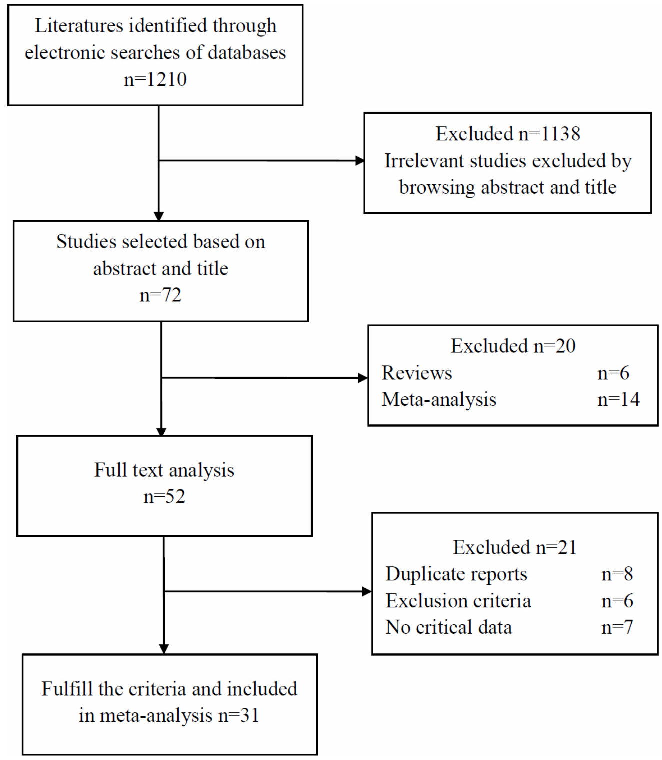


Figure 1 | Flow chart showing selection of studies for meta-analysis.

(14 articles) and systematical reviews (6 articles) were then excluded. Among the remaining 52 studies, 21 were eliminated after the full text analysis for the following reason: overlapping data or duplicated reports from the same study population (8 studies), lack of critical data (7 studies), and matching one of the exclusion criteria (6 studies). In the end, a total of 31 studies were selected, including three randomized controlled trials (RCTs) and 28 nonrandomized controlled trials (NRCTs)[6–10,13–38].

Study Characteristics. The baseline characteristics of included studies are summarized in Table 1. The 31 studies were published between 2004 and 2013, and involved a total of 16,103 patients. 8,252 patients were treated with RFA as the initial treatment and 7,851 patients who were treated with HR. Of these 31 studies, 15 were conducted in China, 6 in Italy, 5 in Japan, 3 in South Korea, 1 in United Kingdom and 1 in United States of America. The mean of age ranged from 41.5 to 68.4 years. The male: female ratio in the pooled data was 2.2 : 1.

Overall Survival Rate. Overall survival rates at 3- and 5-year in the RFA group were 78.6% and 60.8% respectively. The corresponding rates for the HR group were 83.9% and 71.4% (Table 2). The difference was significant and favorable to HR group at 3-year (31 trials, odds ratio (OR): 0.65, 95% confidence intervals (95% CI): 0.53–0.80, Figure 2A), and at 5-year (20 trials, OR: 0.57, 95% CI: 0.48–0.67, Figure 2B).

Disease-free Survival Rate. Disease-free survival rates at 3- and 5-year were 41.1% and 26.6% respectively in the RFA group, 56.7% and 37.8% in the HR group (Table 2). Disease-free survival rates were significantly higher in the HR group for 3-year (27 trials, OR: 0.50, 95% CI: 0.41–0.61, Figure 3A), and 5-year (20 trials, OR: 0.47, 95% CI: 0.35–0.65, Figure 3B).

Complications and Hospital-Stay. The complication rate was 9.3% for RFA group, and 30.1% for HR group (Table 2). Complications were significantly fewer in the RFA group than in the HR group (16 trials, OR: 0.25, 95% CI: 0.17–0.37, Figure 4A). The mean length of hospital-stay was 12.6 days for HR group and 6.8 days for RFA. The HR group had significant longer hospital-stay than RFA group (8 trials, weighted mean difference (WMD):5.83, 95% CI: 4.01–7.66, Figure 4B).

Subgroup Analysis. For tumors smaller than 3 cm, the data presented in Table 2 showed that the difference was significant and favorable to HR group at 3-year (19 trials, OR: 0.62, 95% CI: 0.43–0.89) and at 5-year (16 trials, OR: 0.55, 95% CI: 0.42–0.72). Disease-free survival rates were significantly higher in the HR group for 3-year (17 trials, OR: 0.52, 95% CI: 0.39–0.70) and 5-year (15 trials, OR: 0.57, 95% CI: 0.38–0.87).

In the case of very small tumors (<2 cm), overall survival rates at 3- and 5-year in the RFA group were 80.6% and 69.0% respectively. The corresponding rates for the HR group were 83.7% and 74.2%; disease-free survival rates at 3- and 5-year were 52.4% and 42.5% respectively in the RFA group, 53.7% and 41.6% in the HR group. In terms of overall survival and disease-free survival, there were no significant differences between these two groups.

Sensitivity Analysis and Publication Bias. The results suggested that the influence of each individual data set to the pooled ORs and WMD was not significant. The Egger's test showed no evidence of publication bias for the majority of comparison (Table 2).

Discussion

The choice between RFA and HR for small HCC is still a matter of debate. The results from previous studies that examined the efficacy of RFA and HR in the treatment of small HCC have been inconsistent. The current meta-analysis summarizes the results of 31 studies, with a total of 16,103 patients: 8,252 treated with RFA and 7,851 with HR. Our results showed that HR was associated with better overall and disease-free survival compared with RFA in the treatment of patients with small HCCs.

The main reason for the inferiority of RFA to HR in terms of the survival rates is thought to be its higher local recurrence rate. This could be due to insufficient ablation of the primary tumor, heat sink effect, and the limitations of imaging modalities[39]. Additionally, HR usually removed a relatively suitable margin of the rim of normal liver tissue with the primary tumor and eliminated both the tumor and cancer embolus[40]. Hence, the relatively complete clearance of targeted tumors and potential tissues of microscopic lesions by surgical resection may explain the superior prognosis of HR for patients with small HCCs.

It had been reported that the beneficial effect of HR was more prominent in patients with HCC of more than 2 cm, because HCC of more than 2 cm had a higher incidence of vascular invasion than HCC of 2 cm or less[41]. In subgroup analysis, our results showed that for very early-stage HCC (size $\leq$ 2 cm), there were no significant differences between RFA and HR in terms of overall and disease-free survival. However, the findings need to be carefully interpreted, owing to the fact that this subgroup of patients are likely to have early disease presentation and good tumour biology. Hence, overall satisfactory outcomes can be achieved irrespective of the type of treatment. Although there was no statistically significant difference in terms of disease-free and overall survival, it seems reasonable to offer HR to patients with tumours less than 2 cm if appropriate, and RFA as an alternative treatment if resection is not suitable.

On the other hand, our study suggested that RFA was associated with less complications and shorter hospital-stay compared with HR. In clinical practice, RFA can be performed without general anesthesia. Most patients undergoing percutaneous RFA only require 2–3 days' stay[42]. Therefore, RFA has a considerable advantage over HR in providing a better short-term postoperative result.

Table 1 | Characteristics of studies included in the meta-analysis

Study	Design	Period	Country	Therapy	No. pts.	Age (mean ± SD)	Sex (m/f)	Tumor size (mean ± SD, cm)	Tumor amount (single/multiple)	Child-Pugh class (A/B/C)	Newcastle-Ottawa Scale			
											Total	Selection	Comparability	Outcome
Chen MS 2006[8]	RCT	1999–2004	China	HR	90	49.4 ± 10.9	75/15	≤5 cm	90/0	90/0/0	9	4	2	3
				RFA	71	51.9 ± 11.2	56/15	≤5 cm	71/0	71/0/0				
Huang J 2010[6]	RCT	2003–2005	China	HR	115	55.9 ± 12.7	85/30	≤5 cm	89/26	106/9/0	8	4	1	3
				RFA	115	56.6 ± 14.3	79/36	≤5 cm	84/31	110/5/0				
Feng K 2012[9]	RCT	2005–2008	China	HR	84	47 (18–76)	75/9	2.6 ± 0.8	52/32	43/41/0	9	4	2	3
				RFA	84	51 (24–83)	79/5	2.4 ± 0.6	48/36	39/45/0				
Vivarelli M 2004[36]	NRCT	1998–2002	Italy	HR	79	65.2 ± 8.2	57/22	-	66/13	70/9/0	6	3	0	3
				RFA	79	67.8 ± 8.7	67/12	-	46/33	43/36/0				
Hong SN 2005[14]	NRCT	1999–2001	Korea	HR	93	49.2 ± 9.9	69/24	2.5 ± 0.8	93/0	-	6	3	0	3
				RFA	55	59.1 ± 9.6	41/14	2.4 ± 0.6	55/0	-				
Cho CM 2005[17]	NRCT	2000–2002	Korea	HR	61	57	48/13	3.4 ± 1.0	-	61/0/0	7	3	1	3
				RFA	99	58	76/23	3.1 ± 0.8	-	99/0/0				
Montorsi M 2005[16]	NRCT	1997–2003	Italy	HR	40	67 ± 9	33/7	≤5 cm	40/0	32/8/0	7	3	1	3
				RFA	58	67 ± 6	43/15	≤5 cm	58/0	40/18/0				
Gao W 2007[18]	NRCT	1999-2006	China	HR	34	51.5 (38–67)	28/6	2.6 ± 0.4	32/2	33/1/0	6	3	0	3
				RFA	53	57.1 (31–81)	41/12	2.5 ± 0.4	29/24	40/11/2				
Lupo L 2007[15]	NRCT	1999–2006	Italy	HR	42	67 (28–80)	33/9	4.0 (3.0–5.0)	42/0	28/14/0	8	3	2	3
				RFA	60	68 (42–85)	47/13	3.7 (3.0–5.0)	60/0	44/16/0				
Zhou T 2007[19]	NRCT	2001–2006	China	HR	40	53 ± 13	35/5	≤5 cm	38/2	37/3/0	8	3	2	3
				RFA	47	57 ± 14	37/10	≤5 cm	40/7	40/7/0				
Abu-Hilal M 2008[20]	NRCT	1991–2003	UK	HR	34	67	26/8	3.8	34/0	25/9/0	7	3	1	3
				RFA	34	65	27/7	3.0	34/0	27/7/0				
Hiraoka A 2008[33]	NRCT	2000–2007	Japan	HR	59	62.4 ± 10.6	44 : 15	2.27 ± 0.55	59/0	54/5/0	7	3	1	3
				RFA	105	69.4 ± 9.1	76 : 29	1.98 ± 0.52	105/0	79/26/0				
Guglielmi A 2008[21]	NRCT	1996–2006	Italy	HR	91	-	73/18	≤6 cm	69/21	69/22/0	6	3	0	3
				RFA	109	-	88/21	≤6 cm	65/44	64/45/0				
Bu XY 2009[38]	NRCT	2000–2006	China	HR	42	53.9 ± 10.7	36/6	≤5 cm	38/4	36/6/0	7	3	1	3
				RFA	46	55.9 ± 7.4	40/6	≤5 cm	38/8	25/21/0				
Santambrogio R 2009[22]	NRCT	1997–2007	Italy	HR	78	68 ± 8	55/23	2.91 ± 1.23	78/0	78/0/0	8	3	2	3
				RFA	74	68 ± 7	59/15	2.66 ± 1.06	74/0	74/0/0				
Ueno S 2009[35]	NRCT	2000–2005	Japan	HR	123	67 (28–85)	82/41	2.7 ± 0.1	110/13	91/31/1	6	3	0	3
				RFA	155	66 (40–79)	100/55	2.0 ± 0.1	101/54	52/92/11				
Guo WX 2010[31]	NRCT	2002–2007	China	HR	73	50.5 (17–68)	57/16	3.5	0/73	71/2/0	7	3	1	3
				RFA	86	52.5 (26–80)	63/23	3.2	0/86	84/2/0				
Yun WK 2010[7]	NRCT	2000–2007	Korea	HR	215	51.7 ± 9.7	171/44	2.1 ± 0.5	215/0	215/0/0	6	3	0	3
				RFA	255	57.0 ± 9.9	197/58	2.1 ± 0.5	255/0	255/0/0				
Hung HH 2011[13]	NRCT	2002–2007	China	HR	229	60.1 ± 12.6	184/45	2.88 ± 1.06	181/48	-	6	3	0	3
				RFA	190	67.4 ± 11.5	121/69	2.37 ± 0.92	152/38	-				
Liu H 2011[23]	NRCT	2008–2010	China	HR	35	48.2 ± 15.6	29/6	≤5 cm	35/0	35/0/0	7	3	1	3
				RFA	32	46.1 ± 24.1	26/6	≤5 cm	32/0	32/0/0				
Nishikawa H 2011[10]	NRCT	2004–2010	Japan	HR	69	67.4 ± 9.7	50/19	2.68 ± 0.49	69/0	45/5/0	7	3	1	3
				RFA	162	68.4 ± 8.7	95/67	1.99 ± 0.62	162/0	102/22/3				
Wang JH 2011[26]	NRCT	2002–2009	China	HR	260	-	206/54	≤3 cm	241/19	257/3/0	7	3	1	3
				RFA	345	-	221/124	≤3 cm	264/81	282/63/0				
Zhang J 2011[37]	NRCT	2006–2009	China	HR	103	56.4 ± 15.2	78/25	≤5 cm	89/14	81/22/0	6	3	0	3
				RFA	85	58.5 ± 12.9	62/23	≤5 cm	59/16	31/39/15				
Du JK 2012[24]	NRCT	2003–2007	China	HR	58	56.6 ± 8.6	33/25	≤5 cm	-	-	6	3	0	3
				RFA	58	58.3 ± 8.2	36/22	≤5 cm	-	-				

Table 1 | Continued

Study	Design	Period	Country	Therapy	No. pts.	Age (mean ± SD)	Sex (m/f)	Tumor size (mean ± SD, cm)	Tumor amount (single/multiple)	Child-Pugh class (A/B/C)	Newcastle-Ottawa Scale Total	Selection	Comparability	Outcome
Imai K 2012[34]	NRCT	2000–2011	Japan	HR	101	63.3 ± 1 9.7	75/26	2.14 ± 0.55	101/0	97/4/0	6	3	0	3
				RFA	82	67.6 ± 1 8.5	46/36	1.87 ± 0.50	82/0	60/22/0				
Peng ZW 2012[25]	NRCT	2003–2008	China	HR	74	51.5 ± 12.1	65/9	1.1 ± 0.5	74/0	62/0/12	8	3	2	3
				RFA	71	51.1 ± 12.1	63/8	1.2 ± 0.6	71/0	58/0/13				
Tohme S 2012[29]	NRCT	2001–2011	USA	HR	50	66.3 ± 1	31/19	3.07 ± 1.17	39/11	27/6/17	6	2	1	3
				RFA	60	65.6 ± 12	38/22	2.36 ± 1.94	47/13	40/16/4				
Desiderio J 2013[27]	NRCT	2004–2012	Italy	HR	52	65.6 ± 4.8	37/15	≤3 cm	22/30	52/0/0	7	3	1	3
				RFA	44	64.4 ± 6.5	35/9	≤3 cm	19/25	44/0/0				
Hasegawa K 2013[32]	NRCT	2000–2005	Japan	HR	5361	66 (48–77)	3967/1394	≤3 cm	4458/903	4000/1361/0	6	3	0	3
				RFA	5548	69 (52–80)	3569/1979	≤3 cm	4068/1480	3349/2199/0				
Lai EC 2013[28]	NRCT	2006–2012	China	HR	80	60.8 ± 9.9	55/25	2.9 ± 1.1	71/9	-	7	3	1	3
				RFA	31	63.1 ± 12.8	19/12	1.8 ± 0.6	28/3	-				
Wong KM 2013[30]	NRCT	2004–2009	China	HR	46	55.1 ± 12	30/16	2.1 ± 0.6	46/0	46/0/0	7	3	1	3
				RFA	36	63.5 ± 13	18/18	1.9 ± 0.6	36/0	36/0/0				

Table 2 | Summary of the results on the long-term efficacy of RFA versus HR in the treatment of small HCCs

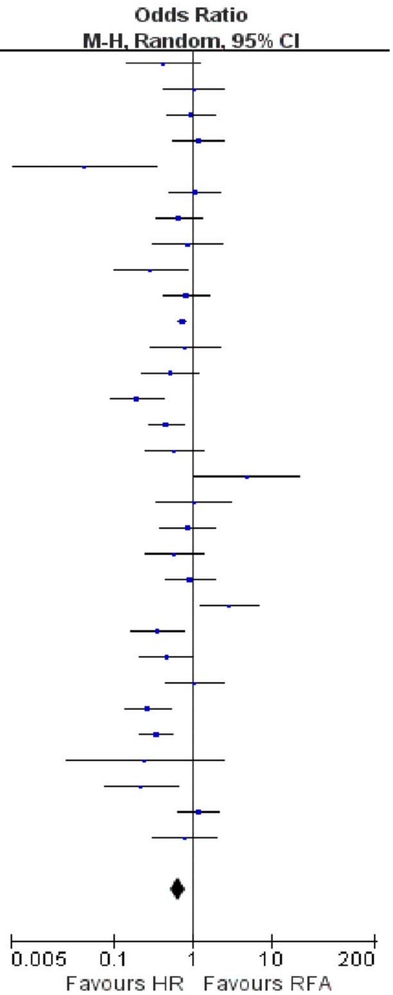
Outcome	No. studies	No. patients	RFA	HR	Odds Ratio [95% CI]	Z test (*P*-value)	I^2	Q test (*P*-value)	Egger's test (*P*-value)
≤5 cm									
Overall survival rate									
3-year	31	16,103	78.6%	83.9%	0.65 [0.53, 0.80]	<0.001	61%	<0.001	0.43
5-year	20	14,665	60.8%	71.4%	0.57 [0.48, 0.67]	<0.001	42%	0.03	0.51
Disease-free survival rate									
3-year	27	15,524	41.1%	56.7%	0.50 [0.41, 0.61]	<0.001	72%	<0.001	0.42
5-year	20	14,640	26.6%	37.8%	0.47 [0.35, 0.65]	<0.001	84%	<0.001	0.08
≤3 cm									
Overall survival rate									
3-year	19	13,298	81.2%	85.7%	0.62 [0.43, 0.89]	0.009	64%	<0.001	0.35
5-year	16	13,075	61.8%	71.9%	0.55 [0.42, 0.72]	<0.001	56%	0.003	0.36
Disease-free survival rate									
3-year	16	13,109	42.5%	57.2%	0.52 [0.39, 0.70]	<0.001	74%	<0.001	0.58
5-year	15	12,912	27.8%	37.3%	0.57 [0.38, 0.87]	0.01	85%	<0.001	0.48
≤2 cm									
Overall survival rate									
3-year	4	442	80.6%	83.7%	0.54 [0.12, 2.37]	0.41	81%	0.001	0.27
5-year	4	442	69.0%	74.2%	0.65 [0.27, 1.55]	0.33	67%	0.03	0.58
Disease-free survival rate									
3-year	4	442	52.4%	53.7%	1.00 [0.47, 2.15]	0.99	72%	0.01	0.99
5-year	4	442	42.5%	41.6%	1.08 [0.56, 2.11]	0.81	61%	0.05	0.60

A

Study or Subgroup	RFA Events	RFA Total	HR Events	HR Total	Weight	Odds Ratio M-H, Random, 95% CI
Abu-Hilal 2008	21	34	27	34	2.4%	0.42 [0.14, 1.24]
Bu XY 2009	30	46	27	42	3.0%	1.04 [0.43, 2.50]
Chen MS 2006	51	71	66	90	3.8%	0.93 [0.46, 1.86]
Cho CM 2005	79	99	47	61	3.5%	1.18 [0.54, 2.55]
Desiderio J 2012	30	44	51	52	0.9%	0.04 [0.01, 0.34]
Du JK 2012	36	58	35	58	3.6%	1.08 [0.51, 2.27]
Feng K 2012	56	84	63	84	4.0%	0.67 [0.34, 1.30]
Gao W 2007	39	53	26	34	2.6%	0.86 [0.32, 2.33]
Guglielmi A 2008	16	32	24	31	2.3%	0.29 [0.10, 0.87]
Guo WX 2010	55	86	50	73	4.0%	0.82 [0.42, 1.58]
Hasegawa K 2013	4494	5548	4573	5361	6.8%	0.73 [0.66, 0.81]
Hiraoka A 2008	92	105	53	59	2.5%	0.80 [0.29, 2.23]
Hong SN 2005	40	55	78	93	3.3%	0.51 [0.23, 1.15]
Huang J 2010	80	115	106	115	3.4%	0.19 [0.09, 0.43]
Hung HH 2011	147	190	202	229	4.7%	0.46 [0.27, 0.77]
Imai K 2012	69	82	91	101	3.0%	0.58 [0.24, 1.41]
Lai EC 2012	29	31	60	80	1.4%	4.83 [1.06, 22.09]
Liu H 2011	24	32	26	35	2.3%	1.04 [0.34, 3.13]
Lupo L 2007	32	60	24	42	3.4%	0.86 [0.39, 1.90]
Montorsi 2005	35	58	29	40	3.1%	0.58 [0.24, 1.38]
Nishikawa H 2011	129	162	56	69	3.7%	0.91 [0.44, 1.85]
Peng ZW 2012	62	71	52	74	3.1%	2.91 [1.23, 6.88]
Santambrogio R 2009	49	74	66	78	3.4%	0.36 [0.16, 0.78]
Tohme S 2012	30	60	34	50	3.4%	0.47 [0.22, 1.03]
Ueno S 2009	143	155	113	123	3.1%	1.05 [0.44, 2.53]
Vivarelli M 2004	26	79	51	79	4.0%	0.27 [0.14, 0.52]
Wang JH 2011	260	345	234	260	5.0%	0.34 [0.21, 0.55]
Wong KM 2012	33	36	45	46	0.7%	0.24 [0.02, 2.46]
Yun WK 2010	235	255	211	215	2.3%	0.22 [0.07, 0.66]
Zhang J 2011	33	85	36	103	4.4%	1.18 [0.65, 2.14]
Zhou T 2007	33	47	30	40	2.8%	0.79 [0.30, 2.03]
Total (95% CI)		**8252**		**7851**	**100.0%**	**0.65 [0.53, 0.79]**
Total events	6488		6586			

Heterogeneity: Tau² = 0.16; Chi² = 77.68, df = 30 (P < 0.00001); I² = 61%

Test for overall effect: Z = 4.17 (P < 0.0001)



B

Study or Subgroup	RFA Events	RFA Total	HR Events	HR Total	Weight	Odds Ratio M-H, Random, 95% CI
Abu-Hilal 2008	19	34	19	34	2.6%	1.00 [0.38, 2.60]
Bu XY 2009	17	46	21	42	3.2%	0.59 [0.25, 1.37]
Desiderio J 2012	16	44	24	52	3.4%	0.67 [0.29, 1.52]
Guglielmi A 2008	9	32	17	31	2.2%	0.32 [0.11, 0.92]
Guo WX 2010	18	86	32	73	4.3%	0.34 [0.17, 0.68]
Hasegawa K 2013	3390	5548	3812	5361	15.8%	0.64 [0.59, 0.69]
Hiraoka A 2008	62	105	35	59	4.8%	0.99 [0.52, 1.89]
Huang J 2010	63	115	87	115	5.8%	0.39 [0.22, 0.68]
Hung HH 2011	128	190	182	229	7.7%	0.53 [0.34, 0.83]
Imai K 2012	49	82	79	101	4.8%	0.41 [0.22, 0.79]
Lai EC 2012	26	31	57	80	2.2%	2.10 [0.72, 6.13]
Lupo L 2007	19	60	18	42	3.4%	0.62 [0.27, 1.40]
Nishikawa H 2011	102	162	51	69	5.1%	0.60 [0.32, 1.12]
Peng ZW 2012	51	71	46	74	4.3%	1.55 [0.77, 3.12]
Santambrogio R 2009	30	74	42	78	4.9%	0.58 [0.31, 1.11]
Tohme S 2012	21	60	24	50	3.7%	0.58 [0.27, 1.26]
Ueno S 2009	98	155	98	123	6.0%	0.44 [0.25, 0.76]
Wang JH 2011	211	345	208	260	9.1%	0.39 [0.27, 0.57]
Wong KM 2012	26	36	39	46	2.1%	0.47 [0.16, 1.38]
Yun WK 2010	222	255	202	215	4.6%	0.43 [0.22, 0.85]
Total (95% CI)		**7531**		**7134**	**100.0%**	**0.57 [0.48, 0.67]**
Total events	4577		5093			

Heterogeneity: Tau² = 0.05; Chi² = 32.67, df = 19 (P = 0.03); I² = 42%

Test for overall effect: Z = 6.53 (P < 0.00001)

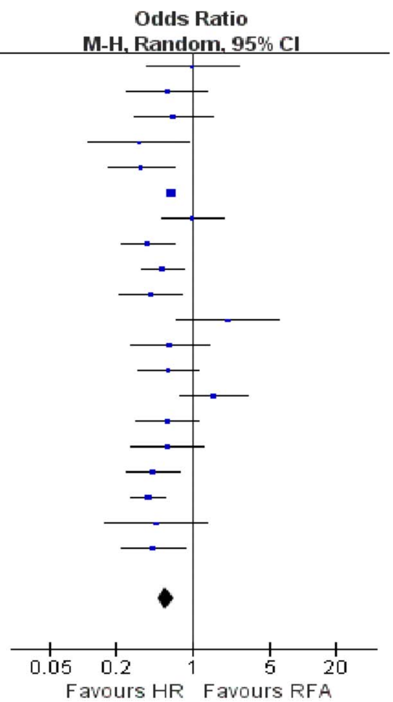


Figure 2 | Results of the meta-analysis on 3-, 5-year overall survival in patients with HCCs smaller than 5 cm. (A) 3-year overall survival; (B) 5-year overall survival.

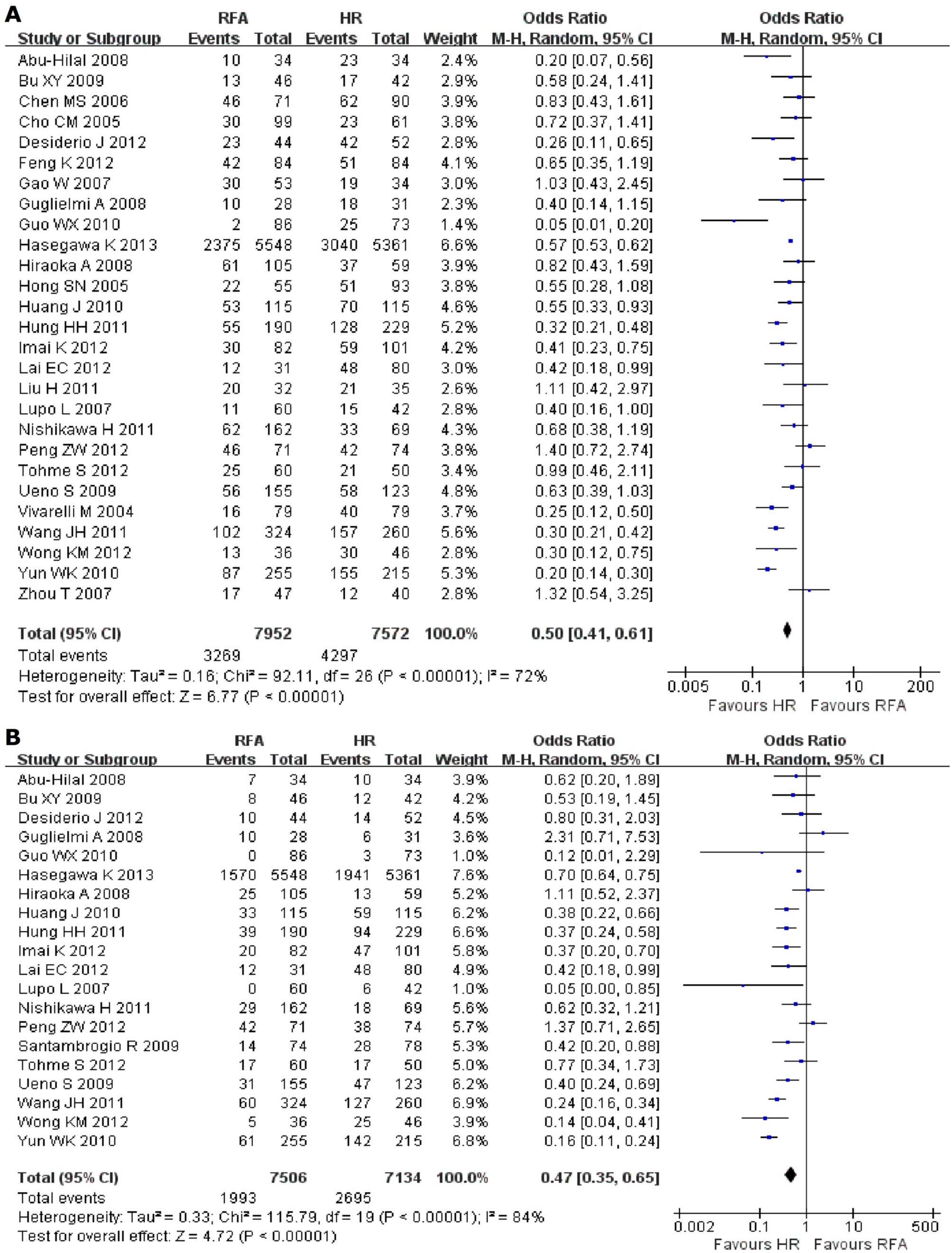


Figure 3 | Results of the meta-analysis on 3-, 5-year disease-free survival in patients with HCCs smaller than 5 cm. (A) 3-year disease-free survival; (B) 5-year disease-free survival.

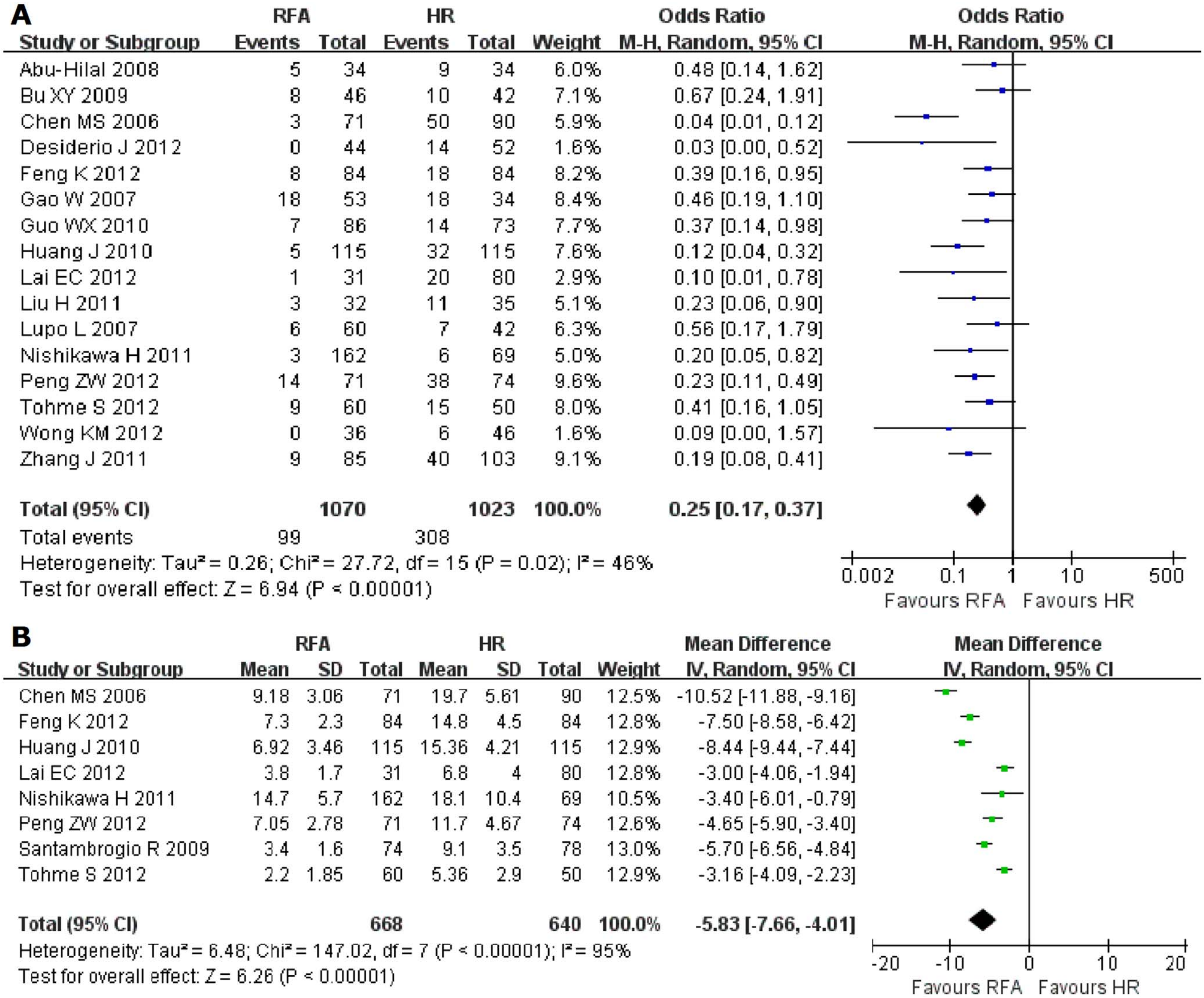


Figure 4 | Results of the meta-analysis on complications and hospital-stay in patients with HCCs smaller than 5 cm. (A) complications; (B) hospital-stay.

Previous meta-analysis studies had compared the efficacy of RFA versus HR in treating small HCCs, but the results remain inconsistent. Zhou *et al.* found that HR was superior to RFA in the treatment of HCC patients, particularly for tumors > 3 cm; for tumors ≤ 3 cm HR did not differ significantly from RFA for survival[43]. However, Xu *et al.* showed that HR was associated with significantly improved survival benefits compared with RFA for HCC ≤ 3 cm[44]. Cucchetti *et al.* recently conducted a systematical review and recommended to offer RFA to very small HCCs (<2 cm), since in this instance complete necrosis is most likely to be achieved. For larger tumors, namely > 2 cm and especially if >3 cm, surgical removal is to be preferred[5]. These results are consistent with our findings. In addition, we considered the current meta-analysis had following improvements: 1) the number of total studies were substantial. Especially, eight recent studies published since 2012 were included, which significantly increased the statistical power of the analysis; 2) we extended our literature search to non-English language journals, and identified additional seven studies published in Chinese and Korean that were not captured by previous reviews; 3) more than 16,000 patients from six different countries were included to yield results that are broader in scope and richer in meaning.

Despite these advantages, some limitations of the current meta-analysis should be acknowledged. The literature review retrieved 31 eligible studies; of them, three RCTs were available whereas the remaining 28 studies were represented by retrospective observational studies. Except for RCTs, there are few "head-to-dead" comparisons between HR and RFA for technically resectable HCCs. In fact, several studies present the use of RFA for treatment of 'unresectable' tumours, mainly associated with advanced disease (Child–Pugh B/C HCC, or multiple tumours)[10,16,18,21,26,32–38], or in older patients unfit for surgery[7,13,14,18,30,31]. Therefore, the results could be potentially biased since HR and RFA patients represent different populations as regards clinical characteristics that are known to influence postoperative outcomes. Although the large pooled population included in the meta-analysis could accommodate the limitations derived from such heterogeneity, further RCTs are warranted to validate the results of the current study. Meanwhile, the between-study heterogeneity observed in the majority of our analyses maybe due to any potentially relevant differences between the study designs and methodologies, such as populations from which the study samples are drawn, as well as number of patients included in each study. We attempted to accommodate this heterogeneity by implementing the random-effects evaluation model. This does not completely rule out the effect of heterogeneity between studies, but one may expect a limited influence.

By summarizing up-to-date studies with regard to the comparison of HR and RFA for small HCC, our results show that HR may provide better disease-free survival and long-term overall survival, whereas RFA is associated with lower treatment-related complication rate and shorter hospital-stay. However, these findings need to be confirmed by future RCTs. In addition, other ablation therapy like microwave ablation has recently gained great attention because of advances in microwave technology. Several studies have shown that MWA maybe as effective as HR and RFA in treating small HCC[45–48]. In the future, a systematic analysis and comparison of HR, MWA and RFA in the treatment of small HCC may be indispensable.

Methods

Search Strategy. This study was conducted in adherence to the PRISMA Statement guidelines[49]. A systematic literature search was performed using Pubmed, MEDLINE, EMBASE and CNKI (China Knowledge Resource Integrated Database) databases. No restriction was set for languages or date of publication. The following search key words were used: surgical resection, hepatic resection or hepatectomy; radiofrequency or radio-frequency; and liver cancer or hepatocellular carcinoma.

Data Extraction and Quality Assessment. Data were extracted independently by two authors (Q.X and K.S) and cross-checked to reach a consensus. The following variables were extracted from each study: (1) first author and year of the publication; (2) study design and patients characteristics; (3) clinical outcomes. The primary endpoint was efficacy, including overall and disease-free survival rates at 3, and 5 years. The secondary endpoints included complications and hospital-stay. The quality of all selected articles was assessed by using the nine-star Newcastle-Ottawa Scale[50].

Eligibility Criteria. Studies were included to fulfill the following criteria: (1) compare the initial therapy effects of RFA and HR for the treatment of small HCC, no matter the etiology of liver disease, differences in viral hepatitis, or cirrhotic status. In the present study, small HCC was defined as tumor(s) $\leq$ 5 cm in size; (2) report on at least one of the clinical outcomes mentioned above; (3) if dual or multiple studies were reported by the same institution and authors, the one of higher quality or the most recent publication was selected.

Letters, editorials and reviews without original data, case reports and studies lacking control groups were excluded. The following studies were also excluded: 1) those dealing with liver metastases or recurrence after hepatectomy; 2) those with no clearly reported outcomes of interest; 3) those sample size for either the RFA group or HR group smaller than 30.

Statistical Analysis. The meta-analysis was performed using the RevMan 5.2 software and R software with "meta" package from the Bioconductor project[51,52]. For dichotomous variables, OR was estimated with a 95% CI. For continuous variables, WMD was calculated. The significance of the pooled effects was determined by Z-test. Statistical heterogeneity among studies was evaluated with Q-test and I^2 statistics[53]. Study-specific results were combined using a random-effects model, which considers both within-study and between-study variation[54]. Sensitivity analysis was performed to evaluate the stability of the results. Each study involved in the meta-analysis was removed each time to reflect the influence of the individual data set on the pooled effects. An estimation of potential publication bias was executed by the funnel plot, in which the SE of log (OR) of each study was plotted against its log (OR). Funnel plot asymmetry was assessed by the method of Egger's linear regression test, a linear regression approach to measure funnel plot asymmetry on the natural logarithm scale of the OR[54]. The significance of the intercept was determined by the t-test suggested by Egger (p-value $<$ 0.05 was considered representative of statistically significant publication bias).

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Author contributions

X.M., Q.X. and S.K. wrote the main manuscript. Q.X. and S.K. collected the data. Q.X., X.Y. and S.K. performed the statistical analysis and prepared figures 1–4. All authors reviewed the manuscript.

Additional information

Competing financial interests: Q.X., X.Y. and X.M. are employees of bio**Mérieux** (Shanghai) Co., Ltd. No other potential conflicts of interest were disclosed by authors.

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