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

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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.

epatocellular carcinoma (HCC) is the fifth most common malignant tumor and the second leading cause of cancer-related deaths worldwide<sup>1</sup>. 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<sup>2</sup>. 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<sup>3</sup>. 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<sup>4</sup>. 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<sup>5</sup>.

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.*<sup>6</sup> and Yun *et al.*<sup>7</sup> reported that HR were more favorable regardless of tumor size. Elsewhere, Chen *et al.*<sup>8</sup> and Feng *et al.*<sup>9</sup> concluded that RFA was as effective as HR in the treatment of small HCCs. Additionally, Nashikawa *et al.*<sup>10</sup> and Peng *et al.*<sup>11</sup> 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<sup>12</sup>. 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)<sup>6–10,13–38</sup>.

**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<sup>39</sup>. 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<sup>40</sup>. 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<sup>41</sup>. 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<sup>42</sup>. Therefore, RFA has a considerable advantage over HR in providing a better short-term postoperative result.

Table 1   Character	istics of	studies include	d in the m	eta-analy	sis									
						Ŷco	200	Timor eizo	Tumor amount	Child_Duck		Newcastle	Ottawa Scale	Ø
Study	Design	Period	Country	Therapy	No. pts.	mean ± SD)	(m/f)	(mean ± SD, cm) (	single/multiple)	class (A/B/C)	Total S	selection Co	mparability (	Outcome
Chen MS 2006 <sup>8</sup>	RCT	1999–2004	China	HR PFA	06 12	$49.4 \pm 10.9$ 51 0 + 11 2	75/15	≤5 cm ≤5 cm	0/06	0/0/06	6	4	2	с
Huang J 2010 <sup>6</sup>	RCT	2003–2005	China	HR 2	115	55.9 ± 12.7	85/30	√ ≥ cm	89/26 84/21	110/5/0	ω	4	L	с
Feng K 2012 $^{\circ}$	RCT	2005–2008	China	HR A	2 8 8 7 8 8	47 (18-76)	75/9	2.6 ± 0.8	52/32 52/32	43/41/0	6	4	2	ю
Vivarelli M 2004 <sup>36</sup>	NRCT	1998–2002	Italy	HR Y	67 6	65.2 ± 8.2	57/22	0.0 	66/13	70/9/0	Ŷ	с	0	с
Hong SN 2005 <sup>14</sup>	NRCT	1999–2001	Korea	ΞΞ	6 6 7 7	49.2 ± 9.9	69/24	$2.5 \pm 0.8$	40/33 93/0 77/0	43/30/0	\$	с	0	e
Cho CM 200517	NRCT	2000–2002	Korea	A H Z	0 0 1 0 0 0 0 0	59.1 ± 9.6 57	41/14 48/13	2.4 ± 0.6 3.4 ± 1.0	0/cc -	61/0/0	$\sim$	б	-	ю
Montorsi M 2005 <sup>16</sup>	NRCT	1997–2003	Italy	ΥΥΥ Υ	6 6 6 6 7 6	6 + 29 6 + 29	/0/23 33/7	3. – ± 0.8 ≦5 cm	40/0	32/8/0	$\sim$	с	-	с
Gao W 2007 <sup>18</sup>	NRCT	1999-2006	China	A H A	3 4 C 3 4 C 2 C	51.5(38-67)	43/15 28/6	≤5 cm 2.6 ± 0.4	38/0 32/2	40/18/0 33/1/0	9	б	0	ო
Lupo L 2007 <sup>15</sup>	NRCT	1999–2006	Italy	HR A	6 7 7 7 7 7	67 (28–80) 67 (28–80)	41/12 33/9	4.0(3.0-5.0)	42/0 42/0	28/11/2 28/14/0	8	с	2	с
Zhou T 2007 <sup>19</sup>	NRCT	2001–2006	China	HR A	00 40 1	53 ± 13 53 ± 13	35/5 37/10	5 cm ≤5 cm	38/2	44/ 10/ 0 37/3/0	8	e	2	e
Abu-Hilal M 2008 <sup>20</sup>	NRCT	1991–2003	Ч	HR A	9 0 0 7 7 7	41 - 10 67 84	26/8 25/7	3.8 3.8	34/0	25/9/0 25/9/0	$\sim$	e	-	e
Hiraoka A 2008 <sup>33</sup>	NRCT	2000-2007	Japan	HR X	50 105 105	62.4 ± 10.6 62.4 ± 0.1	44:15 74:20	$2.27 \pm 0.55$	59/0 59/0	54/5/0 70/26/0	$\sim$	ю	-	ю
Guglielmi A 2008 <sup>21</sup>	NRCT	1996–2006	Italy	LR Z	<u>6</u> 6 6		73/18 73/18	≤ 0.02 ≤ 0.02 ≤ 0.02	69/21	69/22/0	9	с	0	ю
Bu XY 2009 <sup>38</sup>	NRCT	2000-2006	China	ζΞΞ	42	$53.9 \pm 10.7$	36/6	ll 2 cm IN 10 cm	38/4	36/6/0	$\sim$	С	-	с
Santambrogio R 2009 <sup>22</sup>	NRCT	1997–2007	Italy	RFA HR RFA	46 74 74	55.9 ± 7.4 68 ± 8 68 ± 7	40/6 55/23 59/15	≤5 cm 2.91 ± 1.23 2.66 + 1.06	38/8 78/0 74/0	0/0/02 78/0/0 74/0/0	ω	с	2	с
Leno S 2009 <sup>35</sup>	NRCT	2000–2005	Japan	HR V	123	67 (28–85) 64 (40 70)	82/41	2.7 ± 0.1	110/13	91/31/1 52/02/11	6	с	0	e
Guo WX 2010 <sup>31</sup>	NRCT	2002-2007	China	HR HR	73 20 20	50.5 (17-68)	57/16 57/16	2.0 ± 0.1 3.5 3.5	0/73	71/2/0 84/2/0	$\sim$	б	-	ю
Yun WK 2010 <sup>7</sup>	NRCT	2000-2007	Korea	HR	215 255	51.7 ± 9.7 57.0 + 9.9	171/44 197/58	$2.1 \pm 0.5$ $2.1 \pm 0.5$	215/0 255/0	215/0/0 255/0/0	9	с	0	с
Hung HH 2011 <sup>13</sup>	NRCT	2002–2007	China	HR	229 190	$60.1 \pm 12.6$ $67.4 \pm 11.5$	184/45	$2.88 \pm 1.06$ $2.37 \pm 0.92$	181/48 152/38		9	e	0	ю
Liu H 2011 <sup>23</sup>	NRCT	2008–2010	China	HR PF A	35	48.2 ± 15.6	29/6	≤5 cm < 5 cm	35/0	35/0/0		e	-	ო
Nishikawa H 201110	NRCT	2004–2010	Japan	HR HR	69 100	67.4 ± 9.7 68.4 ± 8.7	50/19 50/19	2.68 ± 0.49 1 00 ± 0.62	69/0 162/0	45/5/0 102/22/3	~	с	-	ო
Wang JH 2011 <sup>26</sup>	NRCT	2002–2009	China	HR	260		206/54	1 N S C N	241/19	257/3/0	$\sim$	с	-	e
Zhang J 201 $1^{37}$	NRCT	2006–2009	China	HR A	103 055	56.4 ± 15.2 58.5 ± 12.0	78/25	/ ≤ cm / 5 cm	89/14 89/14	81/22/0 81/22/0	9	e	0	ю
Du JK 2012 <sup>24</sup>	NRCT	2003–2007	China	RFA N	2 2 2 2 2 2 2 2 2 2 2 2	56.6 ± 8.6 58.3 ± 8.6	33/25 36/22	⇒5 cm ≤5 cm	0	0- / 0 / 0	9	ю	0	ю

Table 1   Continue	٩													
						~~~~	S.C.	T	Timor concint	ماحد الم 10 ماليا م		Newcastle	Ottawa Scale	
Study	Design	Period	Country	Therapy	No. pts.	Age (meαn ± SD)	(m/f)	(mean ± SD, cm)	(single/multiple)	class (A/B/C)	Total S	election Co	mparability (	Outcome
Imai K 2012 <sup>34</sup>	NRCT	2000-2011	Japan	HR	101	$63.3 \pm 1.9.7$	75/26	$2.14 \pm 0.55$	101/0	97/4/0	9	с	0	e
				RFA	82	$67.6 \pm 18.5$	46/36	$1.87 \pm 0.50$	82/0	60/22/0				
Peng ZW 2012 <sup>25</sup>	NRCT	2003-2008	China	НR	74	$51.5 \pm 12.1$	65/9	$1.1 \pm 0.5$	74/0	62/0/12	8	ო	2	ო
)				RFA	71	$51.1 \pm 12.1$	63/8	$1.2 \pm 0.6$	71/0	58/0/13				
Tohme S 2012 <sup>29</sup>	NRCT	2001–2011	NSA	Я	50	66.3 ± 1	31/19	$3.07 \pm 1.17$	39/11	27/6/17	9	2	-	ო
				RFA	60	$65.6 \pm 12$	38/22	$2.36 \pm 1.94$	47/13	40/16/4				
Desiderio J 2013 <sup>27</sup>	NRCT	2004–2012	Italy	Ħ	52	$65.6 \pm 4.8$	37/15	≤3 cm	22/30	52/0/0		ო	-	ო
				RFA	44	$64.4 \pm 6.5$	35/9	≤3 cm	19/25	44/0/0				
Hasegawa K	NRCT	2000-2005	Japan	Я	5361	66 (48–77)	3967/1394	≤3 cm	4458/903	4000/1361/0	9	ო	0	ო
201332				RFA	5548	69 (52–80)	3569/1979	≤3 cm	4068/1480	3349/2199/0				
Lai EC 2013 <sup>28</sup>	NRCT	2006–2012	China	НR	80	60.8 ± 9.9	55/25	$2.9 \pm 1.1$	71/9	•		ო	-	ო
				RFA	31	63.1 ± 12.8	19/12	$1.8 \pm 0.6$	28/3					
Wong KM 2013 <sup>30</sup>	NRCT	2004–2009	China	Ħ	46	$55.1 \pm 12$	30/16	$2.1 \pm 0.6$	46/0	46/0/0	~	ო	-	ო
•				RFA	36	$63.5 \pm 13$	18/18	$1.9 \pm 0.6$	36/0	36/0/0				

Table 2   Summary of the r	esults on the long-	-term efficacy of RF	A versus HR in	the treatment	of small HCCs				
Outcome	No. studies	No. patients	RFA	Η	Odds Ratio [95% CI]	Z test (P-value)	2	Q test (P-value)	Egger's test ( <i>P</i> -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					1				
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

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A         RfA         HR         Odds Ratio         Odds Ratio           Study of Support         Ferrar         Total Versith         Total Versith         MH, Random, 5% CI           Atu-Hild 2006         21         34         27         34         2.4%         0.42 (0.14, 1.24)           Atu-Hild 2006         21         34         27         34         2.4%         0.42 (0.14, 1.24)           Chen MS 2006         61         71         66         00         3.8%         0.39 (0.46, 1.88)           Chen MS 2006         61         71         66         90         3.8%         0.16 (0.42, 2.50)           Deciderio J 2012         30         44         61         52         0.9%         0.04 (0.01, 0.34)           Ferry K2012         56         88         64         0.8%         0.07 (0.34, 1.30)           Haroy N2006         61         52         2.44         1.28%         0.02 (0.22, 2.33)           Haroy N2007         0.6         55         78         9.33         0.51 (0.22, 0.14)           Haroy N2008         40         55         7.89         0.38%         0.79 (0.56, 0.81)           Haroy N2006         40         55         7.89         0.38%	•							
Study of Subingroup         Levents         Long         Viewalt         MH, Random, 25% Cl         MH, Random, 25% Cl           Bu XY 2008         30         46         27         32         24         24%         0.42 (0.14, 124)           Bu XY 2008         30         46         27         42         3.0%         1.04 (0.42, 2.50)           Chen MS 2006         61         71         66         90         3.8%         0.89 (0.14, 1.24)           Desiderio J 2012         30         44         51         52         0.9%         0.10 (0.1, 3.4)         30           Gae W 2007         39         63         26         3.4         2.6%         0.26 (0.10, 3.4)         30	A	RFA		HR	_		Odds Ratio	Odds Ratio
Adu-Hild 2008 21 34 27 34 2.4% 0.42 [014, 1.24] Chen MS 2006 51 71 66 90 3.8% 0.39 [0.46, 1.86] Desideno J 2012 30 44 51 52 0.9% 0.04 [0.51, 2.27] Feng X 2012 30 44 51 52 0.9% 0.04 [0.51, 2.27] Feng X 2017 39 53 26 34 2.6% 0.68 [0.32, 2.33] Gual WA 2017 39 53 26 34 2.6% 0.68 [0.32, 2.33] Gual WA 2017 39 53 26 34 2.6% 0.68 [0.32, 2.33] Gual WA 2017 39 53 26 34 2.6% 0.68 [0.32, 2.33] Hareoka A2008 92 105 58 50 73 40% 0.22 [0.42, 1.58] Hasegawa K 2013 4494 5544 4573 5561 6.8% 0.73 [0.66, 0.81] Hareoka A2008 92 105 55 78 93 3.3% 0.51 [0.23, 1.15] Hang V 2005 40 55 78 93 3.3% 0.51 [0.24, 1.15] Hang V 2005 40 55 78 93 3.3% 0.51 [0.24, 1.15] Hang V 2010 80 115 106 115 3.4% 0.19 [0.09, 0.43] Hang V 2010 80 115 106 115 3.4% 0.19 [0.09, 0.43] Hang V 2010 80 115 106 115 3.4% 0.19 [0.09, 0.43] Hang V 2010 80 115 106 115 3.4% 0.19 [0.09, 0.43] Hang V 2010 80 115 106 115 3.4% 0.19 [0.09, 0.43] Hang V 2010 80 115 106 115 3.4% 0.19 [0.09, 0.43] Hang V 2010 80 115 106 115 3.4% 0.19 [0.09, 0.43] Hang V 2010 80 115 106 115 3.4% 0.19 [0.09, 0.43] Hang V 2010 80 115 106 115 3.4% 0.19 [0.09, 0.43] Hang V 2010 80 115 106 115 3.4% 0.19 [0.09, 0.43] Hang V 2010 80 115 106 115 3.4% 0.19 [0.09, 0.43] Hang V 2010 80 115 106 115 3.4% 0.19 [0.09, 0.43] Hang V 2010 80 115 106 115 3.4% 0.19 [0.09, 0.43] Hang V 2010 80 115 106 115 3.4% 0.49 [0.24, 1.03] Hang V 2011 24 32 26 35 2.208] Hang V 2012 30 60 34 50 3.4% 0.47 [0.24, 1.03] Hang V 2012 33 66 46 77 8 3.4% 0.39 [0.16, 1.78] Hang V 2012 33 66 46 67 8 3.4% 0.47 [0.22, 1.03] Hang V 2012 33 66 46 40 7.8 0.24 [0.22, 0.66] Hang V 2012 33 66 46 46 7.8 0.24 [0.22, 0.66] Hang V 2012 33 66 46 46 7.8 0.24 [0.22, 0.66] Hang V 2012 33 66 46 46 7.8 0.24 [0.22, 0.68] Hang V 2010 13 38 65 361 13 4.4% 118 [0.65, 2.14] Hang V 2010 23 265 211 215 2.3% 0.29 [0.26, 0.68] Hang V 2011 33 65 35 11 3.22% 0.29 [0.26, 0.68] Hang V 2012 21 16 42 24 7.2 2.8% 0.59 [0.25, 0.68] Hang V 2012 21 16 42 24 7.2 2.8% 0.29 [0.26, 0.68] Hang V 2012 21 17 33 3.2% 5.4% 0.67 [0.28, 5.60] Han	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Abu-Hilal 2008	21	34	27	34	2.4%	0.42 [0.14, 1.24]	
Chen M3 2006 51 71 66 90 3.8% 0.99 (0.4, 1.86) Desiden 0. 2012 30 44 51 52 0.9% 0.04 (0.01, 0.34) Feng K2012 36 58 35 58 3.5% 1.18 (0.51, 2.27) Feng K2012 56 64 63 64 4.0% 0.67 (0.34, 1.30) Gal W 2007 33 53 26 34 2.6% 0.68 (0.32, 2.33) Gugletmi A 2008 19 32 24 31 2.3% 0.29 (0.10, 0.87) Hasegawa K 2013 4494 5544 4573 5561 6.8% 0.73 (0.68, 0.91) Haraoka A2008 92 105 55 78 93 3.3% 0.51 (0.22, 1.15) Hasegawa K 2013 4494 5544 4573 5561 6.8% 0.73 (0.68, 0.91) Haraoka A2008 92 105 55 78 93 3.3% 0.51 (0.22, 1.15) Haraoka A2008 92 105 55 78 93 3.3% 0.51 (0.22, 1.15) Haraoka A2008 92 105 153 59 2.2.3% Haraoka A2008 92 105 153 59 2.2.4 1.41 Haraoka A2008 92 105 153 59 2.2.3% Haraoka A2008 92 105 153 59 2.2.3% Haraoka A2008 92 105 153 59 2.2.3% Haraoka A2011 147 180 202 2.29 4.7% 0.46 (0.24, 1.38) Haraoka A2011 129 162 56 69 3.7% 0.38 (0.38, 1.90) Haraoka 2012 200 44 74 66 78 3.4% 0.43 (0.31, 0.44, 1.85) Haraoka A2011 129 162 56 69 3.7% 0.31 (0.10, 4.1, 1.85) Haraoka A2011 129 162 56 69 3.7% 0.31 (0.10, 4.1, 1.85) Haraoka A2011 2.3 36 43 0.02 (0.10, 7.8] Haraoka A2011 2.3 36 44 60 7.8 0.4% 0.43 (0.21, 0.31) Haraoka A2011 2.3 36 44 64 7.8 0.4% 0.43 (0.21, 0.31) Haraoka A2011 2.3 36 44 64 7.8 0.40 (0.22, 0.03) Haraoka A2012 33 64 45 0.0% 0.23 (0.02, 2.68) Haraoka A2013 33 654 30 (0.4 0.0001); P = 81% Table Verstal effect Z = 4.17 (P < 0.0001) Haraoka A2003 61 15 63 59 59 40 0.33 (0.22, 0.33) Haraoka A2003 61 15 63 59 59 40 0.33 (0.22, 0.33) Haraoka A2003 61 15 63 59 59 4.03 (0.22, 0.33) Haraoka A2003 62 105 39 59 4.33 (0.24, 0.25) (0.22, 0.48] Haraoka A2003 61 15 63 59 59 4.33 (0.24, 0.38) (0.24, 0.38) Haraoka A2003 61 15 63 59 59 4.33 (0.24, 0.38) (0.23, 0.68) Haraoka A2003 61 15 63 59 59 4.33 (0.24, 0.38) (0.2	Bu XY 2009	30	46	27	42	3.0%	1.04 [0.43, 2.50]	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Chen MS 2006	51	71	66	90	3.8%	0.93 [0.46, 1.86]	
Desidential 2012 30 44 51 52 0.9% 0.04 [0.01, 0.34] Feng K 2012 56 68 463 84 4.0% 0.67 [0.34, 1.30] Gao W 2007 39 63 22 43 31 2.3% 0.28 [0.10, 0.87] Hasegawa K 2013 4494 5548 4573 5361 6.8% 0.73 [0.66, 0.81] Hasegawa K 2013 4494 5548 4573 5361 6.8% 0.73 [0.66, 0.81] Hasegawa K 2013 4494 5548 4573 5361 6.8% 0.73 [0.66, 0.81] Hasegawa K 2013 4494 5548 4573 5361 6.8% 0.73 [0.66, 0.81] Hasegawa K 2013 4494 5548 4573 5361 6.8% 0.73 [0.66, 0.81] Hasegawa K 2013 4494 5548 4573 5361 6.8% 0.73 [0.66, 0.81] Hasegawa K 2013 4494 5548 4573 5361 6.8% 0.73 [0.66, 0.81] Hasegawa K 2013 4494 5548 4573 5361 6.8% 0.73 [0.66, 0.81] Hasegawa K 2013 4494 5548 4573 5361 6.8% 0.73 [0.66, 0.81] Hasegawa K 2013 4494 5548 4573 5361 6.8% 0.73 [0.66, 0.81] Hasegawa K 2013 40 115 106 115 3.4% 0.88 [0.23, 1.15] Hung H 2011 147 190 202 222 44.7% 0.48 [0.27, 0.77] Hasegawa K 2012 29 31 60 80 14% 42.83 [1.66, 22.09] Lupo L 2007 32 60 24 42 3.4% 0.86 [0.39], 1.80] Hontorsi 2005 35 58 29 40 3.1% 0.58 [0.24, 1.38] Hasegawa K 2011 128 152 71 32 74% 0.78 [0.24, 1.38] Hasegawa K 2011 128 152 71 32 74% 0.78 [0.24, 1.38] Hasegawa K 2013 0.60 34 50 3.7% 0.91 [0.44, 1.86] Peng ZW 2012 23 36 45 48 0.7% 0.21 [0.16, 0.78] Hasegawa K 2013 33 65 39 103 4.4% 0.16 [0.6, 0.78] Hasegawa K 2013 33 47 30 40 2.2% 0.72 [0.44, 0.23] Hasegawa K 2013 33 47 30 40 2.2% 0.72 [0.44, 0.23] Hasegawa K 2013 33 45 48 0.7% 0.28 [0.25, 1.39] Hasegawa K 2013 330 5548 392 57851 100.0% 0.65 [0.53, 0.79] Hasegawa K 2013 330 5548 392 57851 100.0% 0.65 [0.53, 0.79] Hasegawa K 2013 330 5548 392 57851 100.0% 0.65 [0.53, 0.79] Hasegawa K 2013 330 5548 392 57851 100.0% 0.65 [0.53, 0.79] Hasegawa K 2013 330 5548 392 5785 100.0% 0.65 [0.53, 0.79] Hasegawa K 2013 330 5548 392 5785 100.0% 0.65 [0.53, 0.79] Hasegawa K 2013 330 5548 392 5785 100.0% 0.65 [0.53, 0.79] Hasegawa K 2013 330 5548 392 5785 100.0% 0.65 [0.53, 0.79] Hasegawa K 2013 330 5548 392 5785 100.0% 0.44 [0.25, 0.78] Hasegawa K 2013 330 5548 392 578 598 4.8% 0.99 [0.52, 1.39] Hasegawa K 2013 3	Cho CM 2005	79	99	47	61	3.5%	1.18 [0.54, 2.55]	
Duuk 2012 38 08 30 98 30 98 30 98 30 98 108 [0.31, 2.21] Gao W 2007 39 63 26 34 2.6% 0.86 [0.32, 2.33] Guo W 2010 55 86 50 73 4.0% 0.87 [0.34, 1.36] Guo W 2010 55 86 50 73 4.0% 0.82 [0.42, 1.58] Hiraoka A 2008 92 105 53 59 2.5% 0.80 [0.29, 2.23] Hiraoka A 2008 92 105 53 59 2.5% 0.80 [0.29, 2.23] Hiraoka A 2008 92 105 53 59 2.5% 0.80 [0.29, 2.23] Hiraoka A 2005 40 55 78 93 3.3% 0.51 [0.23, 1.15] Hiraoka A 2005 40 55 78 93 3.3% 0.51 [0.23, 1.15] Hiraoka A 2005 40 55 78 93 3.3% 0.58 [0.24, 1.41] Lu Hung Hi 2011 147 190 202 229 47% 0.48 [0.27, 0.77] Hiraoka A 2007 32 60 24 42 34 % 0.86 [0.24, 1.41] Lu H 2011 24 32 26 35 2.3% 1.04 [0.34, 3.13] Lu Po L2007 32 60 24 42 3.4% 0.86 [0.24, 1.43] Hiraoka A 2010 40 51 55 59 29 40 3.1% 0.58 [0.24, 1.13] Hiraoka A 2010 20 20 24 42 3.4% 0.86 [0.29, 1.00] Lu H 2011 129 162 56 69 3.7% 0.91 [0.24, 1.13] Hiraoka A 2012 30 60 34 50 3.7% 0.91 [0.24, 1.13] Hiraoka A 2012 30 60 34 50 3.4% 0.47 [0.22, 1.03] Hiraoka A 2012 30 60 34 50 3.4% 0.39 [0.16, 0.78] Santambrogio R 2009 49 74 66 778 3.4% 0.39 [0.16, 0.78] Yua WK 2010 235 255 211 215 2.3% 0.22 [0.07, 0.68] Yua WK 2010 235 255 211 321 3.1% 1.05 [0.44, 2.53] Yua WK 2010 235 255 211 321 5.3% 0.22 [0.07, 0.68] Heterogeneik, Tau <sup>2</sup> = 0.16; Ch <sup>2</sup> = 778 8, d <sup>2</sup> = 30 (P < 0.00001); P = 61% Total events 6488 6566 Heterogeneik, Tau <sup>2</sup> = 0.16; Ch <sup>2</sup> = 778 8, d <sup>2</sup> = 30 (P < 0.00001); P = 61% Testfor overall effect Z = 4.17 (P < 0.0001) B Study or Subaroup Vertex Total Events Total Weight M-H. Random .95% Cl Abu-Hial 2008 19 34 19 34 2.8% 1.00 [0.38, 2.60] Hiraoka 2109 17 46 21 42 2.3 4% 0.68 [0.25, 1.73] Hiraoka A 2008 62 105 33 59 4.8% 0.99 [0.52, 1.89] Hiraoka A 2008 62 105 33 59 4.8% 0.99 [0.52, 1.89] Hiraoka A 2008 62 105 33 59 4.8% 0.99 [0.52, 1.89] Hiraoka A 2008 62 105 33 59 4.8% 0.99 [0.52, 1.89] Hiraoka A 2008 62 105 33 59 4.8% 0.99 [0.52, 1.89] Hiraoka A 2008 62 105 33 59 4.8% 0.99 [0.52, 1.89] Hiraoka A 2008 62 105 33 59 4.8% 0.99 [0.52, 1.89] Hiraoka A 2008 62 105 315 59 4.8% 0.99 [0.52, 1.8	Desiderio J 2012	30	44	51	52	0.9%	0.04 [0.01, 0.34]	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Du JK 2012	36	58	35	58	3.6%	1.08 [0.51, 2.27]	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	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]	
Guo WX 2010 55 86 50 73 4.0% 0.82 [0.42, 1.58] Hasegawa K 2013 449 554 84 673 536 6.8% 0.73 [0.66, 0.81] Hasegawa K 2013 849 554 8473 536 6.8% 0.73 [0.66, 0.81] Hasegawa K 2013 80 115 106 115 3.4% 0.19 [0.09, 0.43] Hung H 2011 80 115 106 115 3.4% 0.19 [0.09, 0.43] Hung H 2011 80 115 106 115 3.4% 0.68 [0.24, 1.41] Lai EC 2012 29 31 60 80 14% 4.83 [1.06, 22.09] Liu H 2011 24 32 26 35 2.3% 1.04 [0.34, 1.38] Hung H 2011 129 162 66 69 3.7% 0.91 [0.44, 1.38] Hishkawa H 2011 129 162 66 69 3.7% 0.91 [0.44, 1.38] Hishkawa H 2011 129 162 66 69 3.7% 0.91 [0.44, 1.86] Peng 2V 2012 62 71 62 74 3.1% 2.91 [1.23, 6.88] Hasegawa K 2013 36 45 46 0.7% 0.24 [0.02, 2.46] Wang JH 2011 26 75 113 123 3.1% 1.05 [0.44, 2.53] Wang JH 2011 26 75 113 123 3.1% 0.27 [0.14, 0.52] Total 95 2009 143 155 113 123 3.1% 0.27 [0.14, 0.52] Hasegawa K 2010 33 45 264 420 5.0% 0.34 [0.21, 0.65] Total 95 C01 33 46 5 46 0.7% 0.24 [0.02, 2.46] Wang JH 2011 260 345 234 260 5.0% 0.34 [0.21, 0.53] Total 95 C01 84 50 113 123 3.1% 1.05 [0.24, 1.52] Hasegawa K 2012 33 36 45 46 0.7% 0.24 [0.02, 2.46] Wang JH 2011 260 345 254 1215 2.3% 0.22 [0.07, 0.66] Total 95 WC1 82 52 7851 100.0% 0.65 [0.53, 0.79] Total 95 WC1 84 548 0558 0.07 0.020001); P 61% Testfor overall effect Z = 4.17 (P < 0.0001) B RFA HC Odds Ratio Stude or Subaroup Feets Total Events Total Weight MH.Random, 95% CI M-H.Random, 95% CI Hasegawa K 2013 3300 5548 3812 5361 15.8% 0.39 [0.25, 1.37] Desiderio J 2012 16 44 24 52 3.4% 0.38 [0.15, 0.79] Hasegawa K 2013 3300 5548 3812 5361 15.8% 0.39 [0.25, 1.37] Desiderio J 2012 16 47 77 80 2.2% 2.10 [0.10, 0.32] Hasegawa K 2013 3300 5548 3812 5361 15.8% 0.39 [0.25, 1.52] Hasegawa K 2013 3300 5548 3812 5361 15.8% 0.39 [0.25, 1.52] Hasegawa K 2013 3300 5548 3812 5361 15.8% 0.39 [0.25, 1.52] Hasegawa K 2013 3300 5548 3812 5361 15.8% 0.39 [0.25, 1.52] Hasegawa K 2013 3300 5548 3812 5361 15.8% 0.39 [0.25, 1.52]	Guglielmi A 2008	16	32	24	31	2.3%	0.29 [0.10, 0.87]	
Hasegawa K 2013 Haseka A2008 Haseka A2008	Guo WX 2010	55	86	50	73	4.0%	0.82 [0.42, 1.58]	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Hasegawa K 2013	4494	5548	4573	5361	6.8%	0.73 [0.66, 0.81]	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Hiraoka A 2008	92	105	53	59	2.5%	0.80 [0.29, 2.23]	
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	Hong SN 2005	40	55	78	93	3.3%	0.51 [0.23, 1.15]	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Huang J 2010	80	115	106	115	3.4%	0.19 [0.09, 0.43]	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Hung HH 2011	147	190	202	229	4.7%	0.46 [0.27, 0.77]	
Late 2 2012 2 29 31 60 80 1.4% 4.83 [1.06, 22.09] Lu H 2011 24 32 26 35 2.3% 1.04 [0.34, 3.13] Lupo L 2007 32 60 24 42 3.4% 0.88 [0.34, 3.0] Montorsi 2005 35 58 29 40 3.1% 0.68 [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] Ueno S 2009 49 74 66 78 3.4% 0.34 [0.16, 0.78] Ueno S 2009 49 74 66 79 51 79 4.0% 0.27 [0.14, 0.52] Warelli M 2004 26 79 51 79 4.0% 0.27 [0.14, 0.52] Warelli M 2004 26 79 51 79 4.0% 0.27 [0.14, 0.52] Warelli M 2012 33 36 45 46 0.7% 0.24 [0.02, 2.46] Wong KM 2012 33 36 45 46 0.7% 0.24 [0.02, 2.46] Wung KM 2012 33 36 45 46 0.7% 0.24 [0.02, 2.46] Wung KM 2012 33 36 45 46 0.7% 0.24 [0.02, 2.46] Wung KM 2012 33 347 30 40 2.8% 0.79 [0.30, 2.03] Total (95% CI) 8252 7851 100.0% 0.65 [0.53, 0.79] Total (95% CI) 8252 7351 100.0% 0.65 [0.53, 0.79] Total (95% CI) 8252 73851 100.0% 0.65 [0.53, 0.79] Total (95% CI) 8252 73 51 100.0% 0.65 [0.53, 0.79] Total (95% CI) 8252 73 51 100.0% 0.65 [0.53, 0.79] Favours HR Favours RFA Heterogenetic Ta <sup>2</sup> = 0.16; Chi <sup>2</sup> = 77.78, 8, df = 30 (P < 0.00001); P = 61% Total 400.4 18 68 321 73 4.3% 0.34 [0.17, 0.68] Hiraoka A 2008 19 32 17 31 2.2% 0.32 [0.11, 0.92] Guigliettin J 2012 16 44 24 52 3.4% 0.67 [0.29, 1.52] Hiraoka A 2008 19 32 17 31 2.2% 0.32 [0.10, 0.39] Hiraoka A 2008 19 10 182 229 7.7% 0.53 [0.25, 1.37] Desiderio J 2012 16 34 57 88 0.43 [0.32, 1.10, 0.32] Hiraoka A 2008 62 105 35 59 4.8% 0.99 [0.52, 1.38] Hiraoka A 2008 62 105 35 69 4.8% 0.99 [0.52, 1.38] Hiraoka A 2008 62 105 35 69 4.8% 0.99 [0.52, 1.38] Hiraoka A 2008 62 105 35 69 4.8% 0.99 [0.52, 1.38] Hirao	Imai K 2012	69	82	91	101	3.0%	0.58 [0.24, 1.41]	
Lul 2017 2207 32 60 24 23 36 2.3% 1.04 [0.34, 3.13] Montorsi 2005 35 58 29 40 3.1% 0.58 [0.24, 1.38] Peng 20V 2012 62 71 62 74 3.1% 2.91 [1.23, 6.88] Santambrogio R 2009 49 74 66 78 3.4% 0.38 [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] 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] Zhang J 2011 233 38 53 61 03 4.4% 1.18 [0.65, 2.04] Zhou T 2007 33 47 30 40 2.8% 0.78 [0.30, 2.03] Total events 6488 6586 Heterogeneity: Tau <sup>2</sup> = 0.16; Chi <sup>2</sup> = 77.68, df = 30 (P < 0.00001); P = 61% Testfor overall effect Z = 4.17 (P < 0.00001) Testfor overall effect Z = 4.17 (P < 0.00001) B RFA HR Odds Ratio Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Abu-Hilal 2008 19 34 19 34 2.6% 1.00 [0.38, 2.60] Favours HR Favours RFA B RFA HR Odds Ratio Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Abu-Hilal 2008 19 34 19 34 2.6% 1.00 [0.38, 2.60] Hasegawa K 2013 3380 5548 3812 5361 15.8% 0.34 [0.27, 1.81] Guigliemin 42008 9 32 17 31 2.2% 0.52 [0.1, 0.92] Guigliemin 42008 19 34 19 34 2.6% 1.00 [0.38, 2.60] Hasegawa K 2013 3380 5548 3812 5361 15.8% 0.34 [0.27, 1.82] Haraka A 2000 62 105 35 59 4.8% 0.99 [0.25, 1.37] Desiderio J 2012 16 44 24 622 3.4% 0.67 [0.29, 1.52] Guigliemin 42008 19 18 86 32 73 4.3% 0.34 [0.17, 0.68] Hasegawa K 2013 3380 5548 3812 5361 15.8% 0.39 [0.22, 1.89] Haraka A 2000 62 105 35 59 4.8% 0.99 [0.52, 1.89] Haraka A 2000 62 105 35 59 4.8% 0.99 [0.52, 1.81] Haraka A 2000 62 105 35 59 4.8% 0.99 [0.52, 1.81] Haraka A 2000 62 105 35 59 4.4% 0.62 [0.27, 1.40] Haraka A 2000 62 105 35 59 4.4% 0.68 [0.27, 1.40] Haraka A 2000 62 105 35 59 4.4% 0.68 [0.27, 1.40] Haraka A 2000 62 105 35 59 4.4% 0.68 [0.27, 1.40] Haraka A 2000 69 19 74 42 78 4.9% 0.65 [0.27, 1.21] Haraka A 2001 29 77 44 27 78 4.9% 0.58 [0.27, 1.21] Haraka A 2001 29 77 4 42 78 4.9% 0.65 [0.27, 1.21] Haraka A 2001 20 76 19 40 22 773 4.3% 0.56 [0.27, 1.20] Harak	Lai EC 2012	29	31	60	80	1.4%	4.83 [1.06, 22.09]	
Lupo L 2007 32 600 24 42 3.4% 0.86 [0.39, 1.30] Montors 2005 35 58 29 40 3.1% 0.58 [0.24, 1.38] Peng ZW 2012 52 71 52 74 3.1% 0.58 [0.24, 1.38] Peng ZW 2012 52 71 52 74 3.1% 0.98 [0.16, 0.78] Jens S 2012 30 60 34 50 3.4% 0.36 [0.16, 0.78] Ueno S 2009 49 74 66 78 3.4% 0.36 [0.16, 0.78] Ueno S 2009 49 74 66 78 3.4% 0.36 [0.16, 0.78] Ueno S 2009 49 74 66 78 3.4% 0.36 [0.16, 0.78] Wang JH 2011 260 345 234 260 5.0% 0.34 [0.21, 0.52] Wang JH 2011 260 345 234 260 5.0% 0.34 [0.21, 0.52] Wang JH 2011 260 345 234 260 5.0% 0.34 [0.21, 0.52] Wang JH 2011 260 345 234 260 5.0% 0.34 [0.22, 0.66] Tothre S 2012 33 64 54 60 0.7% 0.24 [0.02, 2.46] Tothre S 2017 33 47 30 40 2.8% 0.79 [0.30, 2.03] Total (95% CI) 8252 7951 100.0% 0.65 [0.53, 0.79] Total (95% CI) 8252 7951 100.0% 0.65 [0.53, 0.79] Total (95% CI) 8488 5586 Heterogeneity: Tau <sup>2</sup> = 0.16; Chl <sup>2</sup> = 77.68, df = 30 (P < 0.00001); P = 61% Test for overall effect: Z = 4.17 (P < 0.0001) B RFA HR Odds Ratio 0dds Ratio Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Abu-Hial 2008 19 34 19 34 2.6% 1.00 (0.38, 2.60] Bu X7 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] Gug leirni A 2008 69 32 77 31 2.2% 0.33 (0.17, 0.68] Hiaoka A 2008 62 105 35 59 4.8% 0.99 [0.52, 1.37] Has gawa K 2013 319 6548 3812 5.361 15.8% 0.64 (0.59, 0.68] Hiaoka A 2008 62 105 35 59 4.8% 0.99 [0.52, 1.37] Hiaoka A 2008 62 105 35 59 4.8% 0.99 [0.52, 1.89] Hiaoka A 2008 62 105 35 59 4.8% 0.99 [0.52, 1.89] Hiaoka A 2008 62 105 35 59 4.8% 0.99 [0.52, 1.89] Hiaoka A 2008 62 105 35 59 4.8% 0.99 [0.52, 0.68] Hiaoka A 2008 62 105 35 59 4.8% 0.99 [0.52, 1.89] Hiaoka A 2008 62 105 35 59 4.8% 0.99 [0.52, 0.68] Hiaoka A 2008 62 105 35 59 4.8% 0.99 [0.52, 0.68] Hiaoka A 2008 62 105 35 59 4.8% 0.99 [0.52, 0.68] Hiaoka A 2008 62 105 35 59 4.8% 0.99 [0.52, 0.68] Hiaoka A 2008 62 105 35 59 4.8% 0.93 [0.22, 0.68] Hiaoka A 2008 62 105 35 59 4.8% 0.93 [0.22, 0.68] Hiaoka A 2008 62 105 35 59 4.8% 0.93 [0.22, 0.68] Hiaoka A	Liu H 2011	24	32	26	35	2.3%	1.04 [0.34, 3.13]	
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$		32	60	24	42	3.4%	0.86 [0.39, 1.90]	
Nishikawa H 2011       129       162       56       69       3.7%       0.91       10.41, 1851         Sentambrogio R 2009       49       74       66       78       3.4%       0.36 [0.16, 0.78]         Tohme S 2012       30       60       34       50       3.4%       0.36 [0.16, 0.78]         Veno S 2009       143       155       113       123       3.1%       1.05 [0.44, 2.53]         Viarelli M 2004       26       79       51       79       4.0%       0.27 [0.14, 0.52]         Wang JH 2011       285       255       211       215       2.3%       0.22 [0.07, 0.66]         Yun WK 2010       235       255       211       215       2.3%       0.22 [0.07, 0.66]         Zhang J2011       33       85       36       103       4.4%       1.18 [0.65, 2.14]         Zhaug J2011       33       85       8586       0.78 [0.30, 2.03]       0.005         Total events       6488       6586       6586       0.00001); P = 61%       0.005       0.1       1.0       200         Festor overall effect Z = 4.17 (P < 0.0001)	Montorsi 2005	35	58	29	40	3.1%	0.58 [0.24, 1.38]	
Print 2V0 2012       0.2       71       5.2       74       3.1%       2.91 [1.23, 0.88]         Santambrogio R 2009       49       74       66       78       3.4%       0.38 [0.16, 0.78]         Ueno S 2009       14.3       155       113       123       3.1%       1.05 [0.44, 0.52]         Warelil 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]         Yun WK 2010       235       255       211       215       2.3%       0.22 [0.07, 0.66]         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       6586           Heterogeneity: Tau <sup>2</sup> = 0.16; Chi <sup>2</sup> = 77.88, df = 30 (P < 0.00001); P = 61%	Nishikawa H 2011	129	162	56	69	3.7%	0.91 [0.44, 1.85]	
Samambrogio R 2009       49       74       66       78       3.4%       0.36 [0.15, 0.78]         Tohme S 2012       30       60       34       50       3.4%       0.47 [0.12, 0.16]         Ware JH 2011       26       79       51       79       4.0%       0.27 [0.14, 0.52]         Wang JH 2011       26       34       56       50%       0.24 [0.02, 2.46]         Yun WK 2010       235       255       211       215       2.3%       0.22 [0.07, 0.66]         Zhang J2011       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]       0.005       0.1       10       200         Fest for overall effect Z = 4.17 (P < 0.0001)	Peng ZW 2012	62	1	52	74	3.1%	2.91 [1.23, 6.88]	
Informe 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 (0.14, 0.52)         Wang JH 2011       260       345       234       260       5.0%       0.34 (0.21, 0.55)         Yung KM 2012       33       36       45       46       0.7%       0.24 (0.02, 2.46)         Zhang J2011       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)                  5.00001); P = 61%          Total (95% CI)       8252       7851       100.0%       0.65 (0.53, 0.79)                 5.2000001); P = 61%          Study or Subaroup       Events       Total Events       Total Events       Total Meight       M-H, Random, 95% CI           Abu-Hilal 2008       19       34       19       34       2.6%       1.00 (0.38, 2.60)                 Events       Total Events       Total Events <t< td=""><td>Santambrogio R 2009</td><td>49</td><td>74</td><td>66</td><td>78</td><td>3.4%</td><td>0.36 [0.16, 0.78]</td><td></td></t<>	Santambrogio R 2009	49	74	66	78	3.4%	0.36 [0.16, 0.78]	
Open of S 2009       143       155       113       123       3.1%       1.05       1.04, 2.53         Warelil M 2004       26       79       51       79       4.0%       0.27       10.4(, 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%       0.22 [0.07, 0.66]         Zhang J 2011       33       85       36       103       4.4%       1.18 [0.65, 2.14]         Zhang J 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 (95% CI)       8252       7851       100.0%       0.65 [0.53, 0.79]         Test for overall effect Z = 4.17 (P < 0.0001)	Tonme S 2012	30	60	34	50	3.4%	0.47 [0.22, 1.03]	
Warag JH 2014       26       79       51       79       4.0%       0.27 (0.14, 0.52)         Warag JH 2011       260       345       234       260       50%       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 J2011       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]       0.005         Test for overall effect Z = 4.17 (P < 0.0001)	Ueno S 2009	143	155	113	123	3.1%	1.05 [0.44, 2.53]	
Wang KM 2011       200       345       234       200       0.345       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 (95% CI)       8252       7851       100.0%       0.65 [0.53, 0.79]         Total (95% CI)       8252       7851       100.0%       0.65 [0.53, 0.79]         Test for overall effect: $Z = 4.17$ ( $P < 0.0001$ ) $P < 0.00001$ ); $P = 61%$ $P < 0.0001$ Test for overall effect: $Z = 4.17$ ( $P < 0.0001$ ) $P < 0.00001$ ; $P = 61%$ $P < 0.0003, 2.60$ Bu XY 2009       17       46       21       42       3.2%       0.59 [0.25, 1.37]         Desiderio J 2012       16       44       45       23.4%       0.67 [0.29, 1.52] $O < 0.68$ Guglielmi A 2008       9       32       17       31       2.2%       0.32 [0.11, 0.92] $ $	Vivarelli M 2004	26	79	51	79	4.0%	0.27 [0.14, 0.52]	
Wrong KM 2012       33       36       45       46       0.7%       0.24 [0.02, 2.48]         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]	Vvang JH 2011	260	345	234	260	5.0%	0.34 [0.21, 0.55]	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Wong KM 2012	33	36	45	46	0.7%	0.24 [0.02, 2.46]	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Yun VVK 2010	235	255	211	215	2.3%	0.22 [0.07, 0.66]	
Zhou 1 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         Heterogeneily: Tau <sup>2</sup> = 0.16; Chi <sup>2</sup> = 77.68, df = 30 (P < 0.00001); P = 61% $0.005 0.1 1 10 200$ Test for overall effect: Z = 4.17 (P < 0.0001)       RFA       HR       Odds Ratio         Study or Subgroup       Events       Total       Events       Total       Weight       M-H, Random, 95% CI         Abu-Hial 2008       19       34       19       34       2.6%       1.00 [0.38, 2.60]       M-H, Random, 95% CI         B       RFA       HR       Odds Ratio       Odds Ratio         Bu XY 2009       17       46       21       42       3.2%       0.59 [0.25, 1.37]         Desiderio J 2012       16       44       24       52       3.4%       0.34 [0.17, 0.68] $\bullet$ Hasegawa K 2013       3390       5548       3812       5361       15.8%       0.39 [0.22, 0.68] $\bullet$ Hung HH 2011       128       190       182       229       7.7%       0.53 [0.34, 0.83] $\bullet$ Hung HH 2011	Zhang J 2011	33	85	36	103	4.4%	1.18 [0.65, 2.14]	
Total (95% CI)82527851100.0%0.65[0.53, 0.79]Total events64886586Heterogeneity: Tau" = 0.16; Chi" = 77.68, df = 30 (P < 0.00001); P = 61% Test for overall effect: Z = 4.17 (P < 0.0001)	Zhou T 2007	33	47	30	40	2.8%	0.79 [0.30, 2.03]	
Total events       6488       6586         Heterogeneity: Tau <sup>2</sup> = 0.16; Chi <sup>2</sup> = 77.68, df = 30 (P < 0.00001); P = 61%	Total (95% CI)		8252		7851	100.0%	0.65 [0.53, 0.79]	•
Heterogeneity: Tau <sup>2</sup> = 0.16; Chi <sup>2</sup> = 77.68, df = 30 (P < 0.00001); P = 61%         Test for overall effect: $Z = 4.17$ (P < 0.0001)         B       RFA       HR       Odds Ratio         Odds Ratio       Odds Ratio         Study or Subgroup       Events       Total       Weight       M-H, Random, 95% CI         Abu-Hilal 2008       19       34       19       34       2.6%       1.00 [0.38, 2.60]         B       RFA       HR       Odds Ratio         Abu-Hilal 2008       19       34       100       0.05 0.1       100         B       RFA       HR       Odds Ratio         Odds Ratio       Odds Ratio         B       Odds Ratio	Total events	6488		6586				
Test for overall effect: Z = 4.17 (P < 0.0001)       0.0005       0.1       10       200         Fertige of the state of the s	Heterogeneity: Tau <sup>2</sup> = 0.1	l 6; Chi <sup>z</sup> =	77.68,	df = 30 (l	P < 0.0	0001); l <sup>e</sup> =	= 61%	
B         RFA         HR         Odds Ratio         Odds Ratio           Abu-Hilal 2008         19         34         19         34         2.6%         1.00 [0.38, 2.60]         M-H, Random, 95% CI           Abu-Hilal 2008         19         34         19         34         2.6%         1.00 [0.38, 2.60]         M-H, Random, 95% CI           Desiderio J 2012         16         44         24         52         3.4%         0.67 [0.29, 1.52]         Image: Comparison of the	Test for overall effect: Z =	4.17 (P <	< 0.000	1)				Favours HR Favours RFA
Study or Subgroup         Events         Total         Events         Total         Weight         M-H, Random, 95% Cl         M-H, Random, 95% Cl           Abu-Hilal 2008         19         34         19         34         2.6%         1.00 [0.38, 2.60]         M-H, Random, 95% Cl           Bu XY 2009         17         46         21         42         3.2%         0.59 [0.25, 1.37]         Hereica           Desiderio J 2012         16         44         24         52         3.4%         0.67 [0.29, 1.52]         Hereica         Hereica           Guglielmi A 2008         9         32         17         31         2.2%         0.32 [0.11, 0.92]         Hereica         Hereica           Gug WX 2010         18         86         32         73         4.3%         0.34 [0.17, 0.68]         Hereica           Hasegawa K 2013         3390         5548         3812         5361         15.8%         0.39 [0.22, 0.68]         Hereica           Hung J 2010         63         115         87         115         5.8%         0.39 [0.22, 0.68]         Hereica           Hung HH 2011         128         190         182         229         7.7%         0.53 [0.34, 0.83]         Hereica           Lup	R							
Study of Subgroup         Events         Total         Weight         M-H, Random, 95% Cl         M-H, Random, 95% Cl           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]           Huang J 2010         63         115         87         115         5.8%         0.39 [0.22, 0.68]           Huang 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%		RFA		HR			Odds Ratio	Odds Ratio
Abu-Hilai 2008       19       34       19       34       2.6%       1.00 [0.38, 2.60]         Bu XY 2009       17       46       21       42       3.2%       0.69 [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 <t< td=""><td>Study or Subgroup</td><td>Events</td><td>Total</td><td>Events</td><td>lotal</td><td>weight</td><td>M-H, Random, 95% CI</td><td>M-H, Random, 95% Cl</td></t<>	Study or Subgroup	Events	Total	Events	lotal	weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
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	Abu-Hilal 2008	19	34	19	34	2.6%	1.00 [0.38, 2.60]	
Desideno 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 VWX 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	Bu XY 2009	17	46	21	42	3.2%	0.59 [0.25, 1.37]	
Guginerim 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]	Desiderio J 2012	16	44	24	52	3.4%	0.67 [0.29, 1.52]	
Guo vix 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       51.%       0.60 [0.32, 1.12]         Peng ZW 2012       51       71       46       74       4.3%       1.55 [0.77, 3.12]	Guglielmi A 2008	9	32	17	31	2.2%	0.32 [0.11, 0.92]	
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]       -       -         Ueno S 2012       21       60	Guo VVX 2010	18	86	32	73	4.3%	0.34 [0.17, 0.68]	
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 <t< td=""><td>Hasegawa K 2013 Ulina aka 10,000</td><td>3390</td><td>5548</td><td>3812</td><td>5361</td><td>15.8%</td><td>0.64 [0.59, 0.69]</td><td><u> </u></td></t<>	Hasegawa K 2013 Ulina aka 10,000	3390	5548	3812	5361	15.8%	0.64 [0.59, 0.69]	<u> </u>
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]	Hiraoka A 2008	62	105	35	59	4.8%	0.99 [0.52, 1.89]	
Hung HH 2011       128       190       182       228       7.7%       0.53 [0.34, 0.85]         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]	Huang J 2010	100	115	87	220	5.8% 7.70/	0.39 [0.22, 0.68]	_
Imark 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]	Hung HH 2011	128	190	182	229	1.1%		
Large 2012       20       51       57       60       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]	Inial K 2012	49	82	19	101	4.8%	0.41 [0.22, 0.79]	
Laps E 2007       15       50       16       42       3.4%       0.52 [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]		20	31	5/	80	2.2%	2.10[0.72, 0.13]	
Historicawa H 2011       Ho2       Ho3	Lupu L 2007 Niebikowo U 2014	100	160	18	42	5.4% 5.10/	0.02 [0.27, 1.40]	
Santambrogio R 2009       30       74       42       78       4.9%       0.58 [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]	Pana 78(2012	102	74	10	09 74	0.1% 1.0%		<b></b>
Tohme S 2012     21     60     24     50     3.7%     0.58 [0.37, 1.11]       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]	Sentembrogia D 2000	20	74	40 10	79	4.370	0.59 [0.77, 3.12] 0.59 [0.21, 1.44]	
Ueno S 2009 98 155 98 123 6.0% 0.44 [0.25, 0.76]	Tohme S 2012	20	60	42 24	70 50	3,704	0.00 [0.01, 1.11]	
Wang JH 2011 211 345 208 260 9.1% 0.39 [0.27 0.57]	Lieno S 2009	41 QQ	155	4	122	6.0%	0.00 [0.27, 1.20]	
	Wang IH 2011	211	345	208	260	9.1%	0.39 [0.25, 0.70]	

Total (95% CI) 7531 7134 100.0% 0.57 [0.48, 0.67] Total events 4577 5093 Heterogeneity: Tau<sup>2</sup> = 0.05; Chi<sup>2</sup> = 32.67, df = 19 (P = 0.03); I<sup>2</sup> = 42% 0.05 0.2 Test for overall effect: Z = 6.53 (P < 0.00001) Favours HR Favours RFA

39

202

46

215

36

255

26

222

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.

2.1%

4.6%

0.47 [0.16, 1.38]

0.43 [0.22, 0.85]

Wong KM 2012

Yun WK 2010

<u>5</u>

1

20



A	RFA		HR			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Abu-Hilal 2008	10	34	23	34	2.4%	0.20 [0.07, 0.56]	
Bu XY 2009	13	46	17	42	2.9%	0.58 [0.24, 1.41]	
Chen MS 2006	46	71	62	90	3.9%	0.83 [0.43, 1.61]	
Cho CM 2005	30	99	23	61	3.8%	0.72 [0.37, 1.41]	
Desiderio J 2012	23	44	42	52	2.8%	0.26 [0.11, 0.65]	
Feng K 2012	42	84	51	84	4.1%	0.65 [0.35, 1.19]	
Gao W 2007	30	53	19	34	3.0%	1.03 [0.43, 2.45]	
Guglielmi A 2008	10	28	18	31	2.3%	0.40 [0.14, 1.15]	
Guo WX 2010	2	86	25	73	1.4%	0.05 [0.01, 0.20]	
Hasegawa K 2013	2375	5548	3040	5361	6.6%	0.57 [0.53, 0.62]	
Hiraoka A 2008	61	105	37	59	3.9%	0.82 [0.43, 1.59]	
Hong SN 2005	22	55	51	93	3.8%	0.55 [0.28, 1.08]	
Huang J 2010	53	115	70	115	4.6%	0.55 [0.33, 0.93]	
Hung HH 2011	55	190	128	229	5.2%	0.32 [0.21, 0.48]	
lmai K 2012	30	82	59	101	4.2%	0.41 [0.23, 0.75]	
Lai EC 2012	12	31	48	80	3.0%	0.42 [0.18, 0.99]	
Liu H 2011	20	32	21	35	2.6%	1.11 [0.42, 2.97]	—
Lupo L 2007	11	60	15	42	2.8%	0.40 [0.16, 1.00]	
Nishikawa H 2011	62	162	33	69	4.3%	0.68 [0.38, 1.19]	-++
Peng ZW 2012	46	71	42	74	3.8%	1.40 [0.72, 2.74]	
Tohme S 2012	25	60	21	50	3.4%	0.99 [0.46, 2.11]	
Ueno S 2009	56	155	58	123	4.8%	0.63 [0.39, 1.03]	
Vivarelli M 2004	16	79	40	79	3.7%	0.25 [0.12, 0.50]	
Wang JH 2011	102	324	157	260	5.6%	0.30 [0.21, 0.42]	+
Wong KM 2012	13	36	30	46	2.8%	0.30 [0.12, 0.75]	
Yun WK 2010	87	255	155	215	5.3%	0.20 [0.14, 0.30]	-
Zhou T 2007	17	47	12	40	2.8%	1.32 [0.54, 3.25]	- <del>-</del>
Total (95% CI)		7952		7572	100.0%	0.50 [0.41, 0.61]	•
Total events	3269		4297				
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	= 0.16; Chi : Z = 6.77 (	iᢪ = 92. (P ≤ 0.0	11, df= 2 00001)	6 (P < I	0.00001);	I² = 72%	0.005 0.1 1 10 200 Favours HR Favours RFA
D							

В	RFA		HR			Odds Ratio	Odds	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Rand	om, 95% Cl
Abu-Hilal 2008	7	34	10	34	3.9%	0.62 [0.20, 1.89]		-
Bu XY 2009	8	46	12	42	4.2%	0.53 [0.19, 1.45]		-
Desiderio J 2012	10	44	14	52	4.5%	0.80 [0.31, 2.03]		<u> </u>
Guglielmi A 2008	10	28	6	31	3.6%	2.31 [0.71, 7.53]	-	
Guo WX 2010	0	86	3	73	1.0%	0.12 [0.01, 2.29]		
Hasegawa K 2013	1570	5548	1941	5361	7.6%	0.70 [0.64, 0.75]	•	
Hiraoka A 2008	25	105	13	59	5.2%	1.11 [0.52, 2.37]	_	-
Huang J 2010	33	115	59	115	6.2%	0.38 [0.22, 0.66]		
Hung HH 2011	39	190	94	229	6.6%	0.37 [0.24, 0.58]	-	
lmai K 2012	20	82	47	101	5.8%	0.37 [0.20, 0.70]		
Lai EC 2012	12	31	48	80	4.9%	0.42 [0.18, 0.99]		1
Lupo L 2007	0	60	6	42	1.0%	0.05 [0.00, 0.85]		
Nishikawa H 2011	29	162	18	69	5.6%	0.62 [0.32, 1.21]		t
Peng ZW 2012	42	71	38	74	5.7%	1.37 [0.71, 2.65]	-	•
Santambrogio R 2009	14	74	28	78	5.3%	0.42 [0.20, 0.88]		·
Tohme S 2012	17	60	17	50	5.0%	0.77 [0.34, 1.73]		-
Ueno S 2009	31	155	47	123	6.2%	0.40 [0.24, 0.69]		
Wang JH 2011	60	324	127	260	6.9%	0.24 [0.16, 0.34]	+	
Wong KM 2012	5	36	25	46	3.9%	0.14 [0.04, 0.41]		
Yun WK 2010	61	255	142	215	6.8%	0.16 [0.11, 0.24]		
Total (95% CI)		7506		7134	100.0%	0.47 [0.35, 0.65]	•	
Total events	1993		2695			Line [oloo]		
Heterogeneity: $Tau^2 = 0.2$	33: Chi <sup>z</sup> =	115.79	A df = 19	(P < 0 )	000015-15	'= 84%	+ + +	· · · ·
Test for overall effect: 7 =	: 4 72 (P <	< 0.000	0, an = 13 101)	V · 0.	000017,1	- 0 - 70	0.002 0.1	1 10 500
rootion overall effect. Z -	4.12 (1	. 0.000	0.7				Favours HR	Favours RFA

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.





В		RFA			HR			Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl	
Chen MS 2006	9.18	3.06	71	19.7	5.61	90	12.5%	-10.52 [-11.88, -9.16]	-	
Feng K 2012	7.3	2.3	84	14.8	4.5	84	12.8%	-7.50 [-8.58, -6.42]	+	
Huang J 2010	6.92	3.46	115	15.36	4.21	115	12.9%	-8.44 [-9.44, -7.44]	+	
Lai EC 2012	3.8	1.7	31	6.8	4	80	12.8%	-3.00 [-4.06, -1.94]	-	
Nishikawa H 2011	14.7	5.7	162	18.1	10.4	69	10.5%	-3.40 [-6.01, -0.79]		
Peng ZW 2012	7.05	2.78	71	11.7	4.67	74	12.6%	-4.65 [-5.90, -3.40]	-	
Santambrogio R 2009	3.4	1.6	74	9.1	3.5	78	13.0%	-5.70 [-6.56, -4.84]	-	
Tohme S 2012	2.2	1.85	60	5.36	2.9	50	12.9%	-3.16 [-4.09, -2.23]	-	
Total (95% CI)			668			640	100.0%	-5.83 [-7.66, -4.01]	•	
Heterogeneity: Tau <sup>2</sup> = 6.4	48; Chi² - ∈ 26 /⊡	= 147.	02, df =	:7(P≺	0.0000	01); I²=	95%		-20 -10 0 10	20
restion overall effect. Z =	- 0.20 (F	~ 0.01	5001)						Favours RFA Favours HR	



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  $\le 3$  cm HR did not differ significantly from RFA for survival<sup>43</sup>. However, Xu et al. showed that HR was associated with significantly improved survival benefits compared with RFA for HCC  $\leq 3 \text{ cm}^{44}$ . 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<sup>5</sup>. 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 metaanalysis 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<sup>7,13,14,18,30,31</sup>. 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 randomeffects 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<sup>49</sup>. 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<sup>50</sup>.

**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<sup>51,52</sup>. 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<sup>2</sup> statistics<sup>53</sup>. Study-specific results were combined using a random-effects model, which considers both within-study and between-study variation<sup>54</sup>. 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 OR54. 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).

- Ferlay, J. et al. Cancer incidence and mortality worldwide: GLOBOCAN 2012 v1.0, IARC Cancer Base No. 11. (2013). Available from: http://globocan.iarc.fr, accessed on 01/10/2014
- Yang, J. D. & Roberts, L. R. Hepatocellular carcinoma: A global view. Nat Rev Gastroenterol Hepatol 7, 448–58 (2010).
- Poon, R. T., Fan, S. T., Tsang, F. H. & Wong, J. Locoregional therapies for hepatocellular carcinoma: a critical review from the surgeon's perspective. *Ann Surg* 235, 466–86 (2002).
- Minami, Y. & Kudo, M. Radiofrequency ablation of hepatocellular carcinoma: Current status. World J Radiol 2, 417–24 (2010).
- Cucchetti, A., Piscaglia, F., Cescon, M., Ercolani, G. & Pinna, A. D. Systematic review of surgical resection vs radiofrequency ablation for hepatocellular carcinoma. *World J Gastroenterol* 19, 4106–18 (2013).
- Huang, J. et al. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. Ann Surg 252, 903–12 (2010).
- Yun, W. K. *et al.* Superior long-term outcomes after surgery in child-pugh class a patients with single small hepatocellular carcinoma compared to radiofrequency ablation. *Hepatol Int* 5, 722–9 (2011).

- Chen, M. S. *et al.* A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. *Ann Surg* 243, 321–8 (2006).
- Feng, K. *et al.* A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. *J Hepatol* 57, 794–802 (2012).
- Nishikawa, H. et al. Comparison of percutaneous radiofrequency thermal ablation and surgical resection for small hepatocellular carcinoma. BMC Gastroenterol 11, 143 (2011).
- Peng, Z. W. *et al.* Radiofrequency ablation versus hepatic resection for the treatment of hepatocellular carcinomas 2 cm or smaller: a retrospective comparative study. *Radiology* 262, 1022–33 (2012).
- Ramasamy, A., Mondry, A., Holmes, C. C. & Altman, D. G. Key issues in conducting a meta-analysis of gene expression microarray datasets. *PLoS Med* 5, e184 (2008).
- Hung, H. H. *et al.* Survival rates are comparable after radiofrequency ablation or surgery in patients with small hepatocellular carcinomas. *Clin Gastroenterol Hepatol* 9, 79–86 (2011).
- Hong, S. N. *et al.* Comparing the outcomes of radiofrequency ablation and surgery in patients with a single small hepatocellular carcinoma and well-preserved hepatic function. *J Clin Gastroenterol* 39, 247–52 (2005).
- 15. Lupo, L. *et al.* Single hepatocellular carcinoma ranging from 3 to 5 cm: radiofrequency ablation or resection? *HPB (Oxford)* **9**, 429–34 (2007).
- Montorsi, M. *et al.* Survival and recurrences after hepatic resection or radiofrequency for hepatocellular carcinoma in cirrhotic patients: a multivariate analysis. J Gastrointest Surg 9, 62–7; discussion 67–8 (2005).
- Cho, C. M. *et al.* The comparative results of radiofrequency ablation versus surgical resection for the treatment of hepatocellular carcinoma. *Korean J Hepatol* 11, 59–71 (2005).
- Gao, W. *et al.* Therapeutic effect of radiofrequency ablation in unsuitable operative small hepatocellular carcinoma. *Chin J Med Imaging Technol* 23, 254–257 (2007).
- Zhou, T., Qiu, Y., Kong, W., Zhang, W. & Ding, Y. Comparing the effect of radiofrequency ablation and surgical resection for the treatment of small hepatocellular. *J Hepatobiliary Surg* 15, 424–427 (2007).
- Abu-Hilal, M. *et al.* Surgical resection versus radiofrequency ablation in the treatment of small unifocal hepatocellular carcinoma. *J Gastrointest Surg* 12, 1521–6 (2008).
- Guglielmi, A. *et al.* Radiofrequency ablation versus surgical resection for the treatment of hepatocellular carcinoma in cirrhosis. *J Gastrointest Surg* 12, 192–8 (2008).
- 22. Santambrogio, R. *et al.* Surgical resection versus laparoscopic radiofrequency ablation in patients with hepatocellular carcinoma and Child-Pugh class a liver cirrhosis. *Ann Surg Oncol* **16**, 3289–98 (2009).
- Liu, H., Hu, J., Weng, H., Feng, L. & Cao, H. Effect and safety of radiofrequency catheter ablation for single small hepatocellular carcinoma. *Pract Clin Med* 12, 16–18 (2011).
- Du, J. et al. The curative effect of percutaneous RFA and radical resection to small hepatocellular carcinoma. Clin J Med Offic 40, 570–572 (2012).
- Peng, Z. W. *et al.* Radiofrequency ablation versus hepatic resection for the treatment of hepatocellular carcinomas 2 cm or smaller: a retrospective comparative study. *Radiology* 262, 1022–33 (2012).
- Wang, J. H., Wang, C. C., Hung, C. H., Chen, C. L. & Lu, S. N. Survival comparison between surgical resection and radiofrequency ablation for patients in BCLC very early/early stage hepatocellular carcinoma. *J Hepatol* 56, 412–8 (2012).
- Desiderio, J. *et al.* Could radiofrequency ablation replace liver resection for small hepatocellular carcinoma in patients with compensated cirrhosis? A 5-year follow-up. *Langenbecks Arch Surg* 398, 55–62 (2013).
- Lai, E. C. & Tang, C. N. Radiofrequency ablation versus hepatic resection for hepatocellular carcinoma within the Milan criteria-a comparative study. *Int J Surg* 11, 77–80 (2013).
- 29. Tohme, S. *et al.* Radiofrequency ablation compared to resection in early-stage hepatocellular carcinoma. *HPB (Oxford)* **15**, 210–7 (2013).
- Wong, K. M. *et al.* Survival comparison between surgical resection and percutaneous radiofrequency ablation for patients in Barcelona Clinic Liver Cancer early stage hepatocellular carcinoma. *Indian J Gastroenterol* 32, 253–7 (2013).
- Guo, W. X. *et al.* Percutaneous radiofrequency ablation versus partial hepatectomy for multicentric small hepatocellular carcinomas: a nonrandomized comparative study. *World J Surg* 34, 2671–6 (2010).
- Hasegawa, K. *et al.* Comparison of resection and ablation for hepatocellular carcinoma: a cohort study based on a Japanese nationwide survey. *J Hepatol* 58, 724–9 (2013).
- 33. Hiraoka, A. *et al*. Efficacy of radiofrequency ablation therapy compared to surgical resection in 164 patients in Japan with single hepatocellular carcinoma smaller than 3 cm, along with report of complications. *Hepatogastroenterology* 55, 2171–4 (2008).
- 34. Imai, K. *et al.* Comparison between hepatic resection and radiofrequency ablation as first-line treatment for solitary small-sized hepatocellular carcinoma of 3 cm or less. *Hepatol Res* **43**, 853–864 (2013).



- Ueno, S. *et al.* Surgical resection versus radiofrequency ablation for small hepatocellular carcinomas within the Milan criteria. *J Hepatobiliary Pancreat Surg* 16, 359–66 (2009).
- 36. Vivarelli, M. *et al.* Surgical resection versus percutaneous radiofrequency ablation in the treatment of hepatocellular carcinoma on cirrhotic liver. *Ann Surg* 240, 102–7 (2004).
- Zhang, J., Liu, H., Zhou, L., Cui, P. & Si, C. The effectiveness of radiofrequency ablation for the treatment of liver cancer. J Hepatobiliary Surg 19, 30–33 (2011).
- Bu, X., Wang, Y., Ge, Z., Wang, Z. & Zhang, D. Comparison of radiofrequency ablation and surgical resection for small primary liver carcinoma. *Chin Arch Gen Surg* 3, 127–131 (2009).
- Reuter, N. P., Woodall, C. E., Scoggins, C. R., McMasters, K. M. & Martin, R. C. Radiofrequency ablation vs. resection for hepatic colorectal metastasis: therapeutically equivalent? *J Gastrointest Surg* 13, 486–91 (2009).
- 40. Ni, J. *et al.* Percutaneous ablation therapy versus surgical resection in the treatment for early-stage hepatocellular carcinoma: a meta-analysis of 21,494 patients. *J Cancer Res Clin* **139**, 2021–2033 (2013).
- Wakai, T. *et al.* Long-term outcomes of hepatectomy vs percutaneous ablation for treatment of hepatocellular carcinoma < or =4 cm. *World J Gastroenterol* 12, 546–52 (2006).
- 42. Ma, Y. *et al.* Association between vitamin D and risk of colorectal cancer: a systematic review of prospective studies. *J Clin Oncol* **29**, 3775–82 (2011).
- 43. Zhou, Y. *et al.* Meta-analysis of radiofrequency ablation versus hepatic resection for small hepatocellular carcinoma. *BMC Gastroenterol* **10**, 78 (2010).
- 44. Xu, G. *et al.* Meta-analysis of surgical resection and radiofrequency ablation for early hepatocellular carcinoma. *World J Surg Oncol* **10**, 163 (2012).
- Lu, M. D. *et al.* Percutaneous microwave and radiofrequency ablation for hepatocellular carcinoma: a retrospective comparative study. *J Gastroenterol* 40, 1054–60 (2005).
- 46. Ohmoto, K. *et al.* Comparison of therapeutic effects between radiofrequency ablation and percutaneous microwave coagulation therapy for small hepatocellular carcinomas. *J Gastroenterol Hepatol* **24**, 223–7 (2009).
- Qian, G. J. *et al.* Efficacy of microwave versus radiofrequency ablation for treatment of small hepatocellular carcinoma: experimental and clinical studies. *Eur Radiol* 22, 1983–90 (2012).
- Shi, J. *et al.* Comparison of microwave ablation and surgical resection for treatment of hepatocellular carcinomas conforming to Milan criteria. *J Gastroenterol Hepatol* 29, 1500–7 (2014).

- Liberati, A. *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol* 62, e1–34 (2009).
- Stang, A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 25, 603–5 (2010).
- Ihaka, R. & Robert, G. R: A Language for Data Analysis and Graphics. J Comput Graph Stat 5, 299–314 (1996).
- 52. Reimers, M. & Carey, V. J. Bioconductor: an open source framework for
- bioinformatics and computational biology. *Methods Enzymol* 411, 119–34 (2006).
  53. Higgins, J. P. & Thompson, S. G. Quantifying heterogeneity in a meta-analysis. *Stat Med* 21, 1539–58 (2002).
- 54. DerSimonian, R. & Laird, N. Meta-analysis in clinical trials. *Control Clin Trials* 7, 177–88 (1986).

#### 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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