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 ≥ 3 cm, whereas there were no significant differences between the two groups for HCCs ≤ 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 worldwide1. 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 diagnosis2. 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 conditions3. 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 mortality4. 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 most5.

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 findings12. 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...
were significantly fewer in the RFA group than in the HR group (16 for RFA group, and 30.1% for HR group (Table 2). Complications and Hospital-Stay

Disease-free survival rates were significantly higher in the HR group for 3-year (27 trials, OR: 0.50, 95% CI: 0.43–0.89) and at 5-year (16 trials, OR: 0.44–0.72). Disease-free survival rates were significantly higher in the HR group for 3-year (31 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. 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. 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. In subgroup analysis, our results showed that for very early-stage HCC (size ≤ 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. Therefore, RFA has a considerable advantage over HR in providing a better short-term postoperative result.
| 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 |
|---------------------|---------|--------------|---------|---------|---------|----------------|-----------|-----------------------------|-----------------------------|--------------------------|------------------------|
| Chen MS 2006        | RCT     | 1999-2004    | China   | HR      | 90      | 49.4 ± 10.9 | 75/15     | ≤5 cm                       | 90/0                        | 90/0/0                   | 9/4/2/3                 |
| Huang J 2010        | RCT     | 2003-2005    | China   | RFA     | 77      | 51.9 ± 11.2 | 56/15     | ≤5 cm                       | 71/0                        | 71/0/0                   | 8/4/1/3                 |
| Feng K 2012         | RCT     | 2005-2008    | China   | RFA     | 115     | 56.6 ± 14.3 | 79/36     | ≤5 cm                       | 84/31                       | 110/5/0                  | 9/4/2/3                 |
| Vivarelli M 2004    | NRCT    | 1998-2002    | Italy   | RFA     | 84      | 47 [18-76]  | 73/5/9    | 2.6 ± 0.8                   | 52/32                       | 43/41/0                  | 9/4/2/3                 |
| Hong SN 2005        | RCT     | 1999-2001    | Korea   | HR      | 93      | 49.2 ± 9.9   | 69/24     | 2.5 ± 0.8                   | 93/0                        |                         | 6/3/0/3                 |
| Cho CM 2005         | RCT     | 2000-2002    | Korea   | RFA     | 61      | 59 ± 1.1     | 41/14     | 4.1 ± 0.6                   | 55/0                        |                         | 7/3/1/3                 |
| Montorsi M 2005     | NRCT    | 1997-2003    | Italy   | RFA     | 40      | 67 ± 9       | 33/7      | ≤5 cm                       | 40/0                        | 32/8/0                   | 7/3/1/3                 |
| Gao W 2007          | NRCT    | 1999-2006    | China   | RFA     | 34      | 51.5 [38-67] | 20/12     | 2.6 ± 0.4                   | 32/2                        | 33/1/0                   | 6/3/0/3                 |
| Lupo L 2007         | RCT     | 1999-2006    | Italy   | RFA     | 42      | 67 [28-80]   | 33/9      | 4.0 [3.0-5.0]               | 42/0                        | 28/14/0                  | 8/3/2/3                 |
| Zhou T 2007         | NRCT    | 2001-2006    | China   | RFA     | 40      | 53 ± 13      | 35/5      | ≤5 cm                       | 38/2                        | 37/3/0                   | 8/3/2/3                 |
| Abu-Hilal M 2008    | NRCT    | 1991-2003    | UK      | RFA     | 34      | 67           | 26/8      | 3.8                         | 34/0                        | 25/9/0                   | 7/3/1/3                 |
| Hiraoka A 2008      | NRCT    | 2000-2007    | Japan   | RFA     | 34      | 65           | 27/7      | 3.0                         | 34/0                        | 27/7/0                   | 7/3/1/3                 |
| Guglielmi A 2008    | RCT     | 1996-2006    | Italy   | RFA     | 105     | 69.4 ± 9.1  | 76/29     | 1.98 ± 0.52                 | 105/0                       | 79/26/0                  | 6/3/0/3                 |
| Bu XY 2009          | NRCT    | 2000-2006    | China   | RFA     | 109     | 53.9 ± 10.7 | 36/6      | ≤6 cm                       | 65/4                        | 64/4/0                   | 6/3/0/3                 |
| Santambrogio R      | RCT     | 1997-2007    | Italy   | RFA     | 46      | 53.9 ± 7.4  | 40/6      | ≤6 cm                       | 38/0                        | 38/6/0                   | 7/3/1/3                 |
| Ueno S 2009         | NRCT    | 2000-2005    | Japan   | RFA     | 123     | 67 [28-85]   | 82/41     | 2.7 ± 0.1                   | 110/13                      | 91/31/1                  | 6/3/0/3                 |
| Guo WX 2010         | NRCT    | 2002-2007    | China   | RFA     | 73      | 50.5 [17-68] | 57/16     | 3.5                         | 0/73                        | 71/2/0                   | 7/3/1/3                 |
| Yun WK 2010         | RCT     | 2000-2007    | Korea   | RFA     | 86      | 52.5 [26-80] | 63/23     | 3.2                         | 0/86                        | 84/2/0                   | 6/3/0/3                 |
| Hung HH 2011        | NRCT    | 2002-2007    | China   | RFA     | 255     | 57.0 ± 9.9  | 197/58    | 2.1 ± 0.5                   | 215/0                       | 215/0/0                  | 6/3/0/3                 |
| Liu H 2011          | NRCT    | 2008-2010    | China   | RFA     | 190     | 67.4 ± 11.5 | 121/69    | 2.37 ± 0.92                 | 152/38                      |                         | 7/3/1/3                 |
| Nishikawa H         | NRCT    | 2004-2010    | Japan   | RFA     | 32      | 46.1 ± 24.1 | 21/6      | ≤5 cm                       | 35/0                        | 35/0/0                   | 7/3/1/3                 |
| Wang JH 2011        | RCT     | 2002-2009    | China   | RFA     | 162     | 68.4 ± 8.7  | 95/67     | 1.99 ± 0.62                 | 162/0                       | 102/22/3                 | 7/3/1/3                 |
| Zhang J 2011        | NRCT    | 2006-2009    | China   | RFA     | 85      | 58.5 ± 12.9 | 62/23     | ≤5 cm                       | 59/16                       | 81/22/0                  | 6/3/0/3                 |
| Du JK 2012          | RCT     | 2003-2007    | China   | RFA     | 58      | 56.6 ± 8.6  | 33/25     | ≤5 cm                       | .                          | .                        | 6/3/0/3                 |
### 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 |
|-----------|--------|--------------|---------|---------|----------|----------------|-----------|----------------------------|-------------------------------|--------------------------|------------------------|
| Imai K 2012 | NRCT   | 2000-2011    | Japan   | HR      | 101      | 63.3 ± 19.7   | 75/26    | 2.14 ± 0.55               | 101/0                        | 97/4/0                   | 63 3 0 3               |
| Peng ZW 2012 | NRCT   | 2003-2008    | China   | RFA     | 82       | 67.6 ± 18.5   | 46/36    | 1.87 ± 0.50               | 82/0                         | 62/0/12                   | 83 3 2 3               |
| Tohme S 2012 | NRCT   | 2001-2011    | USA     | RFA     | 50       | 66.3 ± 1      | 31/19    | 3.07 ± 1.17               | 39/11                        | 27/6/17                   | 62 1 3 3               |
| Desiderio J 2013 | NRCT   | 2004-2012    | Italy   | HR      | 52       | 65.6 ± 4.8    | 37/15    | ≤3 cm                     | 22/30                       | 52/0/0                    | 73 1 3 3               |
| Hasegawa K 2000-2005 | NRCT    | 2000-2005    | Japan   | RFA     | 5361     | 66 (48-77)    | 3967/1394 | ≤3 cm                     | 4458/903                   | 4000/1361/0               | 63 0 3                 |
| Lai EC 2013 | NRCT   | 2006-2012    | China   | HR      | 80       | 60.8 ± 9.9    | 55/25    | 2.9 ± 1.1                 | 71/9                         | -                         | 73 1 3 3               |
| Wong KM 2004-2009 | NRCT   | 2004-2009    | Japan   | HR      | 46       | 55.1 ± 12     | 30/16    | 2.1 ± 0.6                 | 46/0                         | 46/0/0                    | 73 1 3 3               |

### 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) | I²     | Q test (P-value) | Egger’s test (P-value) |
|--------------------------------|-------------|--------------|--------|-------|---------------------|------------------|--------|-----------------|------------------------|
| Overall survival rate (≤5 cm)  | 31          | 16,103       | 78.6%  | 83.9% | 0.65 [0.53, 0.80]   | <0.001           | 61%    | <0.001          | 0.43                   |
| 3-year                         | 20          | 14,665       | 60.8%  | 71.4% | 0.57 [0.48, 0.67]   | <0.001           | 42%    | <0.001          | 0.03                   |
| 5-year                         | 27          | 15,524       | 41.1%  | 56.7% | 0.50 [0.41, 0.61]   | <0.001           | 72%    | <0.001          | 0.42                   |
| Differences-free survival rate | 20          | 14,640       | 26.6%  | 37.8% | 0.47 [0.35, 0.65]   | <0.001           | 84%    | <0.001          | 0.08                   |
| Overall survival rate (≤3 cm)  | 19          | 13,298       | 81.2%  | 85.7% | 0.62 [0.43, 0.89]   | 0.009            | 64%    | <0.001          | 0.35                   |
| 3-year                         | 16          | 13,075       | 61.8%  | 71.9% | 0.55 [0.42, 0.72]   | <0.001           | 56%    | 0.003           | 0.36                   |
| Differences-free survival rate | 16          | 13,109       | 42.5%  | 57.2% | 0.52 [0.39, 0.70]   | <0.001           | 74%    | <0.001          | 0.58                   |
| Overall survival rate (≤2 cm)  | 15          | 12,912       | 27.8%  | 37.3% | 0.57 [0.38, 0.87]   | 0.01             | 85%    | <0.001          | 0.48                   |
| Differences-free survival rate | 4           | 442          | 80.6%  | 83.7% | 0.54 [0.12, 2.37]   | 0.41             | 81%    | 0.001           | 0.27                   |
| 3-year                         | 4           | 442          | 69.0%  | 74.2% | 0.65 [0.27, 1.55]   | 0.33             | 67%    | 0.03            | 0.58                   |
| Differences-free survival rate | 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                   |
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.
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 surgery7,13,14,18,30,31. 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 in 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. 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. 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 rate 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.

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) ≤ 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. 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 I² statistics. 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. 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**

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