

Radiofrequency Ablation Versus Reresection in Treating Recurrent Hepatocellular Carcinoma

A Meta-Analysis

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Abstract: Treatment for recurrent hepatocellular carcinoma (RHCC) remains controversial. This study tried to compare survival benefits between radiofrequency ablation (RFA) and resection for RHCC patients following curative surgical treatments.

Databases were searched for comparative studies published from 2008 to 2014 on RFA versus resection in treating RHCC. Meta-analysis was performed using a random or fixed-effect model to compare the overall survivals (OSs) and disease-free survivals (DFSs) between RFA and resection. Begg funnel plot and Egger test were performed to assess the publication bias.

Six retrospective comparative studies fulfilled our criteria and were included. For patients with RHCC, RFA was equivalent to resection in 1-year OSs (odds ratio [OR] 0.86; 95% confidence interval [CI], 0.50–1.49; $P=0.587$), 3-year OSs (OR 0.91; 95% CI, 0.64–1.28; $P=0.581$), and 5-year OSs (OR 0.97; 95% CI, 0.69–1.36; $P=0.846$). However, resection was superior to RFA in 3-year DFSs (OR 2.25; 95% CI, 1.37–3.68; $P=0.001$) and 5-year DFSs (OR 3.70; 95% CI, 1.98–6.93; $P=0.000$). The outcome of 1-year DFSs was unstable with statistical heterogeneity among studies included in meta-analysis ($I^2=77.4\%$). No evidence of publication bias was found. RFA was considered as a less invasive modality for RHCC patients.

RFA achieves comparable OSs as resection in the treatment of RHCC, with lower postoperative complications.

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Abbreviations: CI = confidence interval, DFS = disease-free survival, HCC = hepatocellular carcinoma, NRCT = non-randomized controlled trial, OR = odds ratio, OS = overall survival, RCT = randomized controlled trial, RFA = radiofrequency ablation, RHCC = recurrent hepatocellular carcinoma.

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BACKGROUND

Hepatocellular carcinoma (HCC) is the seventh most common malignant tumor and the third leading cause of cancer deaths in the world. It is the third most frequent cancer in China and is increasing in western countries.^{1–3} Liver transplantation, surgical resection, and radiofrequency ablation (RFA) are curative treatment modalities for HCC according to the guidelines of the American Association for the Study of Liver Diseases.⁴ However, the prognosis of curative treatments for HCC is rather disappointing because of a high recurrence rate. A 5-year recurrence rate of >50% has been reported after surgical resection,^{5–8} which is even higher after curative RFA treatment.^{9,10} Even in patients undergoing liver transplantation, the postoperative recurrence rate is between 15% and 20%.¹¹ Therefore, the treatment of recurrent hepatocellular carcinoma (RHCC) is critical in improving the survival of HCC patients. For most patients with intrahepatic recurrence without general metastasis and macrovessel invasion, there are still chances to achieve a curative treatment, with liver transplantation, resection, or RFA. Though liver transplantation is recognized as the best choice for RHCC,¹² the shortage of donor livers has limited its wide application. As to the choice of resection and RFA, no consensus has yet been reached. Though surgical resection is considered the gold standard for the treatment of HCC,⁴ there are drawbacks such as excessive damage to the liver function and more difficulty in a second open surgery for RHCC patients.¹³ RFA, as a less invasive and repeatable modality, is more feasible in RHCC patients with impaired liver function and unresectable tumor lesions.^{14,15} In order to prove that RFA may be a promising alternative to resection, we conducted this evidence-based research to compare the treatment efficacy between RFA and resection in RHCC patients.

METHODS

Search Strategy and Data Extraction

All studies we needed were retrieved by searching databases including Cochrane library, PubMed, and EMBASE using the following keywords: “recurrent hepatocellular carcinoma,” “radiofrequency ablation,” and “re-resection/repeated resection/surgical resection.” In order to cover all relevant studies, reference lists of all these retrieved articles were manually reviewed for more possibly useful information. No language limitation was set. All studies we needed should fulfill the following criteria:

1. Controlled trials directly comparing RFA with resection for clinically or pathologically confirmed RHCC;
2. All RHCC patients received curative treatments before and were scanned by computed tomography (CT) or

magnetic resonance imaging (MRI) to confirm complete clearance or ablation of tumors;

3. RHCC without macrovessel invasion and general metastasis;
4. Data including 1-, 3-, and 5-year overall survival (OS) and disease-free survival (DFS) and local recurrence rate were given in detail.

Articles were excluded when patients with severely impaired liver function or poor general health conditions or patients with tumor residual or insufficient ablation after initial curative treatments were included.

Two trained reviewers (H.C. and W.K., both doctors experienced in the procedure of liver cancer treatment) extracted the data independently on a specially designed form. Qualities of the retrieved studies were assessed according to the Jadad scale. The 2 reviewers were blinded to each other about data extraction and quality assessment result. Data needed in this study included the name of the first author, publishing year, time to recurrence, number of patients, age, sex, tumor size, tumor number, Child-Pugh stage, and long-term survival rates. Any discrepancies were resolved by discussion.

Statistical Analysis

Meta-analysis was performed with the commercially available software STATA, version 12.0 (STATA, College Station, TX). Dichotomous variables were described as relative frequency and were compared by χ^2 test. Odds ratio (OR) with 95% confidence interval (CI) was calculated to compare the primary treatment efficacy between 2 groups. Either a fixed-effect model or a random-effect model was used according to heterogeneity among trials when the meta-analysis was performed. Statistical heterogeneity among the studies was assessed by χ^2 and I^2 test. $I^2 \geq 50\%$ was thought to be with large inconsistency, and a random-effect model was used. Begg funnel plot and Egger test were performed to assess the publication bias. Significance was defined when $P < 0.05$.

RESULTS

Description of Studies Selection

Six retrospective comparative studies¹⁶⁻²¹ published from 2008 to 2014 were included in our analysis, which were all nonrandomized controlled trials (NRCTs) with low Jadad scores. Chan et al²² conducted similar studies in 2012 and 2013. However, the latter was excluded for lack of information of DFS.²² All these retrieved studies involved RHCC patients with previous curative treatments of surgical resection or RFA. In total, there were 642 patients, 314 for RFA and 328 for resection. There were no statistical differences between the 2 treatment groups at previous treatment stage in age, sex, tumor size, tumor number, and liver function. All these patients were scanned by contrast-enhanced CT or MRI after initial treatments to be confirmed "curative treated." Baseline information was shown in Table 1.

OSs for RHCC Treated by RFA or Resection

All 6 studies¹⁶⁻²¹ reported long-term OS. No statistical difference existed between the 2 comparative groups in 1-year OS (OR 0.86; 95% CI, 0.50-1.49; $P=0.587$), 3-year OS (OR 0.91; 95% CI, 0.64-1.28; $P=0.581$), and 5-year OS (OR 0.97; 95% CI, 0.69-1.36; $P=0.846$). There's no

TABLE 1. Baseline Demographic and Clinical Information of Retrieved Comparative Studies

Author	Type	Study Period*	Initial Treatment	Second Treatment	Time to Recurrence, mo	No. of Patients	Sex (M/F)	Age, y	Solitary/Multiple Tumor	Tumor Size, cm	Child-Pugh Staging A/B or C
Liang ¹⁷	NRCT	1999-2007	SR	RFA	NS	66	54/12	54.6 ± 10.8	48/18	NS	64/2
Ren ¹⁶	NRCT	2000-2005	SR	SR	NS	44	39/5	48.8 ± 12.0	34/10	2.0	44/0
Umeda ¹⁸	NRCT	—	SR	RFA	NS	145	127/18	51	126/19	2.0	68/0
Chan ¹⁹	NRCT	2001-008	SR	SR	8.7 (1.0-88.5)	29	—	—	—	2.1 ± 0.3	145/0
Ho ²⁰	NRCT	2001-2007	SR	RFA	12.2 (1.8-84.3)	45	—	59 (36-80)	29/16	3.2 ± 0.57	51/7
Eisele ²¹	NRCT	—	SR + RFA	RFA	20.0 (3-90)	29	—	52 (38-79)	21/8	2.2 (0.8-6.0)	29/0
					23.9 (3-66)	50	39/11	61.0 ± 11.1	—	2.1 (0.8-5.5)	50/0
					21 ± 17	54	40/14	56.3 ± 12.3	—	2.3 ± 1.9	51/3
					39 ± 27	27	7/20	68 ± 7	15/12	2.9 ± 1.8	19/8
						27	12/15	60 ± 17	16/11	4.0 ± 2.3	27/0

M/F = male/female, NRCT = nonrandomized control trial, NS = not significant, RFA = radiofrequency ablation, RHCC = recurrent hepatocellular carcinoma, SR = surgical resection.

*The follow-up period after treatment of RHCC.

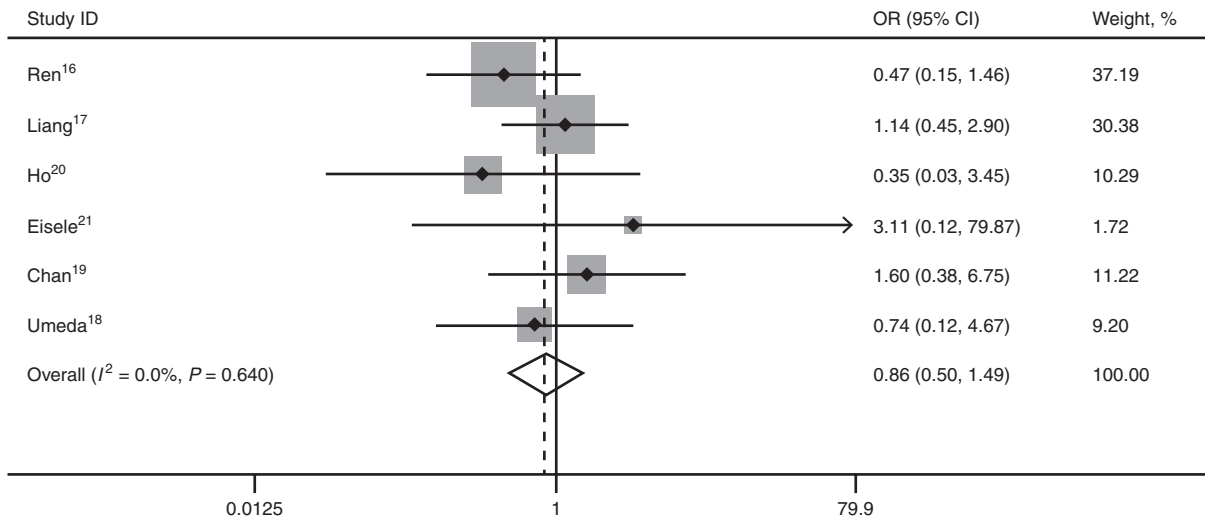


FIGURE 1. Forest plots showing the pooled result of 1-year OS. CI = confidence interval, OR = odds ratio, OS = overall survival.

heterogeneity among the 6 studies, and a fixed-effect model was used (Figures 1–3).

DFSs for RHCC Treated by RFA or Reresection

Three studies^{16,19,21} reported 1-, 3-, and 5-year DFS. SR is superior to RFA for 3-year DFS (OR 2.25; 95% CI, 1.37–3.68; $P = 0.001$) and 5-year DFS (OR 3.70; 95% CI, 1.98–6.93; $P = 0.000$). There was statistical significant heterogeneity among the 3 studies for 1-year DFS ($I^2 = 77.4\%$), and a random-effect model was used (OR 1.56; 95% CI, 0.35–6.89; $P = 0.560$) (Figures 4–6).

Sensitivity Analysis and Bias Analysis

In order to evaluate the stability of the result of meta-analysis, we conducted a sensitivity analysis. The corresponding pooled ORs were not materially altered except for the meta-analysis of 1-year DFS. The difference is statistically significant when a fixed-effect model was used. The

meta-analyses of 1-, 3-, and 5-year OS and 3- and 5-year DFS were relatively stable and credible.

No obvious asymmetry was shown on Begg funnel plot, and Egger test did not show any evidence of publication bias in all comparisons (1-year OS, $P = 0.926$; 3-year OS, $P = 0.789$; 5-year OS, $P = 0.821$; 1-year DFS, $P = 0.503$; 3-year DFS, 0.231; 5-year DFS, 0.163).

DISCUSSION

Intrahepatic recurrence of HCC is not uncommon after curative surgical treatments, and an appropriate treatment of RHCC is critical in improving long-term outcomes after initial therapies. Liver transplantation, resection, and RFA were 3 potential curative treatment options.⁴ However, there is no consensus on the treatment strategy for RHCC. It is currently accepted that liver transplantation is the best treatment option for HCC as it removes not only tumor lesions but also concurrent cirrhosis, blocking the underlying

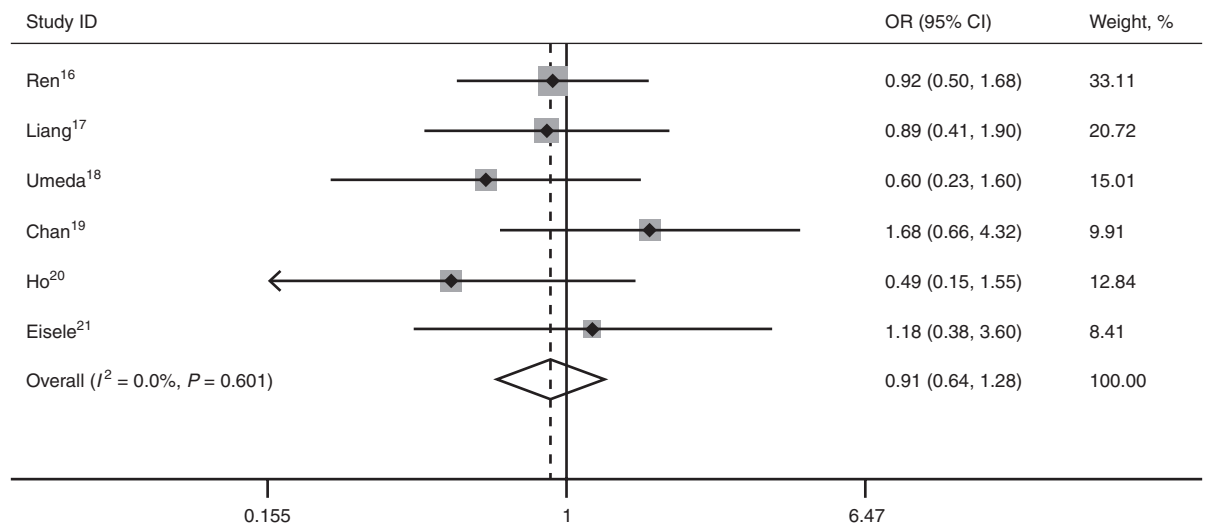


FIGURE 2. Forest plots showing the pooled result of 3-year overall survival. CI = confidence interval, OR = odds ratio, OS = overall survival.

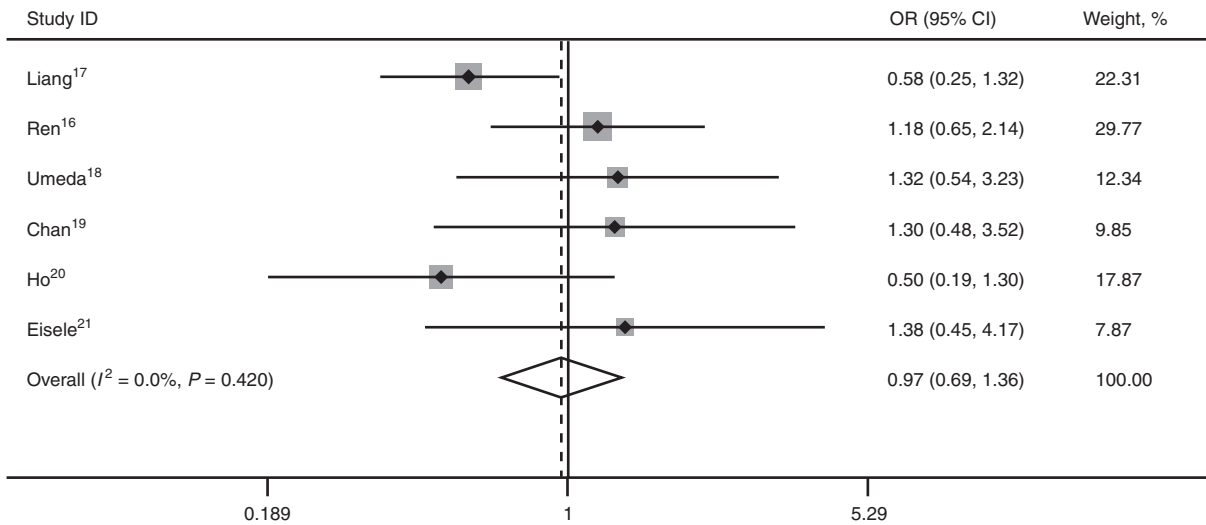


FIGURE 3. Forest plots showing the pooled result of 5-year overall survival. CI = confidence interval, OR = odds ratio, OS = overall survival.

process of carcinogenesis.^{23,24} However, limited liver donor resources make it difficult for patients to be treated on time before tumor progression. Generally speaking, for patients with resectable tumor lesions and well-preserved liver function, resection is usually considered.^{25,26} Nevertheless, only a small proportion of patients with RHCC are amenable to liver transplantation (10%) or resection (12%).²⁷ RFA is offered as an alternative for those with poor liver function or unresectable tumor lesions, which are not suitable for resection.¹⁵ Several retrospective controlled studies compared RFA with resection in the treatment of RHCC.^{16–22} This study was a systematic review and meta-analysis of these important clinical literature.

In our study, baseline demographic data between the 2 groups did not have any statistical difference at initial treatment stage. Patients developing intrahepatic recurrence were treated with either RFA or resection. It showed that RFA was comparable to resection for long-term OSs. However, resection was superior to RFA for long-term disease-free survivals. Ren et al¹⁶ and Liang et al¹⁷ reported

significantly lower complication rate after treatment of RFA. There are some advantages of RFA when compared with resection in treating RHCC. First, as a minimally invasive treatment modality, RFA can be performed percutaneously, therefore avoiding a second laparotomy. Second, in patients with small and cirrhotic liver remnant, RFA may be the only choice for conservation as much of the limited nontumorous liver parenchyma as possible.^{28,29} Therefore, for patients with well preserved liver function and resectable tumor lesions, resection is no doubt preferred to RFA. However, for those who are not candidates for resection, RFA would be a better choice, which shows comparable OSs as resection. Though with higher recurrence rate, RFA serves as an ideal treatment choice for unresectable RHCC for its advantage of less invasiveness and repeatability.

Time to recurrence, which is thought to be an independent prognostic factor of RHCC,³⁰ was comparable between the 2 groups in all studies except that of Eisele et al.²¹ It is reported that tumor recurrence within 1 year is more likely to develop an intrahepatic metastasis, with relatively poor

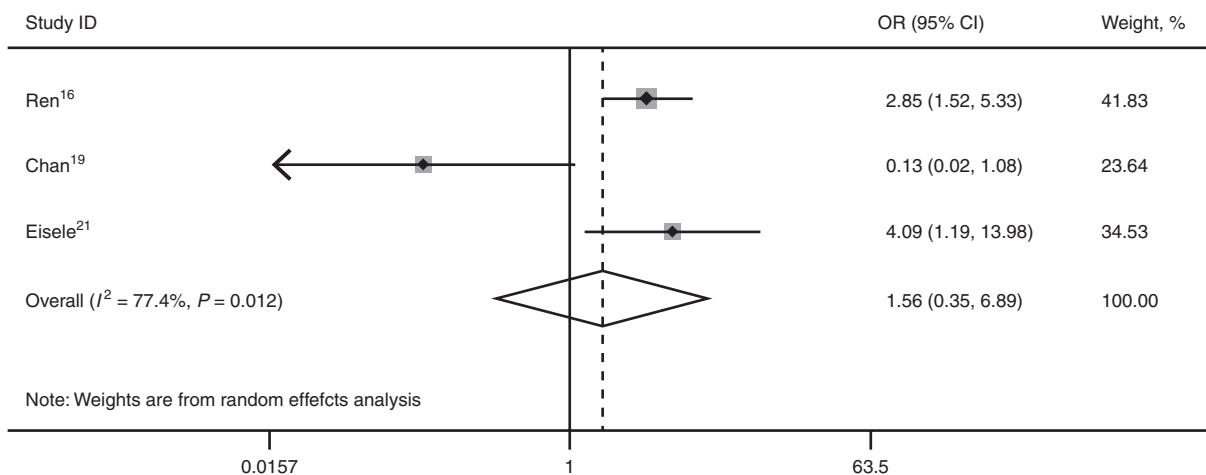


FIGURE 4. Forest plots showing the pooled result of 1-year disease-free survival. CI = confidence interval, OR = odds ratio.

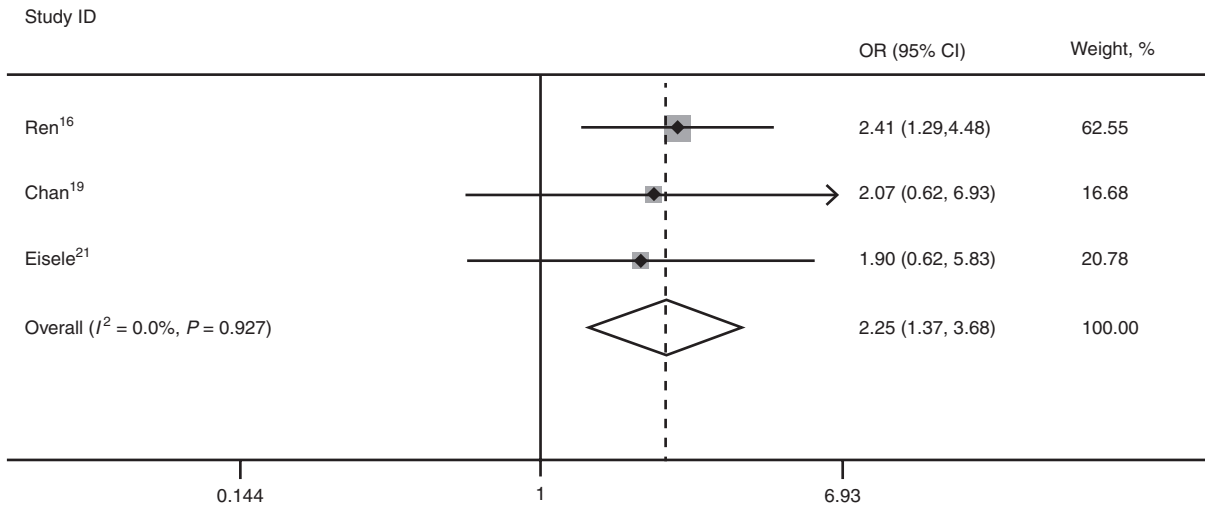


FIGURE 5. Forest plots showing the pooled result of 3-year disease-free survival. CI = confidence interval, OR = odds ratio.

prognosis, unlike tumor recurrence after 1 year, which is prone to be a multicentric occurrence.³⁰ However, even in the study of Eisele et al,²¹ the average time to recurrence was >1 year in either group. Besides, it should be noted that in the study of Umeda et al¹⁸ and Eisele et al,²¹ patients who received resection seemed to get better liver function and larger tumor size than those receiving RFA therapy. Also in the study of Umeda et al,¹⁸ patients in the RFA group seemed to get more multiple lesions at the time of recurrence. However, no statistical evidence was provided. It is reported that liver function, tumor number, and tumor size were important prognostic factors for either RFA or surgical resection.³¹⁻³⁴ However, the effect of these factors still remains uncertain. In order to rule out the influence of these factors, further randomized controlled trials (RCTs) would be necessary.

There are some limitations in our study. First, all the included studies in meta-analysis were retrospective controlled studies, which contributed low evidence level to our study. Selection bias existed that patients with better general health condition are more likely to be allocated to resection group, which may explain the better prognosis of resection.

Second, only a small number of institutions researched on the treatment options for RHCC. In total, 6 studies published results on this aspect and only 3 of them reported DFSs. The total sample size of our study is small because of lack of qualified studies. There is statistical heterogeneity among 3 studies reporting 1-year DFS ($I^2 = 77.4\%$), making the pooled outcome unstable and less convincing. More studies of high quality are needed to be done in future. Third, as we mentioned above, intrahepatic recurrence of HCC is complex on the mechanism, as it can be derived from intrahepatic metastasis or multicentric occurrence.³⁵ Different patterns of recurrence is accompanied with different prognosis.³⁶ However, it is difficult to tell them apart in clinical practice.

To date, no RCTs have been published to compare the treatment efficacy of RFA and resection for RHCC. Still, the result of our study is referential to clinical practice, which may give some advice to hepatobiliary surgeons in the decision-making process for a proper treatment of RHCC. Recent studies reported that RFA, in combination with other treatment modalities such as TACE or molecular targeted therapy, showed better results than RFA treatment alone.^{37,38} We believe that with the development of technology and

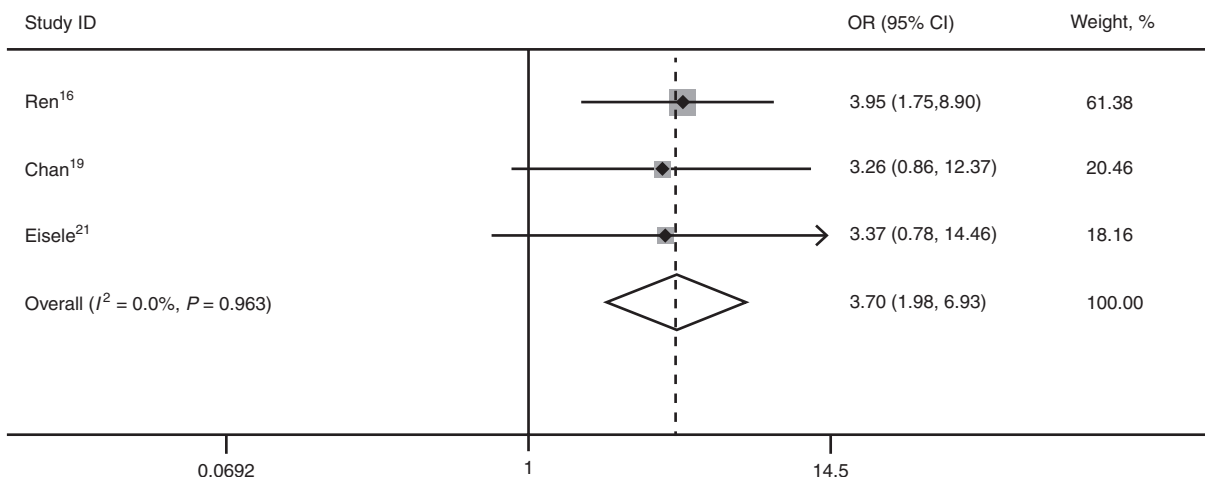


FIGURE 6. Forest plots showing the pooled result of 5-year disease-free survival. CI = confidence interval, OR = odds ratio.

advances in treatment strategy, lower recurrence, and better outcome will be achieved for RHCC patients receiving RFA.

CONCLUSION

RFA achieves comparable OSs as resection in the treatment of RHCC, with lower complications. However, resection is superior to RFA in long-term DFSs.

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