# Repeat resection versus percutaneous ablation for recurrent hepatocellular carcinoma: a meta-analysis

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**Abstract**

***Introduction:*** *Both repeat resection (RR) and percutaneous ablation (PA) have been used for treating recurrent hepatocellular carcinoma (rHCC). Each method has its advantages and disadvantages.*
***Aim:*** *To compare the safety and effectiveness between RR and PA in patients with rHCC.*
***Material and methods:*** *Relevant articles published in the PubMed, Embase, Wanfang, and China National Knowledge Infrastructure (CNKI) databases published as of April 2022 were identified. Primary endpoints for this meta-analysis included patient overall survival (OS) and disease-free survival (DFS), whereas secondary endpoints included rates of repeat recurrence, complications, and the duration of hospitalization.*
***Results:*** *This meta-analysis included a total of 6 relevant studies. Pooled repeat recurrence rates were comparable between the PA and RR groups (p = 0.09), although the pooled 5-year DFS rate (p = 0.01), DFS duration (p = 0.02), and 3-year OS rate (p = 0.04) in the RR group were considerably higher than in the PA group. Pooled rates of both Grade 1/2 (p = 0.04) and Grade 3/4 (p = 0.001) complications, however, were significantly lower for patients who underwent PA as compared to patients who underwent RR. PA was associated with a significantly shorter hospitalization duration relative to RR in this patient cohort (p = 0.0002).*
***Conclusions:*** *According to the obtained findings, RR may be associated with better long-term disease control in rHCC patients than PA, whereas PA is associated with a better safety profile and a shorter duration of hospitalization.*

***Key words:*** *repeat resection, recurrent, ablation, hepatocellular carcinoma, ultrasound.*

## Introduction

Hepatocellular carcinoma (HCC) is considered to be one of the most prevalent, highly aggressive, and rapidly progressive forms of cancer [1–3]. Although surgical tumor excision remains the preferred treatment option for HCC patients who are eligible for such treatment, the 5-year recurrence rate following this procedure can be as high as 60–80% [4–6]. The most effective approaches to managing recurrent HCC (rHCC) are still a subject of controversy. In this view, effective methods for treating such recurring disease are urgently needed to improve the OS of patients.

One common approach to rHCC management is repeat resection (RR) of the recurring tumor mass, while conserving the function and residual volume of the liver is a common method for rHCC treatment. Recent developments in perioperative care and surgical procedures have improved the safety outcomes associated with the underlined treatment [7–9]. However, ultrasound-guided percutaneous ablation (PA) has also been employed as a repeatable and minimally invasive alternative approach to treat rHCC [10–12]. Therefore, in several studies, meta-analyses have been conducted to compare the relative survival outcomes of rHCC patients who un-

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derwent RR or PA procedures [13–15]. However, the majority of the data included in these analyses were derived from retrospective studies, making them highly susceptible to a risk of bias. To validate these previously reported results, there is a need for a meta-analysis that particularly examines data collected from both propensity score-matched (PSM) analyses and randomized controlled trials (RCTs).

## Aim

This meta-analysis included only PSM and RCT studies to explore the relative efficiency and safety of RR and PA in rHCC treatment.

## Material and methods

### Study design

The current study was designed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines registered at https://inplasy.com/ (No. INPLASY202240117).

We used the following search strategy to identify relevant studies published as of April 2022 in the PubMed, Embase, Wanfang, and China National Knowledge Infrastructure (CNKI) databases: (((((liver cancer) or (hepatocellular carcinoma)) or (HCC)) and ((recurrent) or (recurrence))) and (ablation)) and ((surgery) or (resection)).

The following studies met the inclusion criteria in this meta-analysis: a) Research designs: PSM- or RCT-based analyses; b) Diseases: rHCC after surgical resection; c) Types of interventions: RR vs. PA; d) Languages: no restrictions.

Studies were excluded if: a) they were not RCTs or PSM-based analyses; b) they focused on rHCC patients following trans-arterial chemoembolization or ablation; c) they were reviews of case reports.

### Data extraction

Data were extracted from relevant studies by two authors independently, and discrepancies were resolved through consensus via discussing them with a third investigator. The first author, country, publication year, patient number, age, gender, tumor number, tumor diameter, HBsAg(+) status, α-fetoprotein (AFP) levels, and time to recurrence (TTR) were all collected as baseline data in each study. Outcome data collected from each study included the repeat recurrence rate, the overall survival (OS) and disease-free survival (DFS) for included patients over 1-, 3-, and 5-year intervals, total OS and DFS duration, rates of major and minor complications, and the duration of hospitalization.

### Quality assessment

The risk of bias for RCTs was examined with the Cochrane Collaboration tool. The quality of PSM-based studies was evaluated using the Newcastle-Ottawa scale (NOS) [16], with an NOS score ≥ 7 revealing a high-quality study.

### Endpoints

OS and DFS were the primary endpoints for the present meta-analysis, while repeat recurrence rates, complication rates, and duration of hospitalization were considered secondary endpoints. The grade of complications was assessed using the Clavien-Dindo classification [17].

### Statistical analysis

A meta-analysis was conducted using RevMan v5.3. Continuous variables were evaluated using mean difference (MD) values and 95% confidence intervals (CIs), whilst categorical variables were evaluated via pooled odds ratios (ORs) and 95% CIs. Pooled OS and DFS durations were analyzed using hazard ratios (HRs) and 95% CIs. Heterogeneity for pooled results was assessed with Cochran's Q test and Higgins' $I^2$ statistic, with data being analyzed with a fixed-effects model when $p > 0.05$ and $I^2 < 50\%$. In contrast, random-effects models were employed. *Z*-tests were used to assess the significance of pooled estimates, with $p < 0.05$ as the threshold of significance. To conduct sensitivity analyses, pooled data were analyzed while iteratively omitting individual studies to identify possible sources of heterogeneity. Egger's test was utilized to detect possible publication bias using Stata v12.0.

## Results

### Study inclusion

Initial searches of the PubMed, Embase, Wanfang, and CNKI databases respectively yielded 3,232, 7,162, 202, and 96 potentially relevant studies. Of these articles, 20 remained after removing reviews, duplicate studies, irrelevant studies, case reports, and animal-based studies. Furthermore, 14 studies

that were not RCTs or PSM-based studies were excluded. The remaining 6 studies, consisting of 2 RCTs and 4 PSM-based studies, were included in the final meta-analysis (Figure 1).

Table I displays the initial data from 6 studies [18–23]. Of these studies, 5 were carried out in China [18–21, 23], and 1 in Korea [22]. All 3 PSM-based studies exhibited NOS scores of 8. Both RCTs were open-label trials with unclear detection bias and other biases (Figure 2).

In total, these 6 studies included 463 and 422 rHCC patients who were respectively treated via PA and RR (Table II). In all studies that were included, PA was performed via ultrasound-guided radiofrequency ablation (RFA). The baseline for the underlined 5 experiments is presented in Table II.

## Repeat recurrence rates

Repeat recurrence rates were reported in three studies [20, 21, 23], with these rates being similar in the PA and RR groups (63.3% and 54.1%, OR = 1.59, 95% CI: 0.93–2.73, $p$ = 0.09, Figure 3 A). Significant heterogeneity was observed for this endpoint ($I^2$ = 55%), and the study by Liu *et al.* [20] was identified as the source of this heterogeneity. Egger's test did not reveal any significant publication bias ($p$ = 0.142).

## DFS

Five studies [18–21, 23] revealed the 1-year DFS rates for rHCC patients, and the pooled 1-year DFS rates in the PA and RR groups were found to be comparable (70.1% and 76.5%, OR = 0.69, 95% CI: 0.35–

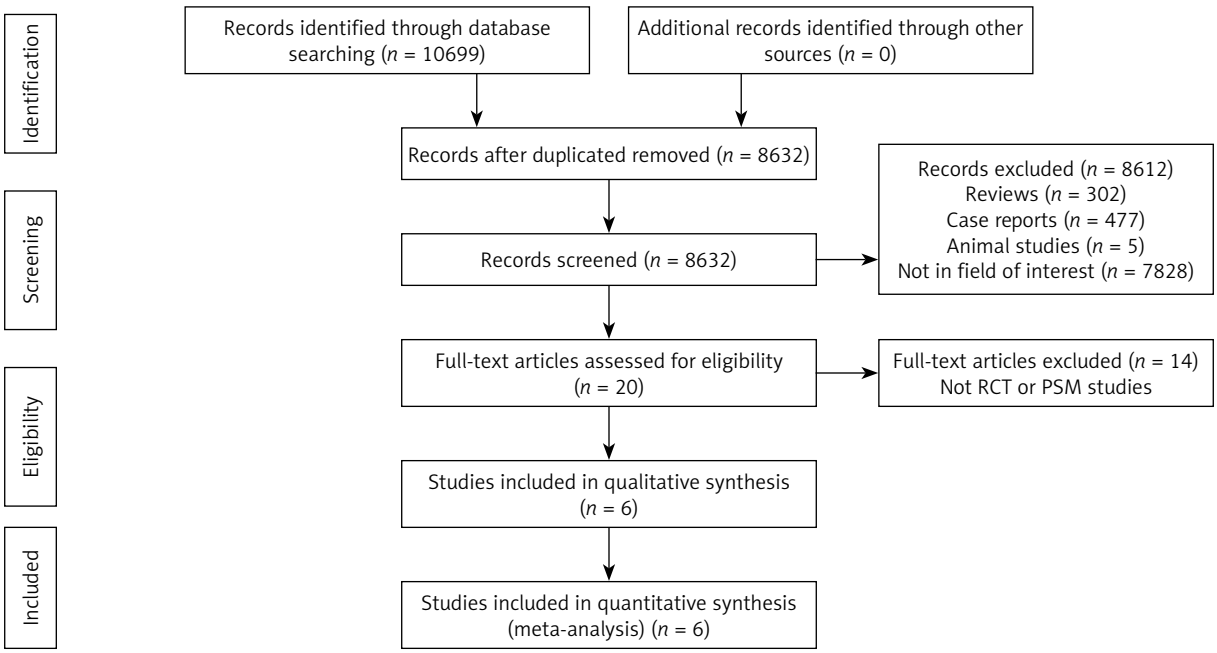



**Figure 1.** Flowchart of this meta-analysis

**Table I.** Baseline data of the included studies

| First author | Year | Country | Design | NOS |
|---|---|---|---|---|
| Feng [18] | 2020 | China | PSM-Retrospective | 8 |
| Li [19] | 2014 | China | Randomized controlled trial | Not applicable |
| Liu [20] | 2019 | China | Randomized controlled trial | Not applicable |
| Lu [21] | 2020 | China | PSM-Retrospective | 8 |
| Song [22] | 2015 | Korea | PSM-Retrospective | 8 |
| Xia [23] | 2020 | China | Randomized controlled trial | Not applicable |

*NOS – Newcastle-Ottawa Scale, PSM – propensity score matching.*

1.36, $p$ = 0.28, Figure 3 B). The heterogeneity was found to be significant ($I^2$ = 73%), and the study by Liu *et al.* [20] was identified as a source of this heterogeneity. Egger's test did not reveal any significant publication bias ($p$ = 0.895).

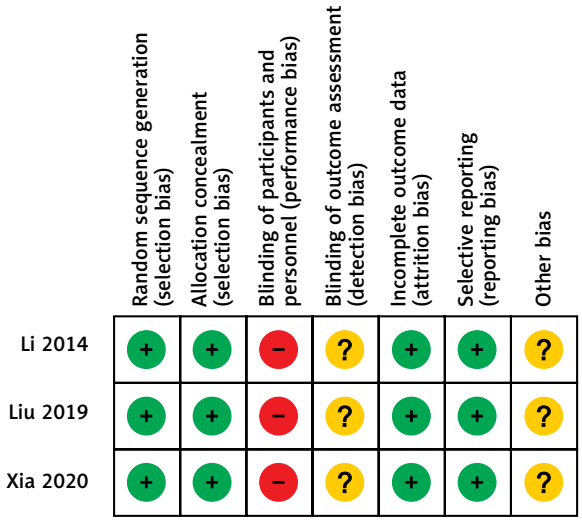



**Figure 2.** Cochrane risk-of-bias tool for the included RCTs

Furthermore, 3-year DFS rates were reported in three studies [18, 19, 23], and pooled 3-year DFS rates were comparable in the PA and RR groups (47.6% and 59.7%, OR = 0.64, 95% CI: 0.32–1.31, $p$ = 0.23, Figure 3 C). Significant heterogeneity was detected for this endpoint ($I^2$ = 73%), but sensitivity analyses failed to identify sources of such heterogeneity, and publication bias was not detected ($p$ = 0.448).

Patient 5-year DFS rates were included in three studies [18, 21, 23], and pooled 5-year DFS rates were higher in the RR group as compared to the PA group (47.2% and 29.9%, OR = 0.44, 95% CI: 0.23–0.84, $p$ = 0.01, Figure 3 D). Significant heterogeneity was detected for this endpoint ($I^2$ = 62%), and by Xia *et al.* study [22] was identified (and the study by Xia *et al.* [23] was identified) as a source of this heterogeneity. Publication bias was found to be absent ($p$ = 0.647).

**Table II.** Baseline data of the patients in the included studies

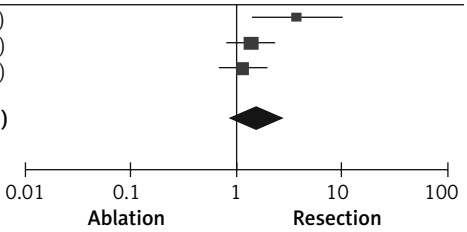
| Author | Groups | Patients (*n*) | Age [years] | Gender (M/F) | HBsAg (+) | Liver cirrhosis (+) | Systemic treatment before rHCC | Tumor diameter [mm] | Tumor number (single/ multiple) | TTR [months] | AFP > 200 ng/ml |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Feng [18] | Ablation | 48 | 58.2 | 42/6 | 48 | 30 | Not given | 25 | 24/14 | >/≤ 12: 35/13 | Not given |
| | RR | 48 | 56.6 | 42/6 | 48 | 30 | Not given | 25 | 27/11 | >/≤ 12: 37/11 | Not given |
| Li [19] | Ablation | 56 | 55.1 | 33/23 | Not given | 47 | Not given | 26 | Not given | 14.6 | Not given |
| | RR | 56 | 54.4 | 32/24 | Not given | 48 | Not given | 27 | Not given | 13.9 | Not given |
| Liu [20] | Ablation | 41 | 48.9 | 37/4 | 37 | 39 | Not given | 18.2 | 38/3 | 21.9 | Not given |
| | RR | 39 | 50.0 | 38/1 | 37 | 37 | Not given | 21.0 | 37/2 | 33.4 | Not given |
| Lu [21] | Ablation | 120 | 50.9 | 104/16 | 108 | Not given | Not given | 22 | 106/14 | >/≤ 24: 58/62 | Not given |
| | RR | 120 | 50.3 | 108/12 | 112 | Not given | Not given | 24 | 106/14 | >/≤ 24: 73/47 | Not given |
| Song [22] | Ablation | 78 | 53.6 | 58/20 | 70 | 46 | Not given | >/≤ 20: 31/47 | Not given | 43.6 | 9 |
| | RR | 39 | 52.5 | 31/8 | 36 | 23 | Not given | >/≤ 20: 17/22 | Not given | 36.3 | 6 |
| Xia [23] | Ablation | 120 | 52 | 109/11 | 90 | 55 | 33 | 27 | 94/26 | 26.3 | 47 |
| | RR | 120 | 50 | 107/13 | 96 | 50 | 29 | 29 | 96/24 | 29.5 | 49 |

*RR – repeat resection, M – male, F – female, rHCC – recurrent hepatocellular carcinoma, TTR – time to recurrence.*

**A**

| Study or subgroup | Ablation Events | Ablation Total | Resection Events | Resection Total | Weight (%) | Odds ratio M-H, random, 95% CI |
|---|---|---|---|---|---|---|
| Liu 2019 | 32 | 41 | 19 | 39 | 20.7 | 3.74 (1.42, 9.87) |
| Lu 2020 | 69 | 120 | 59 | 120 | 40.0 | 1.40 (0.84, 2.33) |
| Xia 2020 | 77 | 120 | 73 | 120 | 39.3 | 1.15 (0.68, 1.95) |
| **Total (95% CI)** | | **281** | | **279** | **100** | **1.59 (0.93, 2.73)** |
| Total events | 178 | | 151 | | | |

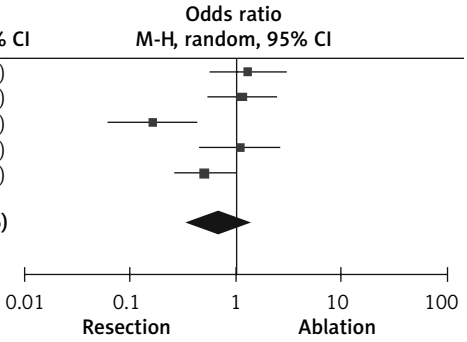
Heterogeneity: $\tau^2 = 0.12$, $\chi^2 = 4.43$, d$f = 2$ ($p = 0.11$), $I^2 = 55\%$
Test for overall effect: $Z = 1.68$ ($p = 0.09$)




**B**

| Study or subgroup | Ablation Events | Ablation Total | Resection Events | Resection Total | Weight (%) | Odds ratio M-H, random, 95% CI |
|---|---|---|---|---|---|---|
| Feng 2020 | 30 | 48 | 27 | 48 | 19.9 | 1.30 (0.57, 2.93) |
| Li 2014 | 31 | 56 | 29 | 56 | 20.9 | 1.15 (0.55, 2.43) |
| Liu 2019 | 11 | 41 | 27 | 39 | 17.8 | 0.16 (0.06, 0.43) |
| Lu 2020 | 109 | 120 | 108 | 120 | 19.3 | 1.10 (0.47, 2.60) |
| Xia 2020 | 89 | 120 | 102 | 120 | 22.2 | 0.51 (0.27, 0.97) |
| **Total (95% CI)** | | **385** | | **383** | **100** | **0.69 (0.35, 1.36)** |
| Total events | 270 | | 293 | | | |

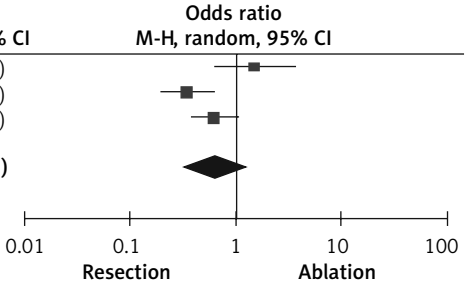
Heterogeneity: $\tau^2 = 0.43$, $\chi^2 = 14.64$, d$f = 4$ ($p = 0.006$), $I^2 = 73\%$
Test for overall effect: $Z = 1.07$ ($p = 0.28$)




**C**

| Study or subgroup | Ablation Events | Ablation Total | Resection Events | Resection Total | Weight (%) | Odds ratio M-H, random, 95% CI |
|---|---|---|---|---|---|---|
| Feng 2020 | 16 | 48 | 12 | 48 | 27.1 | 1.50 (0.62, 3.64) |
| Li 2014 | 73 | 120 | 98 | 120 | 35.3 | 0.35 (0.19, 0.63) |
| Xia 2020 | 48 | 120 | 62 | 120 | 37.6 | 0.62 (0.37, 1.04) |
| **Total (95% CI)** | | **288** | | **288** | **100** | **0.64 (0.32, 1.31)** |
| Total events | 137 | | 172 | | | |

Heterogeneity: $\tau^2 = 0.28$, $\chi^2 = 7.34$, d$f = 2$ ($p = 0.03$), $I^2 = 73\%$
Test for overall effect: $Z = 1.21$ ($p = 0.23$)




**D**

| Study or subgroup | Ablation Events | Ablation Total | Resection Events | Resection Total | Weight (%) | Odds ratio M-H, random, 95% CI |
|---|---|---|---|---|---|---|
| Feng 2020 | 5 | 48 | 10 | 48 | 20.0 | 0.44 (0.14, 1.41) |
| Lu 2020 | 50 | 120 | 86 | 120 | 40.4 | 0.28 (0.16, 0.48) |
| Xia 2020 | 31 | 120 | 40 | 120 | 39.6 | 0.70 (0.40, 1.22) |
| **Total (95% CI)** | | **288** | | **288** | **100** | **0.44 (0.23, 0.84)** |
| Total events | 86 | | 136 | | | |

Heterogeneity: $\tau^2 = 0.19$, $\chi^2 = 5.22$, d$f = 2$ ($p = 0.07$), $I^2 = 62\%$
Test for overall effect: $Z = 2.48$ ($p = 0.01$)

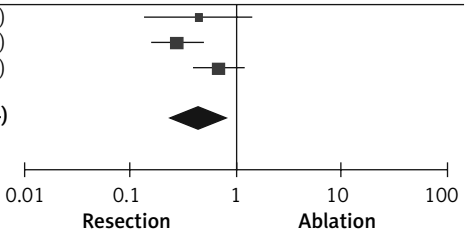
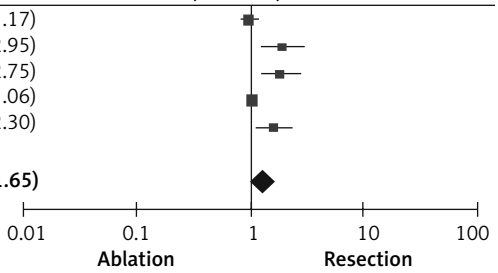



**Figure 3.** Forest plots showing the comparisons in repeat recurrence rates (**A**), 1-year DFS rates (**B**), 3-year DFS rates (**C**), 5-year DFS rates (**D**)

**E**

| Study or subgroup | log(odds ratio) | SE | Weight (%) | Odds ratio IV, random, 95% CI |
|---|---|---|---|---|
| Feng 2020 | –0.02 | 0.09 | 24.6 | 0.98 (0.82, 1.17) |
| Liu 2019 | 0.65 | 0.22 | 14.1 | 1.92 (1.24, 2.95) |
| Lu 2020 | 0.62 | 0.2 | 15.5 | 1.86 (1.26, 2.75) |
| Song 2015 | 0.04 | 0.01 | 28.8 | 1.04 (1.02, 1.06) |
| Xia 2020 | 0.48 | 0.18 | 17.0 | 1.62 (1.14, 2.30) |
| **Total (95% CI)** | | | **100** | **1.32 (1.05, 1.65)** |

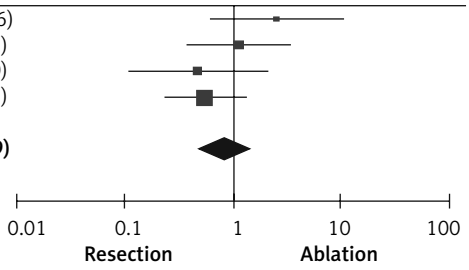
Heterogeneity: $\tau^2 = 0.05$, $\chi^2 = 22.41$, d$f = 4$ ($p = 0.0002$), $I^2 = 82\%$
Test for overall effect: $Z = 2.38$ ($p = 0.02$)




**F**

| Study or subgroup | Ablation Events | Ablation Total | Resection Events | Resection Total | Weight (%) | Odds ratio M-H, fixed, 95% CI |
|---|---|---|---|---|---|---|
| Feng 2020 | 45 | 48 | 41 | 48 | 9.2 | 2.56 (0.62, 10.56) |
| Li 2014 | 49 | 56 | 48 | 56 | 21.6 | 1.17 (0.39, 3.47) |
| Liu 2019 | 35 | 41 | 36 | 39 | 19.4 | 0.49 (0.11, 2.10) |
| Xia 2020 | 105 | 120 | 111 | 120 | 49.8 | 0.57 (0.24, 1.35) |
| **Total (95% CI)** | | **265** | | **263** | **100.0** | **0.86 (0.50, 1.49)** |
| Total events | 234 | | 236 | | | |

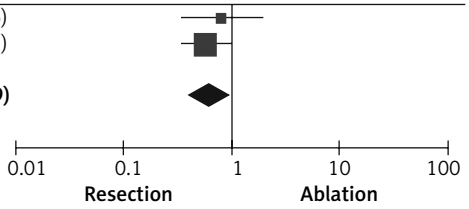
Heterogeneity: $\chi^2 = 4.04$, d$f = 3$ ($p = 0.26$), $I^2 = 26\%$
Test for overall effect: $Z = 0.52$ ($p = 0.60$)




**G**

| Study or subgroup | Ablation Events | Ablation Total | Resection Events | Resection Total | Weight (%) | Odds ratio M-H, fixed, 95% CI |
|---|---|---|---|---|---|---|
| Feng 2020 | 32 | 48 | 34 | 48 | 23.0 | 0.82 (0.35, 1.96) |
| Xia 2020 | 61 | 120 | 77 | 120 | 77.0 | 0.58 (0.34, 0.97) |
| **Total (95% CI)** | | **168** | | **168** | **100.0** | **0.63 (0.41, 0.99)** |
| Total events | 93 | | 111 | | | |

Heterogeneity: $\chi^2 = 0.48$, d$f = 1$ ($p = 0.49$), $I^2 = 0\%$
Test for overall effect: $Z = 2.02$ ($p = 0.04$)




**H**

| Study or subgroup | Ablation Events | Ablation Total | Resection Events | Resection Total | Weight (%) | Odds ratio M-H, random, 95% CI |
|---|---|---|---|---|---|---|
| Feng 2020 | 29 | 48 | 19 | 48 | 46.0 | 2.33 (1.03, 5.28) |
| Xia 2020 | 41 | 120 | 49 | 120 | 54.0 | 0.75 (0.45, 1.27) |
| **Total (95% CI)** | | **168** | | **168** | **100.0** | **1.26 (0.42, 3.82)** |
| Total events | 70 | | 68 | | | |

Heterogeneity: $\tau^2 = 0.52$, $\chi^2 = 5.20$, d$f = 1$ ($p = 0.02$), $I^2 = 81\%$
Test for overall effect: $Z = 0.42$ ($p = 0.68$)

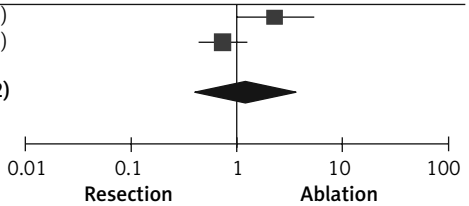
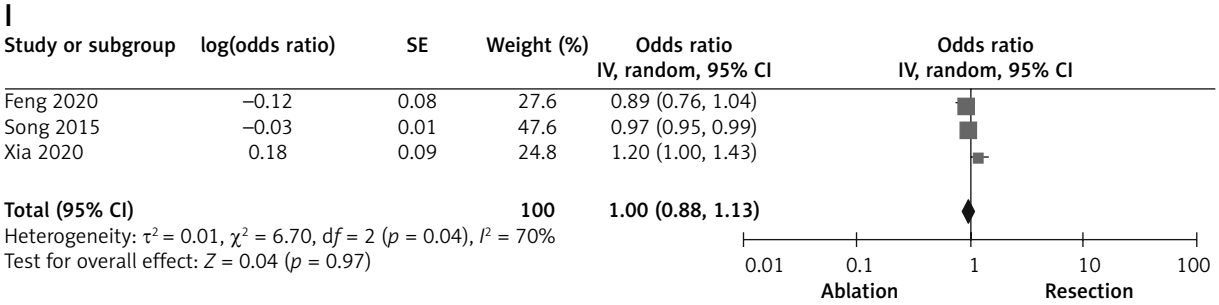
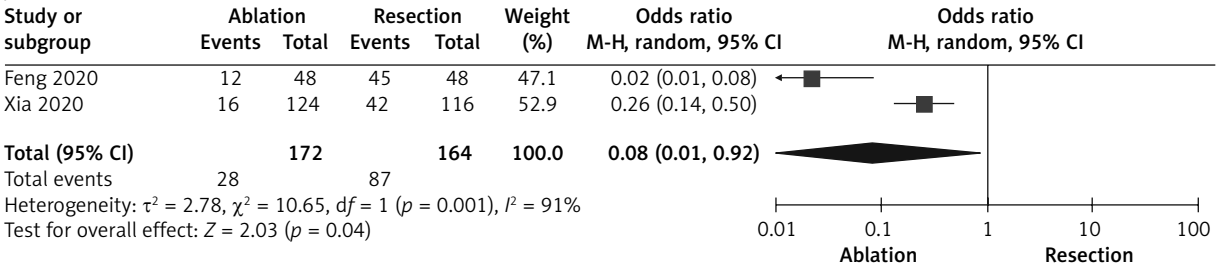



**Figure 3.** Cont. DFS duration (**E**), 1-year OS rates (**F**), 3-year OS rates (**G**), 5-year OS rates (**H**)

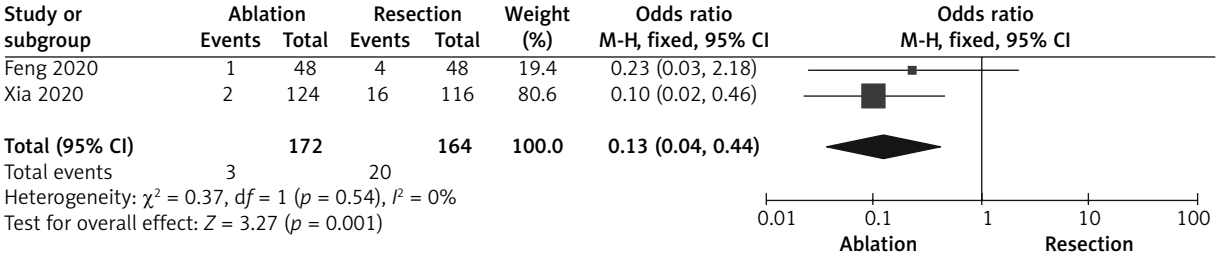
**I**




**J**




**K**




**L**

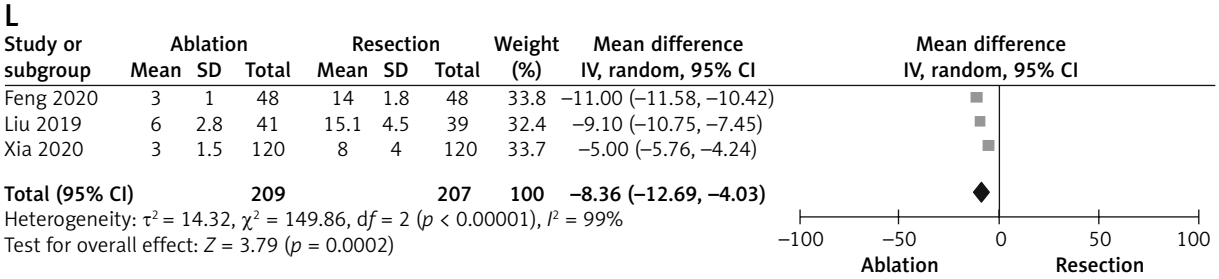



**Figure 3.** Cont. OS duration (**I**), Grade 1/2 complication rates (**J**), Grade 3/4 complication rates (**K**), and hospital stay between 2 groups (**L**)

**Table III.** Meta-analytic pooled results of the complications

| Complication | Number of studies | OR (95% CI) | Heterogeneity | Favor |
|---|---|---|---|---|
| Fever | 2 | 0.19 (0.07, 0.51), $p = 0.001$ | $I^2 = 0\%$ | Ablation |
| Ascites | 4 | 0.38 (0.18, 0.81), $p = 0.01$ | $I^2 = 29\%$ | Ablation |
| Pleural effusion | 2 | 0.38 (0.11, 1.33), $p = 0.13$ | $I^2 = 0\%$ | – |
| Postoperative hemorrhage | 3 | 0.21 (0.04, 0.96), $p = 0.04$ | $I^2 = 0\%$ | Ablation |

*OR – odds ratio.*

The duration of DFS was reported in four studies [18, 20–23], and an analysis of the logHR values for this endpoint with the corresponding standard error revealed significantly longer DFS duration in the RR group than the PA group (OR = 1.32, 95% CI: 1.05–1.65, $p$ = 0.02, Figure 3 E). Significant heterogeneity was detected for this endpoint ($I^2$ = 82%), but sensitivity analyses failed to identify sources of such heterogeneity, with no publication bias ($p$ = 0.426).

## OS

Four studies provided 1-year OS rates [18–20, 23], and pooled 1-year OS rates in the PA and RR groups were similar (88.3% and 89.7%, OR = 0.86, 95% CI: 0.50–1.49, $p$ = 0.60, Figure 3 F). There was no evidence of either publication bias ($p$ = 0.255) or substantial heterogeneity ($I^2$ = 26%).

Rates of 3-year OS were reported in two studies [18, 23], and pooled 3-year OS rates were higher in the RR group than the PA group (66.1% and 55.4%, OR = 0.63, 95% CI: 0.41–0.99, $p$ = 0.04, Figure 3 G). No significant heterogeneity was detected ($I^2$ = 0%), and funnel plots did not reveal any significant publication bias.

Both the PA and RR groups shared comparable 5-year OS rates (41.7% and 40.5%, OR = 1.26, 95% CI: 0.42–3.82, $p$ = 0.68, Figure 3 H), which were found to be reported in two publications [18, 23]. Significant heterogeneity was detected for this endpoint ($I^2$ = 81%), but sensitivity analyses could not be performed as only two studies reported on this endpoint. Moreover, the funnel plots did not reveal any significant publication bias.

Three studies examined the OS length among patients who received RR and PA treatments [18, 22, 23]. Analyses of the corresponding logHR and SE values did not reveal any significant differences in OS duration between the PA and RR groups (OR = 1.00, 95% CI: 0.88–1.13, $p$ = 0.97, Figure 3 I). Significant heterogeneity was detected for this endpoint ($I^2$ = 70%), and the study reported by Xia *et al.* [23] was identified as a source of this heterogeneity. Egger's test revealed no evidence of significant publication bias ($p$ = 0.469).

## Complication rates

Rates of Grade 1/2 complications were reported in two studies [18, 23]. The PA group exhibited a significantly lower pooled Grade 1/2 complication rate relative to the RR group (16.3% vs. 53.0%, OR = 0.08, 95% CI: 0.01–0.92, $p$ = 0.04, Figure 3 J). Since only two studies reported on this endpoint, there was considerable heterogeneity found for it ($I^2$ = 91%), but sensitivity analyses could not be performed. Funnel plots did not reveal any significant publication bias.

Grade 3/4 complication rates for treated rHCC patients were reported in two studies [18, 23], and pooled Grade 3/4 complication rates were significantly lower in the PA group than the RR group (1.7% vs. 12.2%, OR = 0.13, 95% CI: 0.04–0.44, $p$ = 0.001, Figure 3 K). No significant heterogeneity was detected ($I^2$ = 0%). Funnel plots did not reveal any significant publication bias.

Rates of fever were reported in two studies [20, 23], and pooled fever rates were significantly lower in the PA group than the RR group (OR = 0.19, 95% CI: 0.07–0.51, $p$ = 0.001, Table III). No significant heterogeneity was detected ($I^2$ = 0%). Funnel plots did not reveal any significant publication bias.

Rates of ascites were reported in four studies [19–21, 23], and pooled ascites rates were significantly lower in the PA group than the RR group (OR = 0.38, 95% CI: 0.18–0.81, $p$ = 0.01, Table III). No significant heterogeneity was detected ($I^2$ = 29%). Egger's test did not reveal any significant publication bias ($p$ = 0.136).

Rates of pleural effusion were reported in two studies [21, 23], and pooled pleural effusion rates were similar in the PA and RR groups (OR = 0.38, 95% CI: 0.11–1.33, $p$ = 0.13, Table III). No significant heterogeneity was detected ($I^2$ = 0%). Funnel plots did not reveal any significant publication bias.

Rates of postoperative hemorrhage were reported in three studies [20, 21, 23], and pooled postoperative hemorrhage rates were significantly lower in the PA group than the RR group (OR = 0.21, 95% CI: 0.04–0.96, $p$ = 0.04, Table III). No significant heterogeneity was detected ($I^2$ = 0%). Egger's test did not reveal any significant publication bias ($p$ = 0.434).

## Duration of hospitalization

Three studies reported the duration of hospitalization for individuals who received RR and PA treatment [18, 20, 23]. PA group patients exhibited a significantly shorter pooled duration of hospitalization than the RR group (MD = –8.36, 95% CI: –12.69– –4.03, $p$ = 0.0002, Figure 3 L). Significant heterogeneity was detected ($I^2$ = 99%). However, as

only two studies reported on this endpoint, sensitivity analyses could not be performed. Egger's test revealed no significant publication bias ($p = 0.868$).

## Discussion

This meta-analysis was performed to examine the efficacy and safety of PA- and RR-based approaches for the treatment of rHCC patients. To minimize the chances of bias, this study only included RCTs and PSM-based analyses, unlike earlier meta-analyses on this topic [13–15].

All studies employed an ultrasound-guided PA treatment strategy, which offers advantages over computed tomography (CT) guidance including a lack of ionizing radiation exposure and the potential for real-time monitoring [24, 25].

DFS was the primary endpoint of the present meta-analysis, which revealed that patients who received RR treatment had significantly higher pooled 5-year DFS rates and longer DFS duration than individuals who received PA treatment. However, pooled analyses of total repeat recurrence rates did not reveal any considerable differences between these groups. Microvascular invasion (MVI) is a risk factor associated with the recurrence of HCC and with reductions in patient OS [26, 27]. In contrast to ultrasonography, which cannot determine a patient's MVI status, tumor resection enables the removal of the malignant mass as well as the direct assessment of that patient's MVI status. In this view, PA is unable to address this risk factor. These factors are likely associated with the more limited ability of PA to control HCC tumor progression.

OS is a crucial outcome measure when evaluating the efficacy of cancer treatment. Herein, RR treatment was associated with a significantly higher pooled 3-year OS for treated patients as compared to PA, although the pooled HR for OS throughout the entirety of the follow-up period did not achieve significance when comparing these two therapeutic strategies. This contradicts the results of the previous meta-analysis reported by Yang *et al*. [15], who determined that RR treatment was associated with a superior 3-year OS and that LR was superior to RFA concerning the pooled HR for OS. However, as the majority of those findings were based on information from retrospective studies, the validity of these inferences is debatable [15].

Another possible explanation for the failure of the pooled HR for OS to achieve statistical significance may be related to the high degree of repeatability associated with the PA method, as repeated PA is a valid strategy for achieving greater local tumor control. However, further work will be necessary to validate this treatment strategy.

Pooled rates of both Grade 3/4 and Grade 1/2 complications and pooled hospitalization duration were all significantly lower for patients who underwent PA treatment relative to those in the RR group. Furthermore, many important complications, such as fever, ascites, and postoperative hemorrhage rates, were all significantly lower in the PA group. These results are likely attributable to the less invasive nature of the PA procedure. RR implementation is also often restricted by a poor hepatic functional reserve, insufficient residual liver tissue, and/or extensive recurrent intrahepatic disease [28]. Furthermore, because PA is highly selective in its targeting, significant amounts can be conserved in non-cancerous parenchymal liver tissue, resulting in less severe injury or residual cirrhotic liver tissue [15].

Subgroup analyses for different numbers of tumor [18] or TTR [20] were performed in some of the included studies. Feng *et al.* [18] determined that PA was associated with significantly better OS for patients with multiple rHCC tumors as compared to RR (6.4 y vs. 2.2 years, $p = 0.018$), whereas Liu *et al.* [20] reported a significantly higher 5-year progression-free survival rate for patients who underwent RR as compared to those who underwent PA (65.4% vs. 22.7%, $p = 0.004$) among individuals with a TTR of $\leq 2$ years. Herein, it was not feasible to perform subgroup analyses based on TTR or tumor counts because these subgroup analyses were not done in every study.

There are certain limitations to this study. For one, only RCTs and PSM studies were incorporated into this meta-analysis to reduce the potential bias, but the small number of resultant studies may have constrained the reliability of the resultant data. Secondly, all included studies were performed in Asia. The etiology of HCC can vary across different countries owing to the multifactorial nature of this disease. In view of these facts, further research will be essential to establish whether the findings can be generalized to other nations. Third, as radiofrequency ablation approaches were employed by all included studies, we were unable to evaluate the relative benefits associated with the treatment of rHCC via cryotherapy or microwave ablation. Fourth, some factors (such as TTR, AFP, or tumor size) may influence the patient's

prognosis. Based on the underlined criteria, this study was unable to perform the subgroup analyses, because we were unable to stratify the data based on these factors from the included studies.

## Conclusions

These results suggest that RR may exhibit superior long-term disease control in rHCC patients as compared to PA, whereas PA is associated with a better safety profile and a shorter duration.

## Conflict of interest

The authors declare no conflict of interest.

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