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Efficacy and safety of radiofrequency ablation and surgery for hepatocellular carcinoma in patients with cirrhosis

A meta-analysis

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Abstract

Background: The aim of this study was to compare the efficacy and safety of surgical resection (RES) and radiofrequency ablation (RFA) in hepatocellular carcinoma (HCC) patients with cirrhosis and to evaluate short- and long-term clinical outcomes.

Methods: The EMBASE, Cochrane Central Register of Control Trials and Medline databases were searched for comparative studies of RES and RFA in HCC patients with cirrhosis from inception until 30 April 2021. Overall survival (OS), disease-free survival (DFS), local recurrence rate, complication rate, hospitalization duration and operation time were compared between the 2 groups. Begg's funnel plot and Egger's test were performed to assess publication bias.

Results: A total of 16 studies met our inclusion criteria, including 1 randomized controlled trial. A total of 3760 patients were included, of which 2007 received RES and 1753 received RFA. The results showed that the 3-year OS rate, 5-year OS rate, 1-year DFS rate and 3-year DFS rate in the RFA group compared with the RES treatment group were significantly lower, and the local recurrence rate in the RFA group was significantly higher than that in the RES group. Compared with the RES group, the RFA group had lower postoperative complication rates, shorter operative times, and no significant difference in hospitalization duration. Subgroup analysis of laparoscopic RFA showed that there was no significant difference in 1- and 5-year OS rates and 3-year and 5-year DFS rates between the 2 groups, while the 3-year OS rates and 1-year DFS rates in the RES group were better than those in the laparoscopic RFA group.

Conclusion: Surgery is widely applied among HCC patients with cirrhosis, providing acceptable short- and long-term results.

Abbreviations: CI = confidence interval, DFS = disease-free survival, HCC = hepatocellular carcinoma, I^2 = inconsistency factor, LLR = laparoscopic liver resection, LRFA = laparoscopic RFA, OR = odds ratio, OS = overall survival, RCT = randomized controlled trial, RES = surgical resection, RFA = radiofrequency ablation, RoB = risk-of-bias.

Keywords: hepatocellular carcinoma, surgical resection, radiofrequency ablation, overall survival, meta-analysis

1. Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignant tumor in the world and the third leading cause of tumor-related death,[1] posing a serious threat to people's lives and health. Therefore, the treatment of patients with HCC has become a hot research topic. Potential curative therapies for HCC include resection, transplantation, and ablative strategies for small lesions.[2–4] Although liver transplantation is still the most ideal treatment for HCC,[5,6] due to its high cost and lack of donors,[6] Surgical resection (RES) and radiofrequency ablation (RFA) are still the main treatment methods.[7] Several meta-analyses comparing the 2 treatment groups have also shown that RES is associated with higher survival than RFA but is also associated with a higher incidence of complications.[8–11] In addition, the management of patients with HCC is complicated by the presence of underlying liver disease.[4] Eighty percent of HCC patients have a background of liver cirrhosis,[12,13] and there is no consensus on the choice of treatment for HCC in patients with cirrhosis.

Although there have been articles pointing out that choosing RES can improve patient survival compared to choosing RFA, cirrhosis is not explicitly included in these articles as an inclusion

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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criterion,[8–11] or some studies have drawn conflicting conclusions when comparing the efficacy of RES and RFA in HCC patients with cirrhosis. Pompili et al[14] conducted a multicentre study comparing RES and RFA in patients with single HCC ≤ 3 cm and compensated cirrhosis. Despite a higher rate of local tumor progression, studies have shown that RFA can provide results comparable to RES in the treatment of single HCC ≤ 3 cm occurring in compensated cirrhosis. Similarly, the data provided by Santambrogio et al[15] also supported similar survival rates after RES or laparoscopic RFA (LRFA) for single HCC nodules on Child–Pugh class A liver cirrhosis. In contrast, in a comparison of minimally invasive surgery and RFA in patients with solitary HCC ≤ 2 cm with compensated cirrhosis, Lin et al[16] found that the overall survival (OS) and disease-free survival (DFS) rates of minimally invasive surgery were better than those of RFA. In addition, a series of retrospective studies found that the OS and DFS rates in the RES group were also significantly higher than those in the RFA group.[17–20]

Some studies also performed subgroup analysis according to tumor size and number. Huang et al[21] compared the efficacy of RES and RFA in patients with Child class A cirrhosis and concluded that RFA has a recurrence-free survival comparable to RES in treating patients with Child class A cirrhotic liver cancer with solitary HCC ≤ 3 cm. The recurrence-free survival of RFA and RES was comparable, while the OS and DFS rates of the RES group were superior to those of the RFA group. For Child class A cirrhosis with solitary lesions, 3 cm < HCC < 5 cm and multifocal HCC surgical resection were superior to RFA for overall survival, recurrence-free survival, and tumor-free survival. Research by Vivarelli et al[17] reached similar conclusions.

In addition, Casaccia et al[22] compared the efficacy of laparoscopic liver resection (LLR) and LRFA in small HCC with cirrhosis. The experimental results showed that the OS rate in the LLR group was significantly higher than that in the LRFA group, and the DFS rates at 1 and 3 years also showed better effects in the LLR group, although this difference disappeared after 5 years.

Therefore, this study aimed to compare the long- and short-term treatment effects and the safety of RES and RFA in HCC patients with cirrhosis with the OS and DFS rates as the primary endpoints and the recurrence rate, complication rate, operation time, and hospitalization duration as the secondary endpoints. At the same time, we also performed multiple subgroup analyses, including the number of tumors, radiofrequency methods, and Child grades, to evaluate the impact of different tumor characteristics on patient treatment outcomes.

2. Materials and Methods

We followed a predefined protocol written by the American Association for the Study of Liver Diseases clinical practice guidelines for HCC and developed by the Systematic Review Committee. This meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.[23] The ethical approval or informed consent was not required in this study because it belongs to secondary research which based on some previously published data.

2.1. Inclusion and exclusion criteria

The inclusion criteria for this study were as follows: HCC in patients with cirrhosis who had not received relevant treatment, and the size and number of liver cancers were not limited. The included studies were original articles using RES or RFA in the treatment of HCC in patients with cirrhosis. The included studies included at least one of the following outcomes: main indicators: 1-, 3-, and 5-year OS rates and 1-, 3-, and 5-year DFS rates. Secondary indicators: recurrence rate, complication rate, operation time, hospitalization duration and other outcome indicators.

The exclusion criteria for this study were as follows: the subjects were not all hepatocellular carcinoma patients with cirrhosis. Subjects with extrahepatic metastasis, portal vein thrombosis or other serious diseases. Small number of people studied (<10). Nonoriginal research articles, including conference abstracts, review articles and letters. Incomplete data. Study population overlap between studies. The articles for the same institutions.

2.2. Search Strategy

Ovid EMBASE, Ovid Cochrane Central Register of Control Trials, and Ovid Medline were searched from inception until 30 April 2021, and comprehensive searches were performed on several databases in all languages. A combination of MeSH subject headings and free words was used for the literature search and adjusted according to the specific conditions of different databases. The MeSH subjects were Carcinoma, Hepatocellular, Liver Cirrhosis, General Surgery, and Radiofrequency Ablation, and the free words were liver cancer, HCC, hepatic tumor, liver cirrhosis, cirrhosis, hepatocirrhosis, surgery, resection, minimally invasive liver surgery, partial hepatectomy, hepatectomy, RFA, RFA, percutaneous ablative, and percutaneous RFA. In addition, a manual search of all available review articles, major studies, and references listed in the books was conducted to identify additional studies not found in the computer search. Supplemental Digital Content (Appendix 1, http://links.lww.com/MD/I213) shows the detailed search expression.

2.3. Study selection and data extraction

Two reviewers independently screened the literature according to the inclusion and exclusion criteria, and the methods and procedures are shown in the flowchart. Disagreements were resolved by consensus or, if consensus was not possible, by arbitration by a third examiner.

We extracted the following variables from each study: study characteristics, including first author, year of publication, study design (randomized controlled trial [RCT] or non-RCT, period of patient inclusion, patient inclusion criteria, method of surgery and radiofrequency); clinicopathological characteristics of patients, including number of patients, age and sex, number of lesions, size of lesions, liver function (Child–Pugh grade, and cause of cirrhosis); and the outcome indicators of interest, including 1-, 3-, and 5-year OS rates, 1-, 3-, and 5-year DFS rates, recurrence rate, complication rate, operation time, and hospitalization duration. Again, 2 reviewers independently extracted data using the preprepared data extraction form. If there was any disagreement, it was resolved through discussion and submitted to a third party for adjudication if necessary. Data extraction was performed in duplicate.

2.4. Literature quality evaluation

To assess the methodological quality of the included observational studies, the Newcastle–Ottawa scale[24] was used for quality assessment. The evaluation contents included Selection of cohorts (4 items, 4 points), Comparability of cohorts (1 item, 2 points), and Assessment of outcome (3 items, 3 points). There were 8 items, with a full score of 9. The higher the score after evaluation, the higher the research quality. Scores of 0 to 3 were classified as low-quality literature, 4 to 6 as medium-quality literature, and 7 to 9 as high-quality literature. The included RCTs were evaluated using the Cochrane Risk of Bias Assessment Tool recommended by the Cochrane Collaboration. We assessed (RoB) risk-of-bias independently and in duplicate using a modified Cochrane RoB tool[25] for which each domain is rated as "low," "probably low," "high," or "probably high." We

examined the following RoB domains: sequence generation, allocation sequence concealment, blinding, selective outcome reporting, and other bias (such as stopping early and funding source). We rated the overall RoB for an individual study as the highest risk attributed to any domain. Two investigators independently evaluated the included studies and cross-checked them. In case of disagreements, they were resolved through discussion, and they were submitted to a third party for adjudication if necessary. Evaluators hid the information pertaining to author, institution and journal of the study when evaluating.

2.5. Statistical analysis

All analyses were performed using Review Manager version 7.8 (Nordic Cochrane Centre; Oxford, England) and R 4.1.0 (https://www.rproject.org) statistical software. For data evaluation, patients were divided into 2 groups: the RFA treatment group and the RES treatment group. Then, the odds ratio (OR) and mean difference were used as effect indicators to calculate the pooled value and 95% confidence interval (CI) for the dichotomous variables and the continuous variables in the study, respectively. Meanwhile, we explored heterogeneity among trials using the chi-squared (χ^2) test, which included the inconsistency factor (I^2). When $P \leq .05$ or I^2 was greater than 50%,[26] indicated significant statistical heterogeneity between studies, and a random effects model was used; otherwise, a fixed effects model was used.

Subgroup analysis was also performed to further reduce confounding variables. Studies were grouped by predetermined criteria and subjected to separate analyses, in which heterogeneity tests were also performed. Predesigned subgroup analyses included Child class A, single and multiple tumors, LRFA, and percutaneous RFA. In addition, a sensitivity analysis was subsequently conducted by eliminating each study in the analysis at each turn. Potential publication bias was assessed by visually inspecting Begg's funnel plots. A P value of <.05 was considered statistically significant.

2.6. Patients and public involvement

The patients or public were not involved in the study.

3. Results

3.1. Results of the literature search

A total of 1681 studies were identified by our retrieval strategy, and 6 studies were identified by manual retrieval, totaling 1687 studies. A total of 401 duplicates were excluded. After an extensive review of the titles and abstracts, 1213 articles were excluded based on the inclusion and exclusion criteria. Of the 73 articles included in the full-text screening, 57 were excluded due to the exclusion criteria. Finally, 16 studies were included.[14–22,27–33] Two prospective studies (1 RCT study,[29] 1 case–control study[19]) and 14 retrospective studies were included. A flowchart of study selection is shown in Figure 1.

3.2. Characteristics of the included studies

The study designs and patient characteristics of the 16 included studies are summarized in Table 1. The 16 studies included a total of 3760 HCC patients with cirrhosis, of whom 2007 received RES and 1753 received RFA. Among the 16 studies, 4 studies[14,16,19,28] only included HCC patients with a single tumor, 5 studies[14–16,20,21] only included HCC patients with Child class A cirrhosis, 2 studies[14,20] only included patients with tumors ≤ 3 cm, and another study[16] included patients with tumors ≤ 2 cm. Three studies[22,32,33] only included LLR for HCC, 8[16–20,29–31] studies only included percutaneous local ablation (RFA) for HCC, and 4 studies[15,22,28,32] only included LRFA for HCC. The 2 studies[29,31] did not include all HCC patients with cirrhosis, but there were subgroup analysis data of liver cirrhosis, so they were included in this study.

3.3. Quality evaluation of included studies

In the methodological quality assessment of the included studies, the baselines of the 16 included studies were comparable. The methodological quality evaluation of the cohort studies is shown in Table 2. The Newcastle–Ottawa scale scores of the included studies were all ≥ 7 points, so they were all high-quality studies. The methodological quality of the RCTs is summarized in Table 3.

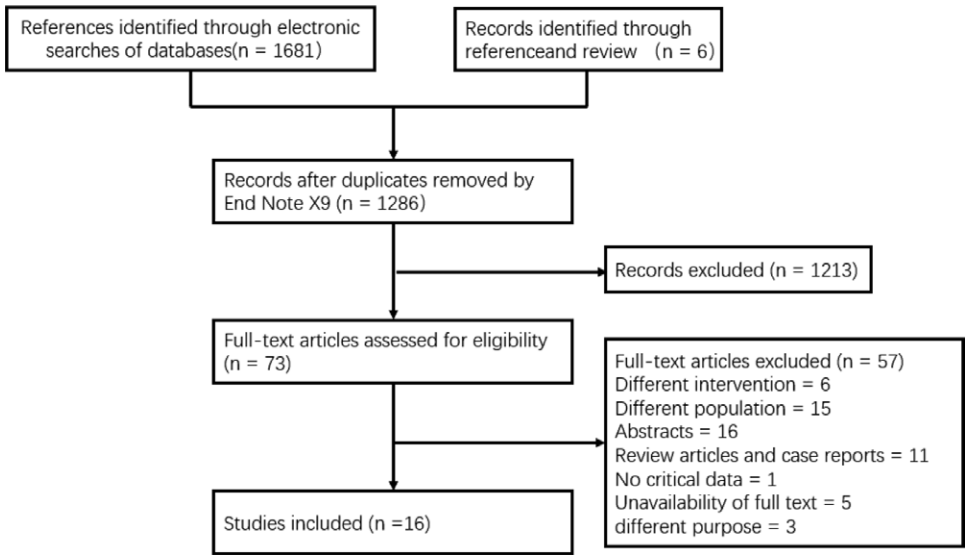

Figure 1. Flowchart presenting study selection process.

Table 1

Summary of included studies and patient characteristics.

Author (year)	Country	Design	Inclusion criteria	Study period	Treatment	Cases	Sex (M/F)	Age (yr)	Tumor number (single/multiple)	Tumor size (cm)	Child–Pugh score A/B (n)	Aetiology of liver disease HBV/HCV	Mean follow up (mo)
Marco V (2004)	Italy	NRCT	NA	1998–2002	RES	79	57/22	65.2 ± 8.2	66/13	≤3/>3 21/58	70/9	16/47	28.9 ± 17.9
					PRFA	79	67/12	67.8 ± 8.7	46/33	≤3/>3 22/57	43/36	10/43	15.6 ± 11.7
Marco M (2005)	Italy	NRCT	1 nodule ≦ 5 cm	1997.2–2003.4	RES	40	33/7	67 ± 9	40/0	NA	32/8	11/29	22.4 ± 16.7
					LRFA	58	43/15	67 ± 6	58/0	NA	40/18	26/42	25.7 ± 17.5
Abu-Hilal M (2008)	UK	NRCT	1 nodule	1991–2003	RES	34	26/8	67	67/0	3.8 (1.3–5)	25/9	NA	43 (2–129)
					PRFA	34	27/7	65	65/0	3 (2–5)	27/7	NA	30 (0–60)
Alfredo G (2008)	Italy	NRCT	Up to 3 nodules all ≦ 6 cm	1996.1–2006.8	RES	91	73/18	≤65/>65 47/44	69/22	≤3/>3 31/60	69/22	10/55	32 (3–120)
					PRFA	109	88/21	≤65/>65 38/71	65/44	≤3/>3 32/77	64/45	14/58	23 (3–92)
Roberto S (2009)	Italy	NRCT	1 nodule ≦ 5 cm	1997.2–2007.5	RES	78	55/23	68 ± 8	55/0	29.1 ± 12.3	78/0	58/10	36.2 ± 23.5
					LRFA	74	59/15	68 ± 7	59/0	26.6 ± 10.6	74/0	49/12	38.2 ± 28.4
Jiwei H (2010)	China	RCT	1 nodule ≦ 5cm or up to 3 nodules all ≦ 3 cm	NA	RES	75	NA	NA	NA	NA	NA	NA	NA
					PRFA	67	NA	NA	NA	NA	NA	NA	NA
Jiwei H (2011)	China	NRCT	Up to 3 nodules all ≦ 5 cm	2000.7–2005.10	RES	648	489/159	46.13 ± 16.89	507/141	3.56 ± 1.47	648/0	598/28	33.7 ± 17.4
					RFA	413	361/52	54.67 ± 12.18	313/100	4.01 ± 1.21	413/0	391/15	36.1 ± 12.4
Jacopo D (2013)	Italy	NRCT	Up to 3 nodules all ≦ 3 cm	2004.1–2012.1	RES	52	37/15	65.6 ± 4.8	22/30	≤3/>3 52/0	52/0	4/24	51.7 (28–60)
					RFA	44	35/9	64.4 ± 6.5	19/25	≤3/>3 44/0	44/0	11/20	47.4 (10–60)
Amilcare P (2013)	Italy	NRCT	Up to 3 nodules all ≦ 6 cm	NA	RES	87	68/19	64.8 ± 4.7	57/30	≤3/>3 37/50	67/20	7/38	43.1 (6–60)
					RFA	53	42/11	65.7 ± 4.3	31/22	≤3/>3 22/31	32/21	4/18	31.5 (4–60)
Maurizio P (2013)	Italy	NRCT	1 nodule ≦ 3 cm	1999–2010	RES	246	200/46	67 (35–85)	246/0	2.5 (0.8–3.0)	246/0	24/144	41 (1–126)
					RFA	298	175/123	68 (36–88)	298/0	2.3 (1.0–3.0)	298/0	32/213	38 (6–132)
Alessandro C (2014)	Italy	NRCT	NA	2001.2–2011.1	RES	388	302/86	65 (58–71)	309/79	3.5 (2.5–4.7)	374/14	82/273	29 (0.5–144)
					RFA	207	142/65	68 (60–75)	184/23	2.4 (2.0–3.0)	163/44	33/136	24 (1–10)
Marco C (2015)	Italy	NRCT	1 nodule ≦ 6.5 cm or up to 3 nodules all ≦ 4.5 cm	2005.6–2010.1	LLR	26	17/9	64.62 ± 9.51	20/6	3	23/3	6/13	NA
					RFA	24	20/4	61.48 ± 7.75	7/17	1.71	13/6	8/10	NA
Arnaud H (2015)	France	NRCT	1 nodule ≦ 5 cm or up to 3 nodules all ≦ 3 cm	2004.1–2013.12	RES	65	NA	NA	NA	NA	NA	NA	NA
					PRFA	170	NA	NA	NA	NA	NA	NA	NA
Marco C (2017)	Italy	NRCT	1 nodule ≦ 6.5 cm or up to 3 nodules all ≦ 4.5 cm	2005.6–2010.11	LLR	24	16/8	63.58 ± 9.55	20/4	3.30 ± 1.383	22/2	6/11	44.74 ± 21.30
					LRFA	22	18/4	60.82 ± 7.25	6/16	2.625 ± 1.313	12/6	8/8	40.27 ± 30.89
Yo-ichi Y (2019)	Japan	NRCT	1 nodule ≦ 5 cm or up to 3 nodules all ≦ 3 cm	2000.4–2016.9	LLR	38	25/13	66.9 ± 9.1	32/6	2.4 ± 0.9	30/8	5/30	37 (1–161)
					RFA	62	40/22	66.5 ± 9.5	42/20	2.0 ± 0.6	57/5	9/45	58 (2–164)
Chih-Hao L (2020)	Taiwan	NRCT	1 nodule ≦ 2 cm	2010–2016	MIS	36	27/9	≤70/>70 28/8	36/0	1.7 ± 0.25	36/0	25/9	60.1 ± 25.48
					PRFA	39	25/14	≤70/>70 25/14	39/0	1.5 ± 0.22	39/0	25/17	53.5 ± 20.89

LLR = laparoscopic liver resection, LRFA = laparoscopic radiofrequency ablation, M/F = male/female, NA = not available, NRCT = non-randomized controlled trial, PRFA = percutaneous radiofrequency ablation, RCT = randomized controlled trial, RES = surgical resection, RFA = radiofrequency ablation.

Table 2

The Newcastle-Ottawa Scale of included NRCT studies.

	Selection criteria					Outcome			
Study	Exposed	Non-exposed	Ascertain	Demonstrate	Comparability	Outcome assessment	Follow-up period	Follow-up adequacy	Score
Marco V		*	*	*	*	*	*	*	7
Marco M		*	*	*	*	*	*	*	7
Abu-Hilal M		*	*	*	**	*	*	*	8
Alfredo G	*	*	*	*	*	*	*	*	8
Roberto S		*	*	*	**	*	*	*	8
Jiwei H		*	*	*	**	*	*	*	8
Jacopo D		*	*	*	**	*	*	*	8
Amilcare P	*	*	*	*	**	*	*	*	9
Maurizio P		*	*	*	*	*	*	*	7
Alessandro C	*	*	*	*		*	*	*	7
Marco C	*	*	*	*		*	*	*	7
Arnaud H	*	*	*	*		*	*	*	7
Marco C	*	*	*	*		*	*	*	7
Yo-ichi Y	*	*	*	*	*	*	*	*	8
Chih-Hao L		*	*	*	*	*	*	*	7

NRCT = non-randomized controlled trial.

Table 3

The Cochrane RoB of included RCT study.

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall RoB
Jiwei H	Low	Probably low	Low	Probably low	Low	Probably low

RCT = randomized controlled trial, RoB = risk-of-bias.

3.4. Comparison of efficacy and safety

3.4..1. Long-term outcomes.

3.4..1..1. Overall survival. Thirteen studies[14–21,27–30,32] reported 1- and 3-year OS rates, and 12 studies[14–18,20,21,27–30,32] reported 5-year OS rates. Significant heterogeneity was observed when assessing the 1-, 3-, and 5-year OS rates (Fig. 2A–C) (1-year: $I^2 = 60\%$, $P < .01$; 3-year: $I^2 = 70\%$, $P < .01$; 5-year: $I^2 = 43\%$, $P = .05$), and a random-effects model was used. The results showed that there was no significant difference in the 1-year OS rate between the 2 groups (OR 0.68; 95% CI: 0.44–1.07). The 3- and 5-year OS rates in the RES group were significantly higher than those in the RFA group (3-year: OR 0.48, 95% CI: 0.35–0.67; 5-year: OR 0.49, 95% CI: 0.38–0.63).

3.4..1..2. Disease-free survival. Seven studies[16–21,32] reported 1-, 3-, and 5-year DFS rates. The heterogeneity test showed significant heterogeneity in the 3- and 5-year DFS rates (Fig. 2E and F) (3-year: $I^2 = 58\%$, $P = .03$; 5-year: $I^2 = 73\%$, $P < .01$), and a random effects model was used. The 1-year DFS rate (Fig. 2D) showed no heterogeneity ($I^2 = 0\%$, $P = .47$), and the fixed-effect model was used. The results showed that there was no significant difference in the 5-year DFS rate between the 2 groups (OR 0.70; 95% CI: 0.40–1.24). The 1- and 3-year DFS rates in the RES group were significantly higher than those in the RFA group (1-year: OR 0.41, 95% CI: 0.32–0.53; 3-year: OR 0.36, 95% CI: 0.24–0.53).

3.4..1..3. Local recurrence rates. Eight studies[14,15,17,19–21,28,30] reported postoperative recurrence rates. The heterogeneity test showed that there was significant heterogeneity in the postoperative local recurrence rate (Fig. 3A) ($I^2 = 84\%$, $P < .01$), and a random-effects model was used. The results showed that the local recurrence rate in the RES group was significantly lower than that in the RFA group (OR 2.37; 95% CI: 1.30–4.33).

3.4..2. Short-term outcomes.

3.4..2..1. Complications. Seven studies[14,15,18–22] reported overall postoperative complications. The heterogeneity test showed that there was no heterogeneity in the incidence of postoperative complications (Fig. 3B) ($I^2 = 28\%$, $P = .22$), and a fixed-effects model was used. The results showed that the overall complication rate in the RFA group was significantly lower than that in the RES group (OR 0.41; 95% CI: 0.30–0.55). Among them, the complications in the surgery group were more serious, mainly hepatic failure, biliary fistula, hemoperitoneum and ascites. RFA only minor complications occurred, such as pain and fever.

3.4..2..2. Operation time and hospitalization duration. Four studies reported the surgical duration[15,22,28,33] and the hospitalization duration.[15,25,26,33] The heterogeneity test showed significant heterogeneity in operation time ($I^2 = 94\%$, $P < .01$) and hospital stay ($I^2 = 97\%$, $P < .01$) (Fig. 3C and D), so a random-effects model was used. The results showed that there was no significant difference in hospitalization time between the 2 groups (standard mean difference = –1.61; 95% CI: –4.19 to 0.97), but the operation time in the RFA group was significantly shorter than that in the RES group (standard mean difference = –2.76; 95% CI: –4.88 to 0.64).

3.4..3. Subgroup analysis. A total of 5 studies[14,15,18,20,21] were included in the subgroup analysis of Child–Pugh classification. The results showed that when the patient's liver function was Child class A, there was no significant difference in the 1-year OS rate and the 5-year DFS rate between the 2 groups, while the 3- and 5-year OS rates and the 1- and 3-year DFS rates in the RES group were significantly better than those in the RFA group (Table 4).

Four studies[14,16,19,28] included subgroup analyses of solitary nodules. The results showed that the 1-, 3-, and 5-year OS rates and the 1-year DFS rates were not significantly different

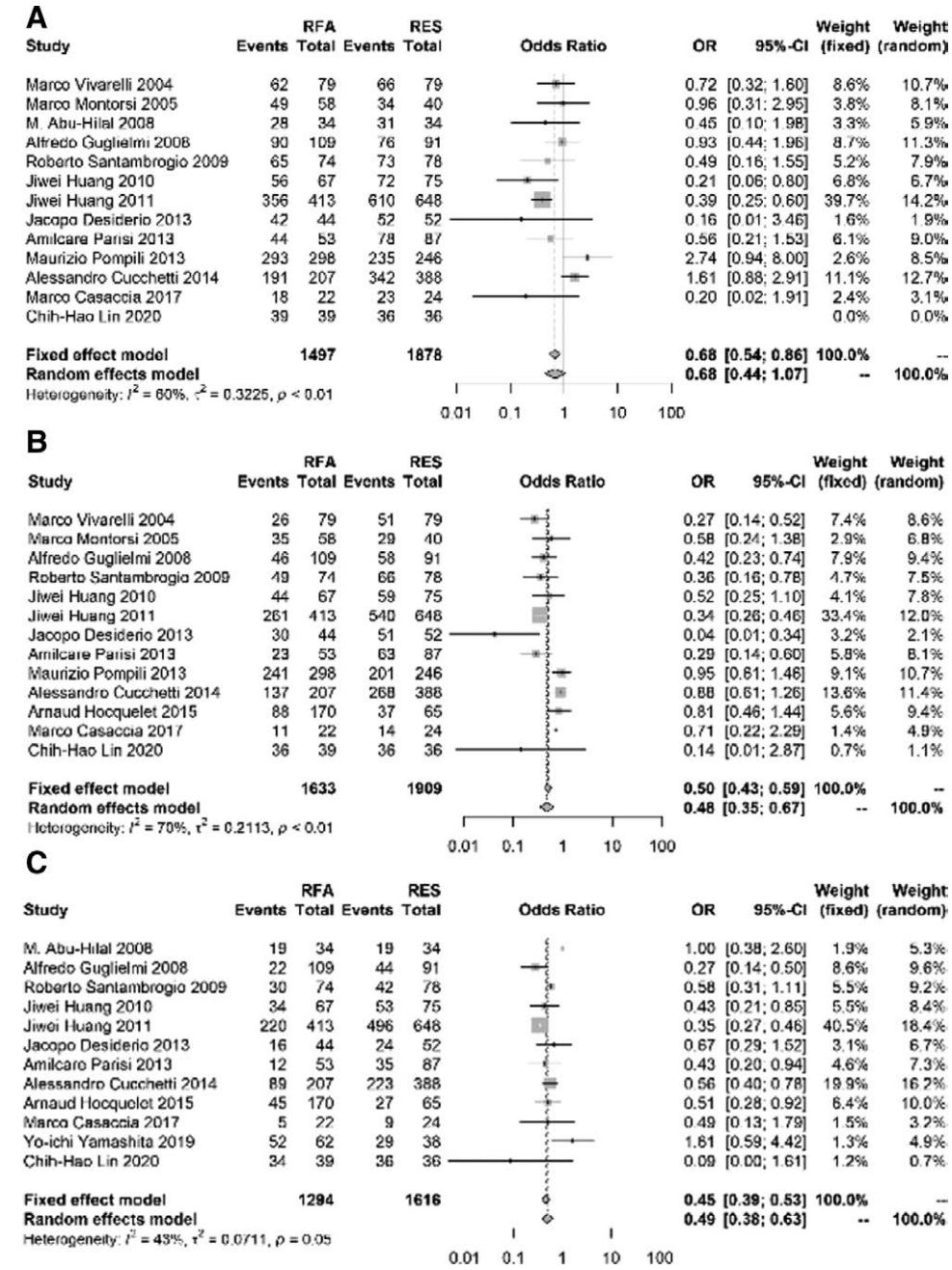

Figure 2. OR meta-analysis plot (A) 1-year OS, (B) 3-year OS, (C) 5-year OS, (D) 1-year DFS, (E) 3-year DFS, (F) 5-year DFS. OR > 1 favors RES. DFS = disease-free survival, OR = odds ratio, OS = overall survival, RES = surgical resection.

between the 2 groups, while the 3- and 5-year DFS rates in the RES group were better than those in the RFA group (Table 4). Ten studies[15,17,18,20,21,27,29–32] were included in the subgroup analysis of multiple nodules. The results showed that compared with the RFA group, the RES group had significant advantages in the 1-, 3-, and 5-year OS rates and the 1- and 3-year DFS rates, while there was no significant difference in the 5-year DFS rates between the 2 groups (Table 4).

In addition, according to the different treatment methods of RFA, they were divided into the LRFA subgroup and the percutaneous RFA subgroup. Three studies[15,28,32] included a subgroup analysis of LRFA. The results showed that there were no significant differences in the 1- and 5-year OS rates and the 3- and 5-year DFS rates between the 2 groups, while the 3-year OS rate and 1-year DFS rate in the RES group were better than those in the RFA group (Table 4). Seven studies[16–20,29,30] were included in the subgroup of percutaneous RFA. The results showed that the 1-, 3-, and 5-year OS rates and the 1- and 3-year DFS rates in the RES group were better than those in the RFA group, while there was no significant difference in 5-year DFS rates between the 2 groups (Table 4).

3.4..4. Sensitivity analysis. In our study, we performed a sensitivity analysis by investigating the effect of a single study on the overall pooled estimate, eliminating 1 study in each turn. Our results showed that the effect of each individual data point on the pooled OR and mean difference was not statistically significant.

3.4..5. Publication bias. Figures S1 to S6, Supplemental Digital Content, http://links.lww.com/MD/I214 show the funnel plots of the OS and DFS rates. The results revealed that, except for the

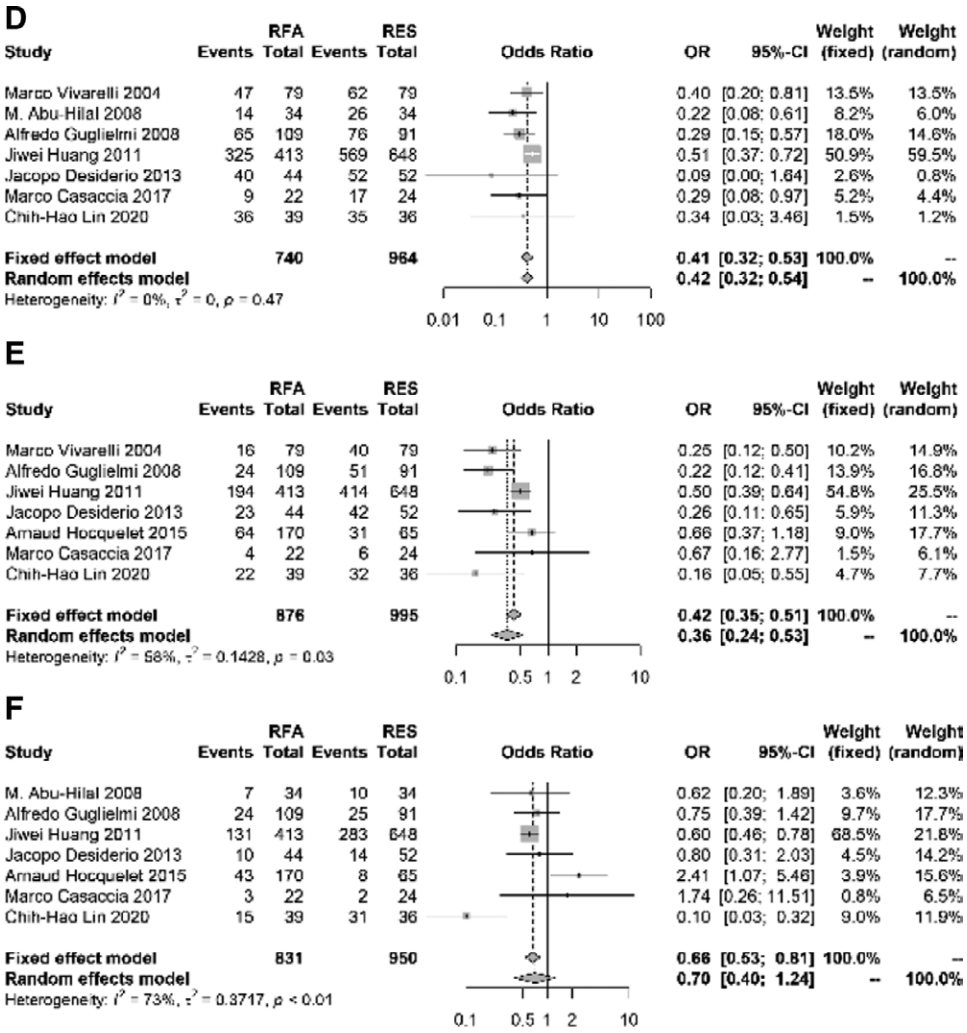

Figure 2. Continued

1-year DFS rate, the other funnel plots of the OS and DFS rates do not show obvious asymmetry, and Egger's test also found possible publication bias only in the 1-year DFS rate (1-year OS: P = .826, 3-year OS: P = .405, 5-year OS: P = .298, 1-year DFS, P = .026, 3-year DFS: P = .216, 5-year DFS: P = .766).

4. Discussion

More than a dozen previous studies have drawn mixed results by comparing the efficacy and safety of RFA and RES in HCC patients with cirrhosis. Therefore, we performed a meta-analysis of these important clinical studies to compare the long- and short-term efficacy and safety of the 2 treatment modalities more comprehensively. The analysis results of this study showed that the 3- and 5-year OS rates and the 1- and 3-year DFS rates in the RES treatment group were significantly higher than those in the RFA treatment group, while there was no significant difference in the 1-year OS rate and the 5-year DFS rate between the 2 groups.

Although guidelines recommend hepatectomy only in patients with Barcelona Clinic Liver Cancer (BCLC) stage 0 or A disease,[2,3,34,35] the results of our study showed that a larger range of patients chose RES and obtained longer OS and DFS than with RFA. Similarly, an analysis of large prospective registries found that the majority (>60%) of hepatectomies were performed in patients who did not meet western guidelines for liver function, presentation status, or tumor characteristics.[36,37] The findings also suggest that the selection criteria for resection can be moderately expanded without affecting outcomes and that some less-than-optimal candidates may still benefit from resection compared with other treatment modalities. This may be due to the improvements in surgical procedures, perioperative management and patient selection. The resectability of tumors is further improved, and the indications for surgery are constantly being broadened.[2] In addition, in the last few years, patients exceeding one or more of the described criteria have been approached with RES in experienced centers. The outcome also suggests that the results achieved in patients undergoing RES in experienced centers (i.e., postoperative mortality and severe postsurgical morbidity of < 3% and < 30%, respectively) seem to favor the use of extended criteria for RES, namely, of HCCs in which one or more conventional selection criteria for RES summarized in the 2018 EASL/AASLD Guidelines are not satisfied.[2,3]

In addition, during follow-up, although the RFA group had a higher rate of local recurrence, there were fewer overall postoperative complications, shorter operative times, and shorter hospital stays (although the differences were not statistically significant, there was a trend). The results of subgroup analysis also showed that RFA treatment seems to be a reasonable alternative for patients with a single HCC nodule, as RFA achieves nearly the same antitumor effect and causes less damage to patients with single-nodule HCC compared with RES. Research by Jia et al[9] also yielded consistent results. Subgroup analysis by RFA treatment also showed that LRFA achieved similar outcomes compared with RES, with only slightly lower results

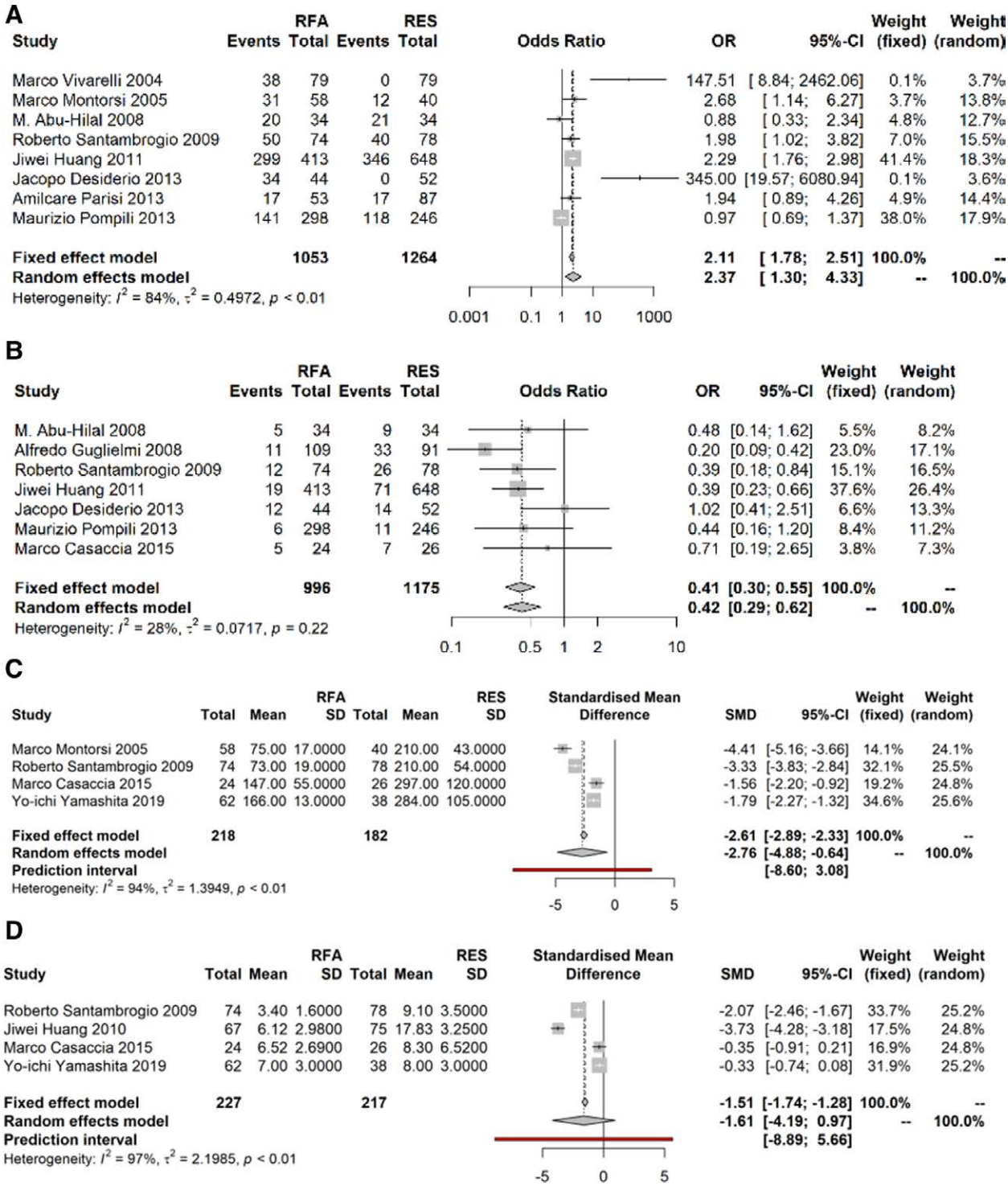

Figure 3. OR meta-analysis plot (A) recurrence number, (B) syndrome number. OR > 1 favors RES. SMD meta-analysis plot (C) time of surgery, (D) time in hospital. SMD > 0 favors RES. OR = odds ratio, RES = surgical resection, SMD = standard mean difference.

in the 3-year OS rate than with RES. In the percutaneous RFA subgroup, the RES group was better than the RFA group in all survival outcomes, but there was no significant difference in the 5-year DFS rate. Our results showed that LRFA treatment is superior to percutaneous RFA, which is consistent with the findings of Si et al.[11] This may be because intraoperative ultrasonography can identify other undetected nodules and provide better tumor visualization and more accurate placement of ablation probes. The study on the Child grading subgroup showed that for Child class A patients, the curative effect of the RES group was significantly better than that of the RFA group, and there were no significant differences in the 1-year OS or 5-year DFS rates, which differed slightly from the meta-analysis performed by Jia et al.[9] Their meta-analysis showed no differences in the 1-year OS, 3-year OS, or 3-year DFS rates among patients eligible for both treatments. This may be due to the small number of included studies and the different patient selection criteria.

Only HCC patients with cirrhosis were included in this study. Some studies did not enroll all HCC patients with cirrhosis but obtained similar findings to ours. A meta-analysis conducted by

Table 4

Subgroup analyses.

Variables	Duration (yr)	Overall survival			Disease-free survival		
		S/P	OR (95% CI)	Model	S/P	OR (95% CI)	Model
Child–Pugh class							
Child A	1	5/1928	0.66 (0.23, 1.92)	Random effects	3/1232	0.49 (0.35, 0.68)	Fixed effects
	3	5/1928	0.37 (0.18, 0.77)	Random effects	3/1232	0.33 (0.17, 0.65)	Random effects
	5	4/1384	0.39 (0.31, 0.49)	Fixed effects	3/1232	0.10 (0.15, 1.06)	Random effects
Nodules							
Single	1	4/785	1.16 (0.43, 3.15)	Random effects	2/143	0.24 (0.09, 0.61)	Fixed effects
	3	3/711	0.82 (0.56, 1.19)	Fixed effects	1/75	0.16 (0.05, 0.55)	
	5	2/143	0.43 (0.04, 4.58)	Random effects	2/143	0.25 (0.04, 1.50)	Random effects
Multiple	1	9/2590	0.59 (0.36, 0.96)	Random effects	5/1561	0.43 (0.33, 0.56)	Fixed effects
	3	10/2825	0.44 (0.31, 0.63)	Random effects	6/1832	0.38 (0.26, 0.57)	Random effects
	5	10/2767	0.45 (0.38, 0.53)	Fixed effects	5/1638	0.94 (0.54, 1.61)	Random effects
RFA approach							
Laparoscopic	1	3/296	0.59 (0.28, 1.28)	Fixed effects	1/46	0.29 (0.08, 0.97)	
	3	3/296	0.48 (0.29, 0.81)	Fixed effects	1/46	0.67 (0.16, 2.77)	
	5	2/198	0.56 (0.32, 1.00)	Fixed effects	1/46	1.74 (0.26, 11.51)	
Percutaneous	1	7/879	0.60 (0.39, 0.91)	Fixed effects	5/597	0.30 (0.20, 0.46)	Fixed effects
	3	7/1046	0.38 (0.24, 0.61)	Random effects	5/764	0.30 (0.18, 0.50)	Random effects
	5	7/956	0.45 (0.34, 0.60)	Fixed effects	5/674	0.65 (0.27, 1.60)	Random effects

CI = confidence interval, OR = odds ratio, RFA = radiofrequency ablation, P = patients, S = Study.

Feng et al in 2015[8] included a total of 15,482 patients with small hepatocellular carcinoma by including 3 randomized controlled trials and twenty retrospective studies. The results showed that the 1-, 3-, and 5-year OS rates and recurrence-free survival rates of the RES group were significantly higher than those of the RFA group, and the complication rate was slightly higher than that of the RFA group. The results showed that the 1-, 3-, and 5-year OS rates and recurrence-free survival rates in the RES group were significantly higher than those in the RFA group, while the complication rate was slightly higher than that in the RFA group. In 2018, Yin et al[38] conducted a meta-analysis of 729 patients with very early HCC in Barcelona Clinic Liver Cancer staging in 5 articles. The results also showed that the 3- and 5-year OS rates in the RES group were significantly better than those in the RFA group, and the postoperative tumor recurrence rate in the RES group was also lower. This may be attributable to the presence of cirrhosis in more than 80% of patients diagnosed with HCC.

Our meta-analysis adds several key insights. First, we only included HCC patients with cirrhosis. According to our retrieval, this is the second meta-analysis that only includes HCC patients with a cirrhosis background, which can provide certain guidance for the treatment of HCC patients with cirrhosis. Second, all the included studies were of high quality, and were all head-to-head studies to reduce bias due to different patient populations through direct comparisons. Finally, we also performed several different subgroup analyses based on the characteristics of the included studies to reduce selection bias due to patient selection. Among them, the subgroup analysis of percutaneous RFA and LRFA therapy was the first meta-analysis to compare the 2 therapies and drew relatively good results.

There are some limitations to our study. Only one of the studies included in the meta-analysis was a randomized controlled study. Unpredictable confounding factors may affect our data analysis, which is also the main cause of the heterogeneity. Even though we performed some subgroup analyses, heterogeneity persisted. In addition, although we searched the Cochrane Library, Embase, and Medline databases and performed manual searches of references listed in the original text and the review, there were still relatively few studies enrolled, among which only 4 studies reported the time of surgery and the length of hospitalization duration, and there was no subgroup analysis of tumor diameter. Therefore, it is expected that there will be more RCTs with rigorous designs, large sample sizes and high quality to further verify the efficacy and safety of RES and RFA in the treatment of liver cancer in the future. At present, there is no unified operation specification and efficacy evaluation standard for RES and RFA, and the skill level of surgical personnel may also affect the survival rate of patients to a certain extent. Therefore, the standardization of surgical operations and the technical training of surgeons will also achieve better outcomes for patient prognosis.

5. Conclusions

In conclusion, our meta-analysis results suggest that RES improves overall survival and recurrence-free survival in patients of liver cancer with a cirrhosis background, and that nonideal patients may still benefit from modestly expanding the selection criteria for resection. It is hoped that this study will also promote more prospective multicenter high-quality studies to better reveal the proportion of patients with intermediate and advanced liver cancer who benefit from surgical treatment.

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Project administration: Tong Zhang.
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Validation: Tong Zhang, He Hu, Hui Wu.
Visualization: All authors.
Writing – original draft preparation: Tong Zhang.
Writing – review and editing: All authors.
All authors have read and agreed to the published version of the manuscript.

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