

Radiofrequency ablation versus resection for Barcelona clinic liver cancer very early/early stage hepatocellular carcinoma: a systematic review

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Aim: To compare the long-term survival outcomes of radiofrequency ablation and liver resection for single very early/early stage hepatocellular carcinoma (HCC).

Methods: The Cochrane Library (Issue 3, 2015), Embase (1974 to March 15, 2015), PubMed (1950 to March 15, 2015), Web of Science (1900 to March 15, 2015), and Chinese Biomedical Literature Database (1978 to March 15, 2015) were searched to identify relevant trials. Only trials that compared radiofrequency ablation and liver resection for single very early stage (≤ 2 cm) or early stage (≤ 3 cm) HCC according to the Barcelona clinic liver cancer (BCLC) staging system were considered for inclusion in this review. The primary outcomes that we analyzed were the 3-year and 5-year overall survival (OS) rates, and the secondary outcomes that we analyzed were the 3-year and 5-year disease-free survival (DFS) rates. Review Manager 5.3 was used to perform a cumulative meta-analysis. Possible publication bias was examined using a funnel plot. A random-effects model was applied to summarize the various outcomes.

Results: Six studies involving 947 patients were identified that compared radiofrequency ablation ($n=528$) to liver resection ($n=419$) for single BCLC very early HCC. In these six studies, the rates of 3-year OS, 5-year OS, 3-year DFS, and 5-year DFS were significantly lower in the radiofrequency ablation group than in the liver resection group (risk ratio [RR] = 0.90, 95% confidence interval [CI]: 0.83–0.98, $P=0.01$; RR = 0.84, 95% CI: 0.75–0.95, $P=0.004$; RR = 0.77, 95% CI: 0.60–0.98, $P=0.04$; and RR = 0.70, 95% CI: 0.52–0.94, $P=0.02$, respectively). Ten studies involving 2,501 patients were identified that compared radiofrequency ablation ($n=1,476$) to liver resection ($n=1,025$) for single BCLC early HCC. In these ten studies, the rates of 3-year OS, 5-year OS, 3-year DFS, and 5-year DFS were also significantly lower in the radiofrequency ablation group than in the liver resection group (RR = 0.93, 95% CI: 0.88–0.98, $P=0.003$; RR = 0.84, 95% CI: 0.75–0.94, $P=0.002$; RR = 0.72, 95% CI: 0.58–0.89, $P=0.002$; and RR = 0.47, 95% CI: 0.33–0.67, $P<0.0001$, respectively).

Conclusion: The long-term survival outcomes for patients with single BCLC very early/early stage HCC appear to be superior after liver resection compared to radiofrequency ablation.

Keywords: radiofrequency ablation, liver resection, hepatocellular carcinoma, systematic review

Introduction

Hepatocellular carcinoma (HCC) ranks sixth in terms of the most common neoplasms.^{1–3} The age-adjusted overall incidence of HCC was ~16 cases per 100,000 individuals in 2008.^{1–3} HCC is highly prevalent in Asia, and its incidence is increasing in Europe and in the US.⁴ In recent decades, the development of diagnostic technology and the widespread screening of populations with a high risk of developing HCC have increased the detection of early stage HCC.^{5–7}



Liver transplantation is regarded as the best curative approach for early stage HCC. However, only a small percentage of patients are offered this treatment due to high hospital costs and a shortage of liver donors.⁵⁻⁹ Liver resection is also a good surgical treatment for early stage HCC, and the 5-year survival rate of this procedure is >50%.⁶⁻⁸ However, some patients with HCC cannot undergo a liver resection due to either poor liver function or rejection. Many nonsurgical treatments have been proposed for these patients, such as radiofrequency ablation, microwave coagulation, and high-intensity focused ultrasound.¹⁰⁻¹⁴

The management of very early stage (Child-Pugh A, solitary ≤ 2 cm) and early stage (Child-Pugh A or B, solitary ≤ 3 cm) HCC, according to the Barcelona clinic liver cancer (BCLC) staging system, is controversial.¹⁵ Various systematic reviews and meta-analyses have confirmed the short-term efficacy of radiofrequency ablation for BCLC early stage HCC.¹⁶ The role of radiofrequency ablation in the management of BCLC very early stage HCC has not been systematically evaluated. The long-term survival outcome of patients with HCC is an important measure for the evaluation of various treatments.⁵⁻⁷ This systematic review compares the long-term survival outcomes of radiofrequency ablation versus liver resection for patients with single BCLC very early/early stage HCC.

Materials and methods

Study selection

The Cochrane Library (Issue 3, 2015), Embase (1974 to March 15, 2015), PubMed (1950 to March 15, 2015), Web of Science (1900 to March 15, 2015), and Chinese Biomedical Literature Database (1978 to March 15, 2015) were searched to identify trials that compared radiofrequency ablation with liver resection in the management of single BCLC very early/early stage HCC. The following keywords were used in these searches: catheter ablation, radiofrequency ablation, liver resection, hepatectomy, liver cancer, HCC, and liver neoplasm. The references of the relevant publications were also manually searched to identify any additional relevant clinical trials.

Criteria for inclusion and exclusion

The criteria for inclusion of the identified studies were as follows: 1) conformance to the BCLC staging classification: very early stage (Child-Pugh A, solitary ≤ 2 cm) or early stage (Child-Pugh A or B, solitary ≤ 3 cm); 2) comparison of the effects of radiofrequency ablation versus liver resection for single BCLC very early/early stage HCC, irrespective of

etiology or the presence of liver cirrhosis or viral hepatitis; and 3) at least one outcome of interest reported.

The criteria for exclusion were as follows: 1) investigation of HCC nodules of >3 cm; 2) investigation of recurrent HCC; and 3) investigation of patients with cholangiocarcinomas or liver metastases.

Data extraction

The following data were extracted from each trial by two independent authors: 1) study design; 2) year of publication and authors; 3) number and characteristics of patients; and 4) outcome measures. The discrepancy between the two authors was resolved by discussion.

Outcomes

The primary outcomes measured in this review were the 3-year and 5-year overall survival (OS) rates. The secondary outcomes measured in this review were the 3-year and 5-year disease-free survival (DFS) rates.

Quality and publication bias assessment

The quality of each trial was evaluated using the GRADE system.¹⁷ Funnel plots were applied to evaluate publication bias.¹⁸ Both visual asymmetry and Egger's linear regression test were used to examine the existence of publication bias.¹⁹

Statistical analysis

Review Manager 5.3 (RevMan; Cochrane Collaboration, Oxford, UK) was used to perform a meta-analysis. Statistical heterogeneity among trials was determined by the chi-square test.²⁰ The risk ratio (RR) and 95% confidence interval (CI) were used to evaluate the treatment efficacy.²⁰ A result was regarded as statistically significant if the *P*-value was <0.05.²⁰ A random-effects model was used to summarize the various outcomes for conservative estimates. We conducted the meta-analysis and systematic review according to the Cochrane Handbook for Systematic Reviews of Interventions and Preferred Reporting Items for Systematic Reviews and Meta-Analyses.^{21,22}

Results

Search results

A total of 4,830 records were identified by electronic searches of the Cochrane Library (n=322), Embase (n=1,847), PubMed (n=1,581), Web of Science (n=820), and Chinese Biomedical Literature Database (n=260) and a manual search of the reference lists of the included trials (n=6). We excluded 1,200 duplicated records and 3,612 irrelevant records by

screening titles and abstracts. Twenty-four full-text articles were retrieved for further assessment. We excluded eleven articles for the reasons listed in Figure 1.

Description of studies

Thirteen studies published between 2008 and 2015 fulfilled the inclusion criteria, including two randomized controlled trials (RCTs) and eleven nonrandomized studies (NRS).^{23–35} Three studies compared radiofrequency ablation with liver resection for BCLC very early stage HCC,^{25,29,30} seven studies compared radiofrequency ablation with liver resection for BCLC early stage HCC,^{23,24,31–35} and three studies compared radiofrequency ablation with liver resection for both BCLC very early stage and early stage HCC.^{26–28} A total of six studies including 947 patients (528 radiofrequency ablations and 419 liver resections) compared radiofrequency ablation

with liver resection for BCLC very early stage HCC.^{25–30} Ten studies with a total of 2,501 patients (1,476 radiofrequency ablations and 1,025 liver resections) compared radiofrequency ablation with liver resection for BCLC early stage HCC.^{23–25,29–35} The characteristics and quality of the included trials are presented in Tables 1 and 2.

Effects of interventions

Radiofrequency ablation versus liver resection for single BCLC very early stage HCC

The outcome measures data are presented in Table 3.

Three-year OS rate: Five studies^{25–27,29,30} reported this outcome. Patients in the radiofrequency ablation group had significantly lower 3-year OS rate than those in the liver resection group (RR =0.90, 95% CI: 0.83–0.98, $P=0.01$; heterogeneity: $I^2=54%$, $P=0.07$; Figure 2A).

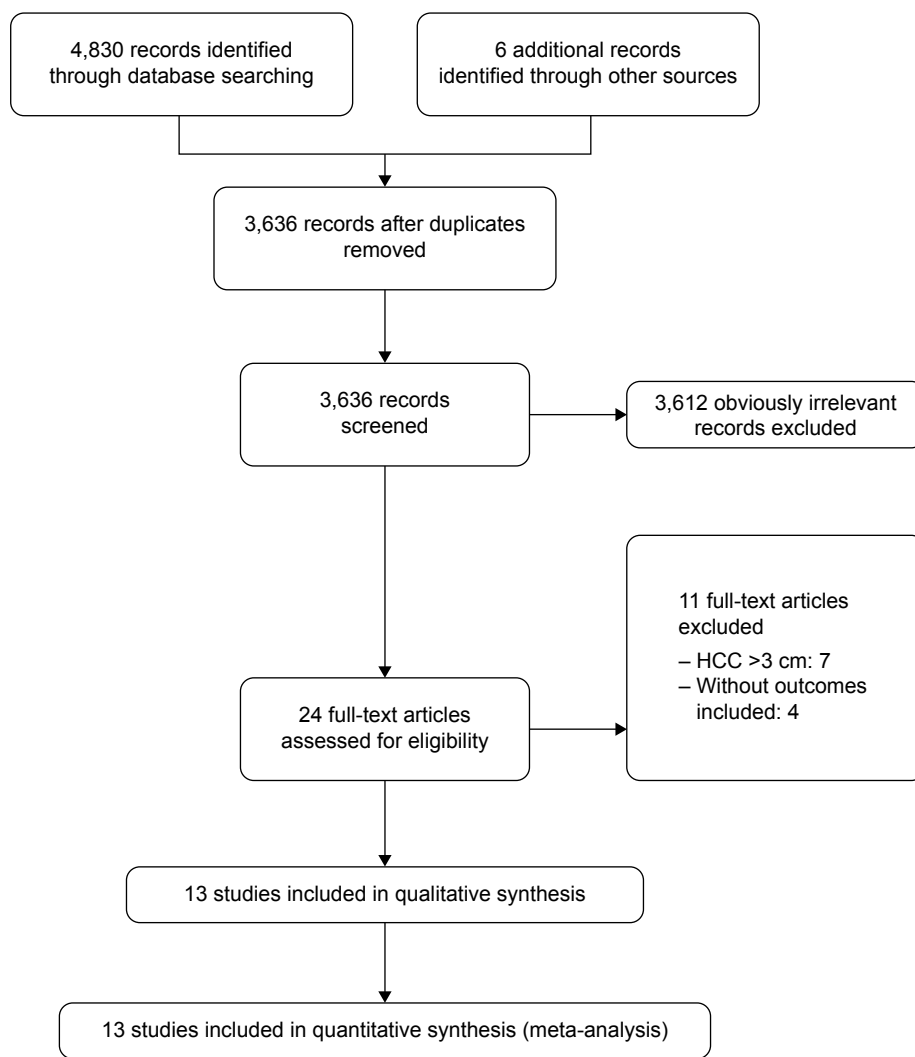


Figure 1 Flow diagram showing study selection process.
Abbreviation: HCC, hepatocellular carcinoma.

Table 1 Characteristics and quality of included studies for single BCLC very early stage HCC

Author	Year	Country	Design	Participants (RFA/LR)	Sex (M/F)	Quality of the evidence (grade)
Livraghi et al ²⁵	2008	Italy	NRS	118/100	122/96	Low
Wang et al ²⁶	2012	People's Republic of China	NRS	91/52	98/41	Very low
Pompili et al ²⁷	2013	Italy	NRS	109/99	NA	Very low
Imai et al ²⁸	2013	Japan	NRS	51/38	NA	Very low
Zhou et al ²⁹	2014	People's Republic of China	NRS	31/21	35/17	Very low
Liu et al ³⁰	2015	People's Republic of China	NRS	128/109	162/75	Very low

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; LR, liver resection; M, male; F, female; NRS, nonrandomized studies; NA, not applicable.

Five-year OS rate: Five studies^{25,26,28–30} reported this outcome. Patients in the radiofrequency ablation group had significantly lower 5-year OS rate than those in the liver resection group (RR =0.84, 95% CI: 0.75–0.95, $P=0.004$; heterogeneity: $I^2=50%$, $P=0.09$; Figure 2B).

Three-year DFS rate: Four studies^{26,27,29,30} reported this outcome. Patients in the radiofrequency ablation group had significantly lower 3-year DFS rate than those in the liver resection group (RR =0.77, 95% CI: 0.60–0.98, $P=0.04$; heterogeneity: $I^2=69%$, $P=0.02$; Figure 2C).

Five-year DFS rate: Four studies^{26,28–30} reported this outcome. Patients in the radiofrequency ablation group had significantly lower 5-year DFS rate than those in the liver resection group (RR =0.70, 95% CI: 0.52–0.94, $P=0.02$; heterogeneity: $I^2=52%$, $P=0.10$; Figure 2D).

Radiofrequency ablation versus liver resection for single BCLC early stage HCC

The outcome measures data are presented in Table 4.

Three-year OS rate: Ten studies^{23,24,26–28,31–35} reported this outcome. Patients in the radiofrequency ablation group had significantly lower 3-year OS rate than those in the liver

resection group (RR =0.93, 95% CI: 0.88–0.98, $P=0.003$; heterogeneity: $I^2=59%$, $P=0.008$; Figure 3A).

Five-year OS rate: Seven studies^{23,26,28,31–33,35} reported this outcome. Patients in the radiofrequency ablation group had significantly lower 5-year OS rate than those in the liver resection group (RR =0.84, 95% CI: 0.75–0.94, $P=0.002$; heterogeneity: $I^2=76%$, $P=0.0004$; Figure 3B).

Three-year DFS rate: Eight studies^{24,26–28,31,32,34,35} reported this outcome. Patients in the radiofrequency ablation group had significantly lower 3-year DFS rate than those in the liver resection group (RR =0.72, 95% CI: 0.58–0.89, $P=0.002$; heterogeneity: $I^2=83%$, $P<0.00001$; Figure 3C).

Five-year DFS rate: Six studies^{26,28,31–33,35} reported this outcome. Patients in the radiofrequency ablation group had significantly lower 5-year DFS rate than those in the liver resection group (RR =0.47, 95% CI: 0.33–0.67, $P<0.0001$; heterogeneity: $I^2=77%$, $P=0.0005$; Figure 3D).

Quality of evidence and publication bias

Only one study had a moderate quality,²³ and the quality of all other studies varied from low to very low (Tables 1 and 2). Thus, the current quality of evidence is considered very low.

Table 2 Characteristics and quality of included studies for single BCLC early stage HCC

Author	Year	Country	Design	Participants (RFA/LR)	Sex (M/F)	Child-Pugh A/B	Quality of the evidence (grade)
Hiraoka et al ³¹	2008	Japan	NRS	105/59	120/44	133/31	Very low
Huang et al ²³	2010	People's Republic of China	RCT	57/45	NA	NA	Moderate
Wang et al ²⁶	2012	People's Republic of China	NRS	254/208	NA	396/66	Very low
Imai et al ²⁸	2013	Japan	NRS	82/101	121/62	167/26	Very low
Wong et al ³²	2013	People's Republic of China	NRS	36/46	48/34	82/0	Very low
Pompili et al ²⁷	2013	Italy	NRS	298/246	375/169	544/0	Low
Yang et al ³³	2014	Korea	NRS	79/52	97/34	118/13	Low
Fang et al ²⁴	2014	People's Republic of China	RCT	60/60	88/32	75/45	Low
Kim et al ³⁴	2014	Korea	NRS	67/66	100/33	133/0	Very low
Kang et al ³⁵	2015	Korea	NRS	438/142	444/136	502/78	Low

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; LR, liver resection; M, male; F, female; NRS, nonrandomized studies; RCT, randomized controlled trial; NA, not applicable.

Table 3 The long-term outcomes of radiofrequency ablation versus liver resection for single BCLC very early stage HCC

Studies	Overall survival rates (%)				Disease-free survival rates (%)			
	3-year		5-year		3-year		5-year	
	RFA	LR	RFA	LR	RFA	LR	RFA	LR
Livraghi et al ²⁵	75.0	89.0	47.0	68.0	NA	NA	NA	NA
Wang et al ²⁶	81.3	98.0	72.0	91.5	39.8	62.1	29.3	41.7
Pompili et al ²⁷	77.1	82.1	NA	NA	39.8	50.9	NA	NA
Imai et al ²⁸	NA	NA	74.0	90.5	NA	NA	30.5	46.9
Zhou et al ²⁹	90.3	85.7	80.6	81.0	83.9	81.0	71.0	76.2
Liu et al ³⁰	88.0	97.0	76.0	81.0	38.0	64.0	24.0	49.0

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; LR, Liver resection; NA, not applicable.

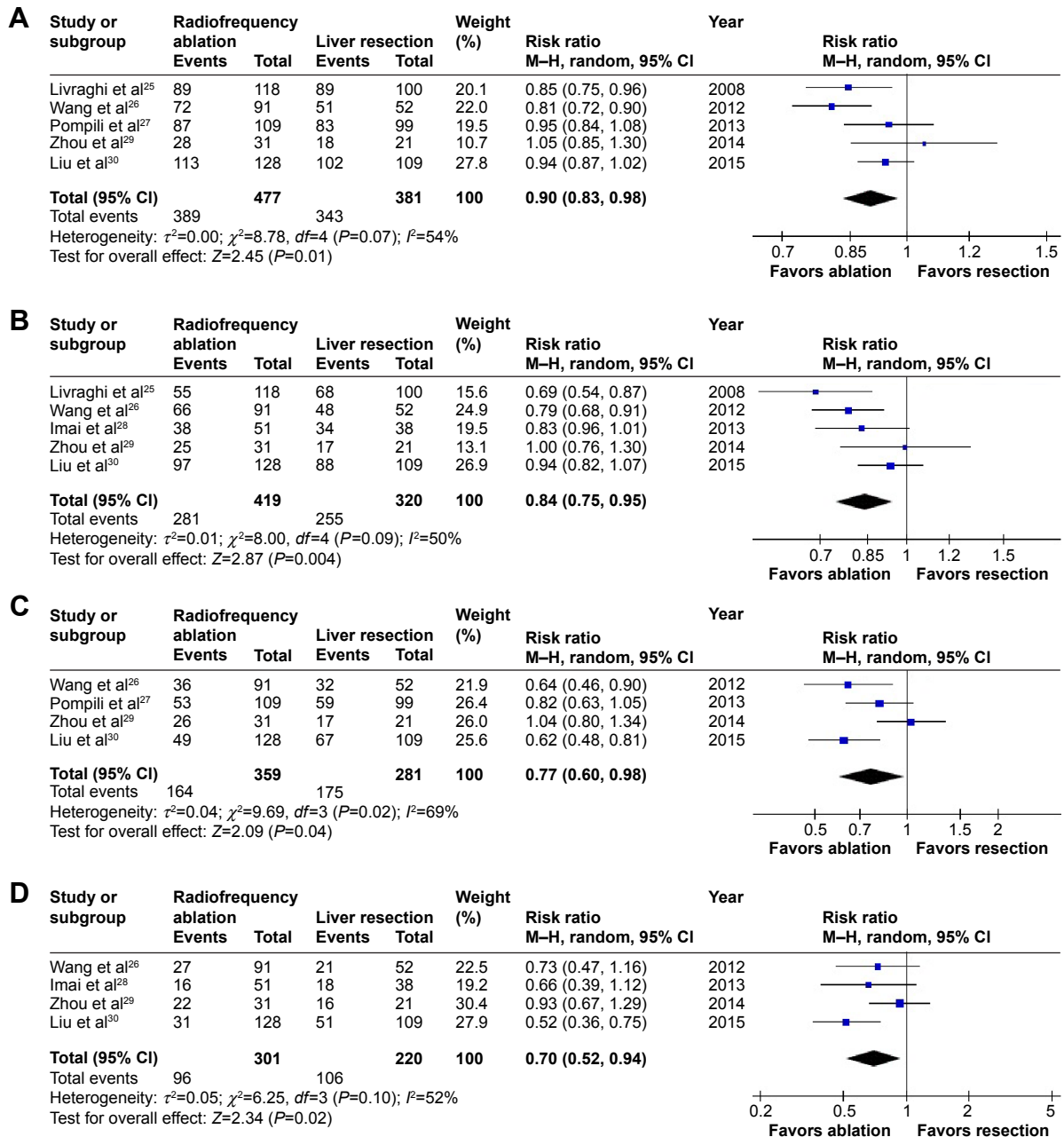


Figure 2 Forest plots of meta-analysis.

Notes: (A) radiofrequency ablation versus liver resection for single BCLC very early stage HCC in 3-year overall survival rates; (B) Radiofrequency ablation versus liver resection for single BCLC very early stage HCC in 5-year overall survival rates; (C) Radiofrequency ablation versus liver resection for single BCLC very early stage HCC in 3-year disease-free survival rates; (D) Radiofrequency ablation versus liver resection for single BCLC very early stage HCC in 5-year disease-free survival rates.

Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel test.

Table 4 The long-term outcomes of radiofrequency ablation versus liver resection for single BCLC early stage HCC

Studies	Overall survival rates (%)				Disease-free survival rates (%)			
	3-year		5-year		3-year		5-year	
	RFA	LR	RFA	LR	RFA	LR	RFA	LR
Hiraoka et al ³¹	87.8	91.4	59.3	59.4	58.7	64.3	24.6	22.4
Huang et al ²³	77.2	95.6	61.4	82.2	NA	NA	NA	NA
Wang et al ²⁶	73.5	87.8	57.4	77.2	28.3	59.9	14.1	50.8
Imai et al ²⁸	84.6	92.5	59.4	87.5	36.3	58.7	23.9	46.8
Wong et al ³²	91.0	97.0	72.8	84.6	34.8	65.8	14.9	57.3
Pompili et al ²⁷	80.9	81.9	NA	NA	48.9	55.1	NA	NA
Yang et al ³³	90.9	96.0	86.6	93.6	NA	NA	26.8	54.4
Fang et al ²⁴	82.5	77.5	NA	NA	55.4	41.3	NA	NA
Kim et al ³⁴	74.4	92.3	NA	NA	39.6	60.0	NA	NA
Kang et al ³⁵	92.4	93.4	85.5	90.9	43.8	71.5	31.7	61.1

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; LR, liver resection; NA, not applicable.

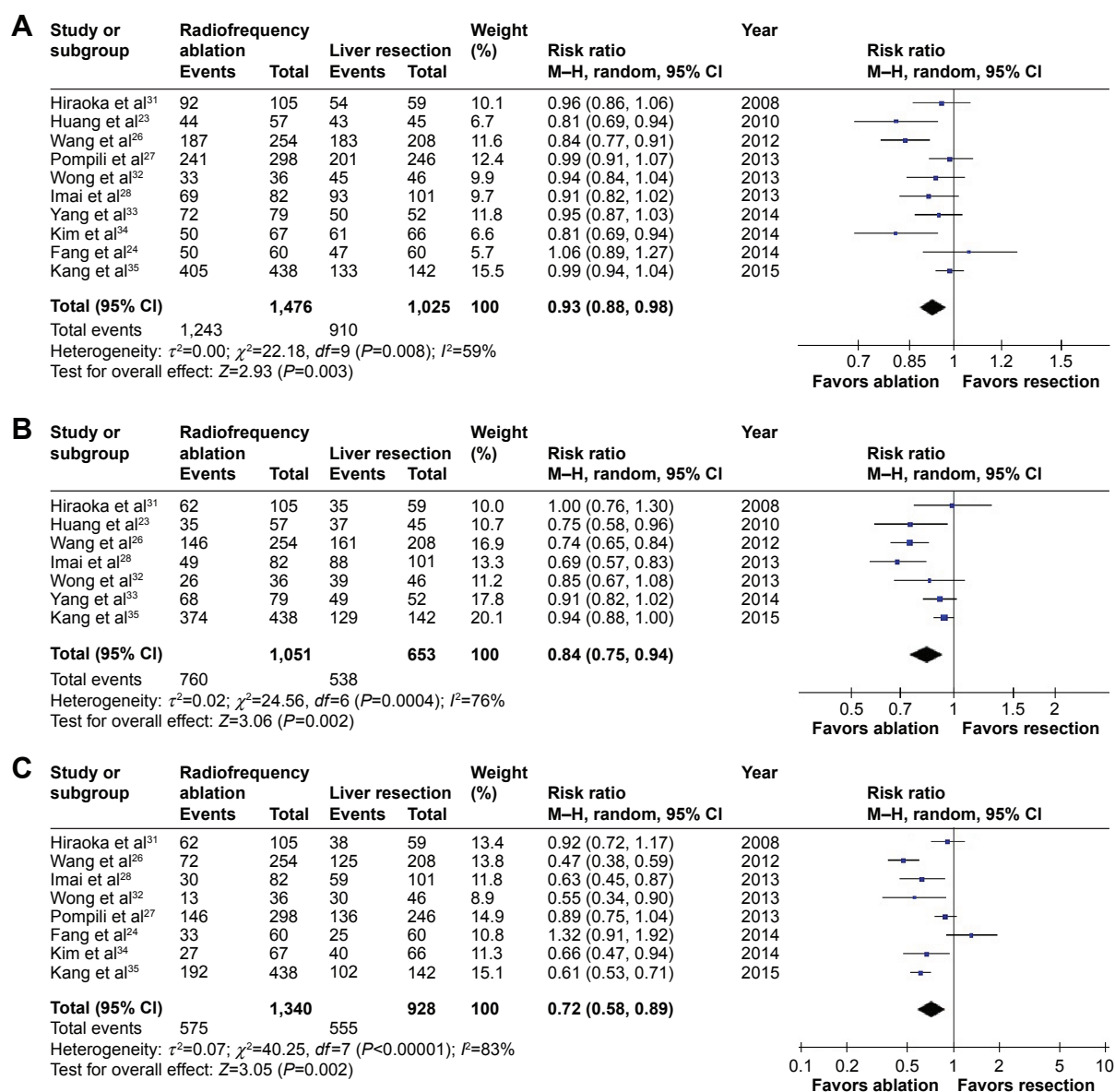


Figure 3 (Continued)

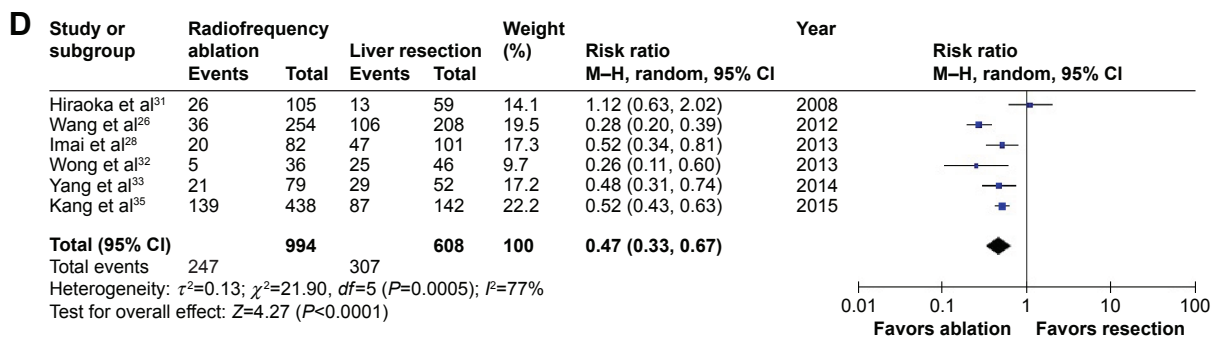


Figure 3 Forest plots of meta-analysis.

Notes: (A) Radiofrequency ablation versus liver resection for single BCLC early stage HCC in 3-year overall survival rates; (B) Radiofrequency ablation versus liver resection for single BCLC early stage HCC in 5-year overall survival rates; (C) Radiofrequency ablation versus liver resection for single BCLC early stage HCC in 3-year disease-free survival rates; (D) Radiofrequency ablation versus liver resection for single BCLC early stage HCC in 5-year disease-free survival rates.

Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel test; MELD, model for end-stage liver disease; TNM, tumor node metastasis; CLIP, cancer of the liver Italian program; JIS, Japan integrated staging.

A funnel plot of the 3-year OS rate is presented in Figure 4. Neither visual asymmetry nor Egger’s linear regression test ($P=0.15$) of the funnel plot indicated publication bias.

Discussion

This systematic review comprehensively collected the available long-term survival outcomes for radiotherapy versus liver resection for single BCLC very early/early stage HCC. The results indicated that liver resection led to significantly better long-term survival outcomes than radiofrequency ablation in the management of single BCLC very early/early stage HCC.

There are several HCC staging systems (eg, Child-Pugh, MELD, TNM, Okuda, CLIP, JIS, and BCLC),⁵⁻⁹ of which the BCLC staging system is the most commonly used.¹⁵ The BCLC staging system is recommended by both the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL).^{6,7}

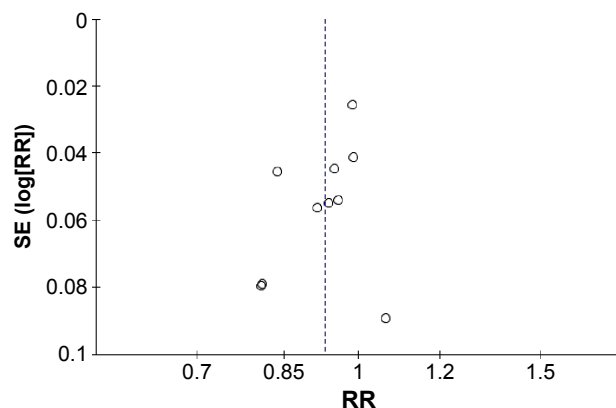


Figure 4 Funnel plot of the 3-year disease-free survival rate. Note: Dashed line represents the extension of the combined effect. Abbreviations: SE, standard error; RR, risk ratio.

According to the current AASLD and EASL guidelines, liver transplantation, liver resection, and radiofrequency ablation are the recommended treatment choices for single BCLC very early/early stage HCC.^{6,7} There is little evidence available on the optimal management of single BCLC very early/early stage HCC.²⁵⁻³⁰ The AASLD and EASL guidelines are based on several retrospective cohort studies.^{6,7} The National Comprehensive Cancer Network and the Asian Pacific Association for the Study of the Liver do not mention the management of single BCLC very early stage HCC.^{8,9} Due to the shortcomings of liver transplantation, radiofrequency ablation and liver resection are commonly used to treat single BCLC very early/early stage HCC.²⁴⁻³⁵

Currently, the management of single BCLC very early/early stage HCC is controversial. With a 5-year OS rate of $>50\%$, liver resection is generally considered the preferred first-line treatment.^{6,7} Liver resection offers the possibility of the curative excision of the entire tumor and microscopic tumor thrombi.³⁶ Alternatively, radiofrequency ablation is a minimally invasive technique that can be performed using a percutaneous or laparoscopic approach.³⁷ Many systematic reviews have demonstrated comparable short-term survival outcomes, lower morbidity, and shorter hospitalization in the radiofrequency ablation group when compared to the liver resection group.¹⁶ However, the quality of published systematic reviews on this topic is poor due to the low quality of evidence and high clinical heterogeneity of the included studies.¹⁶

Compared to previous systematic reviews, the major advantages of this systematic review are the use of the BCLC staging system and the evaluation of long-term survival outcomes. The findings of this review suggest that liver resection results in significantly better survival outcomes than radiofrequency ablation in the management of single BCLC

very early/early stage HCC. The improvement in survival outcomes over time after liver resection may be associated with an improved understanding of liver anatomy, improved perioperative care, and increased surgical experience. Furthermore, radiofrequency ablation has some disadvantages. Radiofrequency ablation causes thermal injury and is therefore not suitable for the treatment of HCC located close to other organs (eg, gallbladder, colon, or kidney). In addition, the heat-sink effect of radiofrequency ablation complicates the complete ablation of HCC adjacent to large vessels.

Our review is subject to the following limitations. First, only two RCTs with sample sizes were included in the meta-analysis; the other studies were all NRS. Second, much of the data in this review were from NRS, and the Jadad scores of those NRS were very low; therefore, the quality of evidence is considered very low. Third, most of the included studies were conducted in Eastern countries, and thus, the results of this review are only applicable to Eastern populations.

Conclusion

In summary, this review encompasses all currently available evidence regarding the comparison of radiofrequency ablation with liver resection for single BCLC very early/early stage HCC. Based on this evidence, liver resection appears to be superior to radiofrequency ablation in terms of long-term survival outcomes. Future high-quality RCTs from Western countries are necessary to confirm our findings.

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Author contributions

He Z-X and Zhang W designed the study. Xiang P and Gong J-P performed the literature research and collected the data. Cheng N-S analyzed the data. He Z-X and Zhang W wrote the paper. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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