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RESEARCH

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# Comparison of liver resection and radiofrequency ablation in long-term survival among patients with early-stage hepatocellular carcinoma: a meta-analysis of randomized trials and high-quality propensity score-matched studies

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**Abstract**

**Background** Whether radiofrequency ablation (RFA) and liver resection (LR) are comparable treatments for early-stage hepatocellular carcinoma (HCC) is controversial. We conducted this study to provide ample clinical evidence for the argument.

**Methods** The PubMed, Embase, Web of Science, and Cochrane Library databases were systematically searched to identify randomized controlled trials (RCTs) and propensity score-matched (PSM) studies that compared long-term outcomes of both RFA and LR for patients with early-stage HCC. The hazard ratios (HRs) with 95% confidence intervals (95% CI) of overall survival (OS) and disease-free survival (DFS) were calculated.

**Results** Thirty-six studies consisting of six RCTs and 30 PSM studies were included in this study, and a total of 7384 patients were involved, with 3694 patients being treated with LR and 3690 patients with RFA. Meta-analysis showed that LR provided better OS and DFS than RFA (*HR*: 1.22, 95% *CI*: 1.13–1.31; *HR*: 1.56, 95% *CI*: 1.39–1.74, respectively). A sensitivity analysis indicated that the results were stable. For the subgroup of patients with BCLC 0 stage, RFA and LR resulted in similar OS and DFS. For the subgroup of patients with single tumor sizes less than 3 cm, RFA reached similar OS (*HR*: 1.19, 95% *CI*: 0.90–1.58) but worse DFS compared with LR (*HR*: 1.45, 95% *CI*: 1.11–1.90). For the subgroup of ablation margin larger than 0.5 cm, LR still resulted in better OS than RFA (*HR*: 1.29, 95% *CI*: 1.09–1.53); while the ablation margin was larger than 1 cm, both RFA and LR resulted in similar OS. The modality of RFA was also a factor that affected results. Subgroup analysis showed that patients receiving ultrasound-guided RFA had worse OS and DFS than LR (*HR*: 1.24, 95% *CI*: 1.14–1.36; *HR*: 1.44, 95% *CI*: 1.25–1.66, respectively).

**Conclusions** Meta-analysis showed that LR provided better OS and DFS for patients with early-stage HCC. However, RFA and LR had similar effects on long-term survival in patients with BCLC 0 stage HCC. RFA and LR probably had similar effects on OS in patients with solitary HCC less than 3 cm or when the ablation margin was larger than 1 cm which

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need more studies to confirm. The effects of different modalities of RFA on long-term survival are needed for further assessment.

**Keywords** Radiofrequency ablation, Liver resection, Hepatocellular carcinoma, Early stage, Meta-analysis

## Introduction

Owing to its noticeable incidence, hepatocellular carcinoma (HCC) has markedly attracted clinicians' attention [1]. A remarkable number of early-stage HCC (ES-HCC) cases were detected because of the regular surveillance for HCC recommended by the guidelines in Western countries [2, 3]. At present, liver transplantation is an ideal treatment for ES-HCC, which could satisfy the Milan criteria with a high 5-year survival rate [4]. Nevertheless, the shortage of liver donation and the high cost of liver transplantation restrict its widespread utilization. Thus, liver resection is recommended by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases for ES-HCC [2, 3]. However, most patients who are eligible for resection are also candidates for thermal ablation. Radiofrequency ablation (RFA) is a less morbid procedure, and long-term outcomes may be similar to resection, particularly for tumors with a size of < 2 cm. Therefore, RFA has been particularly recommended to treat ES-HCC [5–8].

Many retrospective studies demonstrated that RFA and LR had similar survival benefits for ES-HCC patients [9–19]. However, this conclusion is controversial. A noticeable number of retrospective studies indicated that LR could prolong the overall survival (OS) and disease-free survival (DFS) for ES-HCC compared with RFA [20–24]. The benefit of RFA over LR for treating potentially resectable HCC has been studied in several RCTs conducted in China, Japan, and Hong Kong [25–30]. However, these studies had mixed results; some concluded that LR is superior, while others noted that both yielded similar outcomes. Besides, the criteria differentiating tumor characteristics were consistent among RCTs [31]. Hence, whether RFA can be the primary treatment for ES-HCC remains controversial.

Hence, we conducted the present meta-analysis of RCTs and high-quality propensity score-matched (PSM) studies to elucidate the comparative survival benefits and detrimental influences of LR versus RFA for ES-HCC.

## Methods

### Search strategy

The current meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [32]. Two scholars independently conducted a comprehensive systematic search on the PubMed, Web of Science, and Cochrane Library databases to retrieve relevant articles published until December 21, 2022. Disagreements were resolved through discussions. The keywords used in the search included "hepatocellular carcinoma," "HCC," "radiofrequency ablation," "hepatectomy," and "liver resection." The details of the search strategy are summarized in Supplementary materials S1.

### Eligibility criteria

The inclusion criteria were as follows:

(1) definitive diagnosis of ES-HCC described in the previously published guidelines.
(2) satisfying the Milan criteria for ES-HCC cases.
(3) RCTs and propensity score-matched (PSM) studies.
(4) reporting at least one survival outcome.
(5) the availability of full text of searched articles.
(6) researches published in English.

The exclusion criteria were as follows:

(1) other types of liver cancer, such as cholangiocarcinoma or metastasized liver cancer.
(2) data extracted from national databases.
(3) articles without outcomes of interest.
(4) reviews, case reports, and meeting abstracts.

### Data collection and quality assessment

Two scholars independently retrieved data from the included studies. The following data were collected: the first author's name, year of publication, country, study design, inclusion criteria, number of participants, characteristics of participants and tumors, hazard ratios (HRs) of OS and DFS, the incidence of morbidity, and the length of hospitalization. The two scholars also independently assessed the quality of eligible studies with the Cochrane risk-of-bias tool for RCTs [33] and the Newcastle–Ottawa scale (NOS) score for PSM studies. Further information regarding the complementary criteria is summarized in Table 1. Disagreements between the two scholars were resolved through discussion.

**Table 1** Characteristics of included studies

| Author | Region | Design | Inclusion criteria | Group | Modality of RFA | No. of patients | Age | Gender (M/F) | HBV/HCV | Child–Pugh A/B | AFP (ng/ml) | Tumor size (cm) | Solitary/multiple | 100% AR/NAR | 100% LH (Y/N) | Resection margin | Ablation margin | Follow-up (months) | Survival (median (95% *CI*)) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zhang | China | PSM | Single tumor; ≤ 3 cm | LR | | 67 | 57.51 ± 8.37 | 50/17 | 56/6 | 67/0 | 189.00 ± 568.99 | 24.67 ± 5.97* | 67/0 | AR | NR | > 1 cm | | 96ψ | mOS: not reached mRFS: 47 (42–NA) |
| 2022 | | | | RFA | Ultra-sound guided or laparo-scopic | 67 | 57.78 ± 10.97 | 49/18 | 56/7 | 67/0 | 258.39 ± 578.19 | 24.2 8 ± 5.73* | 67/0 | | | | > 1 cm | 96ψ | mOS: 95 (79–NA) mRFS: 33 (26–51) |
| Takay-ama | Japan | RCT | ≤ 3 nod-ules; ≤ 3 cm | LR | | 150 | 68 (63–74)ζ | 112/38 | 27/97 | 139/10 | NR | 1.8 (1.5–2.2)ζ | 135/15 | NR | NR | NA | | 5.04 (0.36–9.49) η,δ | mRFS: 3.46δ |
| 2022 | | | | RFA | Ultra-sound guided | 151 | 69 (63–74)ζ | 108/43 | 33/94 | 149/2 | NR | 1.8 (1.5–2.3)ζ | 136/15 | | | | NA | 4.99 (0.00–8.70) η,δ | mRFS: 3.04δ |
| Liu | China | PSM | ≤ 3 nod-ules; ≤ 3 cm | LR | | 103 | 63 (55–71)ζ | 76/27 | 48/43 | 102/1 | 5(> 400) | 56 (> 20)* | 94/9 | NR | Y | NA | | 14.5 (9.9–57.7)ζ | mOS: 73.6 mRFS: 49.5 |
| 2022 | | | | RFA | Ultra-sound guided | 103 | 63 (54–70)ζ | 75/28 | 54/42 | 102/1 | 9(> 400) | 60 (> 20)* | 89/14 | | | | NA | 14.5 (9.9–57.7)ζ | mOS: 81 mRFS: 36.4 |
| Ko | Korea | PSM | Single tumor; 1–3 cm | LR | | 23 | NR | NR | NR | NR | NR | NR | 23/0 | NR | Y | NA | | NR | NR |
| 2022 | | | | RFA | laparo-scopic | 23 | NR | NR | NR | NR | NR | NR | 23/0 | | | | NA | NR | NR |
| Kim | Korea | PSM | Single tumor; ≤ 4 cm | LR | | 61 | 59.4ψ | 43/18 | 43/3 | 59/2 | 304.6 ± 1215.3 | 2.29 ± 0.8 | 61/0 | NR | Y | NA | | NR | NR |
| 2022 | | | | RFA | Ultra-sound guided | 61 | 62.2ψ | 52/9 | 46/3 | 55/6 | 173.6 ± 765.6 | 2.2 ± 0.8 | 61/0 | | | | NA | NR | NR |
| Filippo | Italy | PSM | BCLC 0/A stage | LR | | 22 | 82.8 ± 3.2 | 13/9 | 13/2 | 19/3 | NR | 15 (> 20)* | 20/2 | NR | NR | NA | | NR | NR |
| 2022 | | | | RFA | Ultra-sound guided or open or laparo-scopic | 22 | 82.2 ± 2.4 | 16/6 | 15/1 | 21/1 | NR | 15 (> 20)* | 20/2 | | | | NA | NR | NR |
| Cheng | China | PSM | BCLC 0/A stage | LR | | 99 | 63.60 ± 9.86 | 82/17 | 82/12 | 83/2 | 47 (6.0–423.0)ζ | 2.31 ± 1.93 | 96/3 | NR | Y | NA | | 34 (1–175) η | NR |
| 2022 | | | | RFA | Ultra-sound or CT guided | 31 | 65.48 ± 11.73 | 22/9 | 22/8 | 27/2 | 34 (3.5–242.5)ζ | 1.14 ± 0.70 | 28/3 | | | | > 1 cm | 34 (1–175) η | NR |
| Li | China | PSM | Single tumor; ≤ 2 cm | LR | | 59 | 61 (35–82)ζ | 39/19 | 28/34 | 56/2 | 5 (> 200) | 1.9 (1.0–2.0)ζ | 58/0 | NR | NR | NA | | NR | NR |

**Table 1** (continued)

| Author | Region | Design | Inclusion criteria | Group | Modality of RFA | No. of patients | Age | Gender (M/F) | HBV/HCV | Child–Pugh A/B | AFP (ng/ml) | Tumor size (cm) | Solitary/multiple | 100% AR/NAR | 100% LH (Y/N) | Resection margin | Ablation margin | Follow-up (months) | Survival (median (95% *CI*)) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2021 | | | | RFA | NA | 59 | 61 (34–80)ζ | 39/19 | 23/27 | 57/1 | 12 (> 200) | 1.8 (1.0–2.0)ζ | 58/0 | | | | NA | NR | NR |
| Lee,D | Korea | PSM | Single tumor; ≤ 3 cm | LR | | 118 | 59.5 ± 8.7 | 91/27 | 90/10 | 118/0 | 90.2 ± 309.0 | 1.84 ± 0.56 | 118/0 | NR | Y | NA | | NR | NR |
| 2021 | | | | RFA | Ultra-sound guided | 118 | 60.5 ± 10.3 | 88/30 | 84/12 | 118/0 | 67.6 ± 173.4 | 1.87 ± 0.51 | 118/0 | | | | Com-pleted | NR | NR |
| Contic-chio | France and Italy | PSM | BCLC 0/A stage | LR | | 136 | 74.7 (70–86.1) η | 104/32 | 22/68 | 116/20 | NR | 24.5 (7–50)*η | 120/16 | NR | NR | NA | | NR | NR |
| 2021 | | | | RFA | Ultra-sound guided or open or laparo-scopic | 136 | 75 (70–88)η | 98/38 | 10/73 | 114/22 | NR | 25 (10–50)*η | 117/19 | | | | NA | NR | NR |
| Bai 1 | China | PSM | BCLC 0/A stage | LR | | 250 | 45 (> 60) | 212/38 | 250/0 | 226/24 | 126 (< 400) | 94 (≤ 3) | 199/51 | NR | NR | > 0.5 cm | | 60.5 (3.1–154.6) η | NR |
| 2021 | | | | RFA | Ultra-sound guided | 250 | 57 (> 60) | 202/48 | 250/0 | 222/28 | 144(< 400) | 106 (≤ 3) | 207/43 | | | | > 0.5 cm | 58.7 (3.3–147.5) η | NR |
| Bai 2 | China | PSM | BCLC 0/A stage | LR | | 423 | 98(> 60) | 260/55 | 423/0 | 287/28 | 368 (< 400) | 357 (≤ 3) | 411/12 | NR | NR | NA | | 60.5 (3.1–154.6) η | NR |
| 2021 | | | | RFA | Ultra-sound guided | 423 | 101 (> 60) | 264/51 | 423/0 | 285/30 | 367(< 400) | 349 (≤ 3) | 415/8 | | | | NA | 58.7 (3.3–147.5) η | NR |
| Pan | China | PSM | BCLC 0/A stage | LR | | 118 | 53.0 (45.2–61.0)ζ | 101/17 | 100/NR | NR | 22.6 (3.94–218)ζ | 2.50 (1.85–3.50)ζ | 98/20 | NR | NR | NA | | 26.22 (1.30–44.73)η | mOS: 25.6 mRFS: 22.0 |
| 2020 | | | | RFA | Ultra-sound guided | 236 | 56.0 (45.0–64.0)ζ | 206/30 | 215/NR | NR | 8.61 (3.12–165)$^{ζ}$ | 2.55 (1.90–3.23)ζ | 199/37 | | | | Com-pleted | 24.20 (0.97–44.73)η | mOS: 23.4 mRFS: 13.3 |
| Oh | Korea | PSM | Multiple, BCLC 0/A stage | LR | | 31 | 56.0 (52.0–66.0)ζ | 23/8 | 27/NR | 31/0 | 12.7 (6.9–63.4)ζ | 14 (≤ 2) | 0/31 | NR | NR | NA | | 5.8 (3.4–7.1)η | NR |
| 2020 | | | | RFA | NA | 31 | 57.0 (50.0–66.0)ζ | 26/5 | 25/NR | 31/0 | 16.1 (6.3–127.4) ζ | 18 (≤ 2) | 0/31 | | | | NA | 5.8 (3.4–7.1)η | NR |
| Chong | China | PSM | BCLC 0/A stage | LR | | 59 | 57.7 ± 10.5 | 46/13 | 48/4 | 59/0 | 71 (4.0–436)ζ | 2.0 (1.6–2.8)ζ | 56/3 | NR | Y | NA | | NR | NR |
| 2020 | | | | RFA | Ultra-sound or CT guided or laparo-scopic | 59 | 59.3 ± 11.0 | 46/13 | 48/4 | 58/1 | 15 (4.0–305.0)ζ | 2.3 (1.5–2.7)ζ | 56/3 | | | | NA | NR | NR |

**Table 1** (continued)

| Author | Region | Design | Inclusion criteria | Group | Modality of RFA | No. of patients | Age | Gender (M/F) | HBV/ HCV | Child–Pugh A/B | AFP (ng/ml) | Tumor size (cm) | Solitary/ multiple | 100% AR/ NAR | 100% LH (Y/N) | Resection margin | Ablation margin | Follow-up (months) | Survival (median (95% *CI*)) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ye | China | PSM | Single tumor; 3–5 cm | LR | | 154 | 103 (> 60) | 141/13 | 135/2 | 139/15 | 78 (< 20)<br>29 (≥ 400) | 113 (3–4)<br>41 (4–5) | 154/0 | NR | NR | | | NR | NR |
| 2019 | | | | RFA | Ultra-sound guided | 154 | 103 (> 60) | 134/20 | 134/5 | 144/10 | 77 (< 20)<br>27 (≥ 400) | 111 (3–4)<br>43 (4–5) | 154/0 | | | NA | | NR | NR |
| Wang | China | PSM | Single tumor; ≤ 2 cm | LR | | 80 | 56 (41–62) | 66/14 | 74/6 | 66/14 | 17 (3–378) | 1.8 (1.5–2.0) | 80/0 | NR | NR | | 0.5–1.0 cm | 27ψ | NR |
| 2019 | | | | RFA | NA | 80 | 52 (44–62) | 64/16 | 74/6 | 62/18 | 34 (6–348) | 1.7 (1.5–2.0) | 80/0 | | | NA | | 27ψ | NR |
| K im | Korea | PSM | Single tumor; ≤ 2 cm | LR | | 48 | 56.2 ± 8.9 | 38/10 | 36/5 | 48/0 | 137.1 ± 255.3 | 1.57 ± 0.30 | 48/0 | NR | NR | | | 59.1 ± 37.3 | NR |
| 2019 | | | | RFA | Ultra-sound or CT guided | 48 | 58.7 ± 9.8 | 35/13 | 34/8 | 48/0 | 146.2 ± 280.7 | 1.53 ± 0.32 | 48/0 | | | | > 0.5 cm | 63.3 ± 30.4 | NR |
| Di Sandro | Italy | PSM | BCLC 0/A stage | LR | | 91 | 65 (62–72)ζ | NR | 15/58 | NR | 27 (≤ 5)<br>24 (5–22)<br>23 (> 22) | 20 (19–28)*ζ | 91/0 | NR | NR | NA | | 33 (17–56)ζ | NR |
| 2019 | | | | RFA | Percu-taneous ablation | 91 | 65 (56–76)ζ | NR | 13/62 | NR | 26 (≤ 5) 26 (5–22)<br>26 (> 22) | 20 (17–26)*ζ | 91/0 | | | | NA | 33 (17–56)ζ | NR |
| Min | Korea | PSM | Multiple, BCLC A stage | LR | | 20 | NR | NR | NR | NR | NR | NR | 0/20 | NR | NR | NA | | NR | NR |
| 2019 | | | | RFA | Ultra-sound or CT guided (*n* = 54) or intra-operative (*n* = 8) | 20 | NR | NR | NR | NR | NR | NR | 0/20 | NR | NR | | > 0.5 cm | NR | NR |
| Lee, S | Korea | PSM | Single tumor; ≤ 3 cm; perivascular | LR | | 62 | 55.2 ± 8.6 | NR | 47/9 | NR | 28.8 (7.4–135.8) ζ | NR | 62/0 | NR | NR | NA | | NR | NR |
| 2018 | | | | RFA | Ultra-sound guided | 62 | 56.0 ± 9.7 | NR | 49/8 | NR | 15 (5.7–73.2)ζ | NR | 62/0 | | | | > 0.5 cm | NR | NR |
| Lee,H | Korea | RCT (termi-nated) | Single tumor; 2–4 cm | LR | | 29 | 55.6 ± 7.9 | 23/6 | 20/3 | 29/0 | 1671.6 ± 5887.5 | 22 (≤ 3)<br>7 (3–4) | 29/0 | NR | NR | NA | | NR | NR |
| 2018 | | | | RFA | Ultra-sound guided | 34 | 56.1 ± 7.4 | 24/10 | 23/4 | 34/0 | 158.7 ± 286.9 | 26 (≤ 3)<br>8 (3–4) | 34/0 | | | | 0.5–1 cm | NR | NR |
| Kato | Japan | PSM | BCLC 0/A stage | LR | | 70 | 68 (39–79)$^{\eta}$ | 55/15 | NR | 69/1 | 13.3 (1.4–2813.3)η | 20 (9–30)*η | 59/11 | NAR | NR | NA | | NR | mOS: 59.5<br>mRFS: 26.1 |

**Table 1** (continued)

| Author | Region | Design | Inclusion criteria | Group | Modality of RFA | No. of patients | Age | Gender (M/F) | HBV/HCV | Child–Pugh A/B | AFP (ng/ml) | Tumor size (cm) | Solitary/multiple | 100% AR/NAR | 100% LH (Y/N) | Resection margin | Ablation margin | Follow-up (months) | Survival (median (95% *CI*)) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2018 | | | | RFA | Ultrasound or CT guided | 70 | 70(27–85)η | 53/17 | NR | 69/1 | 12.8 (2.0–4556.4)η | 20 (6–30)*η | 60/10 | | | | NA | NR | mOS: 45.4 mRFS: 16.1 |
| Chong | China | PSM | BCLC 0/A stage | LR | | 121 | 59.5 ± 9.5 | 101/20 | 110/0 | 121/0 | 31 (6–357) | 25 (20–36)*ζ | 121/0 | NR | NR | NA | | NR | NR |
| 2018 | | | | RFA | NA | 121 | 62.0 ± 10.0 | 95/26 | 106/0 | 121/0 | 17 (6–129) | 25 (20–35)*ζ | 121/0 | | | | NA | NR | NR |
| Ng | China | RCT | BCLC 0/A stage | LR | | 109 | 55 (31–82)η | 89/20 | 99/5 | 107/2 | 58 (1–4880)η | 2.9 (1–5)η | 99/10 | NR | NR | NA | | 93ψ | mOS: 118.8 mRFS: 39.5 |
| 2017 | | | | RFA | Ultrasound guided | 109 | 57 (23–78)η | 86/23 | 95/0 | 104/5 | 63.5 (2–18 070)η | 2.6 (1–5)η | 90/19 | | | | > 1 cm | 93ψ | mOS: 93.5 mRFS: 23.7 |
| Song | China | PSM | Single tumor; ≤ 4 cm | LR | | 78 | 48 (44–57)ζ | 70/8 | 73/NR | 78/0 | 38.5 (6.9, 281.9)ζ | 33 (≤ 2) 45 (2–4) | 78/0 | NR | Y | NA | | 31.2 (21.1–49.5) η | mOS: 75 (66.8–83.9) mRFS: 75 (26–51) |
| 2016 | | | | RFA | Ultrasound guided | 78 | 48 (43–58)ζ | 70/8 | 77/NR | 76/2 | 43.0 (6.0, 181.7)ζ | 40 (≤ 2) 38 (2–4) | 78/0 | | | | > cm | 43ψ | mOS: 70 (62.9–77.9) mRFS: 75 (26–51) |
| Liu | China | PSM | Single tumor; ≤ 2 cm | LR | | 79 | 61 ± 13 | 55/24 | 46/31 | NR | 136 ± 233 | NR | 79/0 | NR | NR | > 1 cm | | 44ψ | NR |
| 2016 | | | | RFA | Ultrasound guided | 79 | 63 ± 12 | 52/27 | 36/30 | NR | 127 ± 307 | NR | 79/0 | | | | NA | | NR |
| He | China | PSM | BCLC 0/A stage | LR | | 150 | 51.2 ± 12.1 | 124/26 | 150/0 | 146/4 | 29 (200–400) 121 (≥ 400) | 2.8 ± 1.0 | 138/12 | NR | NR | NA | | 58.2ψ | NR |
| 2016 | | | | RFA | Ultrasound guided | 109 | 52.8 ± 12.9 | 96/13 | 109/0 | 105/4 | 31 (200–400) 78 (≥ 400) | 2.6 ± 1.0 | 100/9 | | | | > 1 cm | 42.0ψ | NR |
| Yune | Korea | PSM | BCLC 0/A stage | LR | | 17 | 60.2¶ | 14/3 | 9/1 | 16/1 | 281,800¶ | 2.2¶ | NA | NAR | NR | NA | | 41ψ | NR |
| 2015 | | | | RFA | Ultrasound guided or laparoscopic | 17 | 64.1¶ | 11/6 | 11/2 | 16/1 | 79,500¶ | 1.8¶ | NA | | | | > 1 cm | 26ψ | NR |
| Lee1 | Korea | PSM | BCLC 0/A stage | LR | | 147 | 64 ± 10 | 110/37 | 69/40 | 147/0 | 443 ± 2036 | 126 (≤ 3) 21 (> 3) | 115/32 | NR | NR | NA | | NR | NR |
| 2015 | | | | RFA | NA | 147 | 64 ± 11 | 101/46 | 57/53 | 147/0 | 297 ± 1415 | 115 (≤ 3) 32 (> 3) | 121/26 | | | | NA | NR | NR |
| Lee2 | Korea | PSM | BCLC 0/A stage | LR | | 48 | 62 ± 12 | 37/11 | 20/12 | 35/12 | 332 ± 951 | 38 (≤ 3) 10 (> 3) | 41/7 | NR | NR | NA | | NR | NR |
| 2015 | | | | RFA | NA | 48 | 67 ± 12 | 32/16 | 11/16 | 32/15 | 526 ± 1517 | 35 (≤ 3) 13 (> 3) | 38/10 | | | | NA | NR | NR |

**Table 1** (continued)

| Author | Region | Design | Inclusion criteria | Group | Modality of RFA | No. of patients | Age | Gender (M/F) | HBV/HCV | Child–Pugh A/B | AFP (ng/ml) | Tumor size (cm) | Solitary/multiple | 100% AR/NAR | 100% LH (Y/N) | Resection margin | Ablation margin | Follow-up (months) | Survival (median (95% *CI*)) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Kang | China | PSM | BCLC 0/A stage | LR | | 99 | 54 (31–74)η | 77/22 | 83/8 | 95/4 | 15.2 (1.0–3412.2)η | 2 (1.1–3.0) | 99/0 | NAR | NR | NA | | NR | NR |
| 2015 | | | | RFA | Ultra-sound or CT guided | 99 | 55 (32–80)η | 77/22 | 83/8 | 95/4 | 25.6 (1.0–1873) η | 1.9 (1.1–3.0) | 99/0 | | | | > 0.5 cm | NR | NR |
| Jiang | China | PSM | Multiple, BCLC A stage | LR | | 140 | 53 ± 12 | 123/17 | 129/NR | 139/1 | 91 (< 400) | 2.4 ± 0.6 | 0/140 | NR | NR | NA | | NR | NR |
| 2015 | | | | RFA | Percu-taneous (*n* = 81), laparo-scopic (*n* = 19), and open (*n* = 60) | 140 | 55 ± 12 | 118/22 | 121/NR | 135/5 | 105 (< 400) | 2.3 ± 0.6 | 0/140 | | | | NA | NR | NR |
| Fang | China | RCT | BCLC 0/A stage | LR | | 60 | 53.5 ± 11.0 | 46/14 | 52/NR | 43/17 | 50 (> 200) | 22.8 ± 3.5* | 49/11 | NR | NR | 96.7% completed | | NR | NR |
| 2014 | | | | RFA | Ultra-sound or CT guided | 60 | 51.4 ± 8.1 | 42/18 | 55/NR | 32/23 | 52 (> 200) | 22.1 ± 5.2* | 41/19 | | | | 95% com-pleted | NR | NR |
| Pompili | Italy | PSM | Single tumor; ≤ 3 cm | LR | | 116 | 67 (41–83)η | 87/29 | 11/78 | NR | 11 (1–9000)η | 2.3 (0.8–3.0)η | 116/0 | NR | NR | NA | | NR | NR |
| 2013 | | | | RFA | NA | 116 | 69 (38–85)η | 92/24 | 17/78 | NR | 20 (2–1105)$^{\eta}$ | 2.3 (1.3–3.0)$^{\eta}$ | 116/0 | | | | NA | NR | NR |
| Wang | China | PSM | BCLC 0 stage | LR | | 52 | 35 (≤ 60) | 38/14 | 34/14 | NR | 11 (> 200) | NR | 52/0 | NR | NR | NA | | 2.3 (1.5 > 3.7) ζ,δ | NR |
| 2012 | | | | RFA | Ultra-sound guided | 52 | 29 (≤ 60) | 35/17 | 32/18 | NR | 10 (> 200) | NR | 52/0 | | | | NA | 2.5 (1.4–4.1) ζ,δ | NR |
| Huang | China | RCT | BCLC 0/A stage | LR | | 115 | 55.91 ± 12.68 | 85/30 | 104/6 | 106/9 | 32(> 400) | NR | 89/26 | NR | NR | > 1 cm | | 3.87 (0.1–) η,δ | NR |
| 2010 | | | | RFA | Ultra-sound guided | 115 | 56.57 ± 14.30 | 79/36 | 101/4 | 110/5 | 21 (> 400) | NR | 84/31 | | | | 0.5–1 cm | 3.1 (0.5–5) η,δ | NR |
| Chen | China | RCT | Single tumor; ≤ 5 cm | LR | | 90 | 49.4 ± 10.9 | 75/15 | NR | 90/0 | 60 (< 200)<br>6 (200–399)<br>24 (≥ 400) | 42 (≤ 3)<br>48 (> 3) | 90/0 | NR | NR | > 1 cm | | NR | NR |
| 2005 | | | | RFA | Ultra-sound guided | 71 | 51.9 ± 11.2 | 56/15 | NR | 71/0 | 40 (< 200)<br>8 (200–399)<br>23 (≥ 400) | 37 (≤ 3)<br>34 (> 3) | 71/0 | | | | NA | NR | NR |

*PSM* propensity score match,*RCT* randomized controlled trial, *BCLC* Barcelona Clinic Liver Cancer, *LR* liver resection, *RFA* radiofrequency ablation, *NR* not reported, *M*, male, *F* female, *HBV* hepatitis virus, B; *HCV* hepatitis virus C; *AFP* alpha-fetoprotein, *AR*, anatomic resection, *NAR* nonanatomic resection, *LH* laparoscopic hepatectomy, *CI* confidence interval, *OS* overall survival, *RFS* recurrence-free survival. *The unit of this data is millimeter. ζData were presented as median (interquartile range). ηData were presented as median (range). ψData were presented as median. ¶Data were presented as mean. δThe unit of this data is year

### Study definition and the target outcomes

Solitary tumors with a size of less than 5 cm and maximally three nodules with a size of less than 3 cm were considered early-stage HCC [2]. Herein, OS and DFS were considered as primary time-to-event outcomes. Data from multivariate Cox proportional hazard models were used to compute HRs and 95% confidence intervals (CIs) to estimate OS and DFS. The approach introduced by Tierney et al. was utilized as an alternative for computing HRs from Kaplan–Meier curves in case of the absence of survival data, especially the absence of HRs or 95% CIs [34]. Major complications were defined as Clavien-Dindo grade III or above [35].

### Statistical analysis

An inverse variance model was utilized to analyze OS and DFS, particularly log-transformed HRs and 95% Cis. The Mantel–Haenszel method was utilized for calculating the odds ratios (OR) and 95% CI of dichotomous outcome variables. Heterogeneity was assessed using the $\chi^2$ method ($I^2$ of 25% as low heterogeneity; 50% as moderate heterogeneity). The selection of the test model was based on the heterogeneity level with the random-effects model for $I^2 > 50\%$ [36]. The robustness of the conclusion was assessed by the sensitivity analysis. A funnel plot was used to visually illustrate the publication bias through regressive approaches introduced by Egger and Begg. Meta-regression was carried out based on the published year, sample size, study design, region, and inclusion criteria. Subgroup analysis was conducted considering the tumor size and number (single tumor less than 2 cm or 3 cm or 5 cm), laparoscopic hepatectomy (LH), nonanatomic resection (NAR), anatomic resection (AR), modality of RFA, surgical margin, ablation margin, and the results of meta-regression. The level of statistical significance was set at $P < 0.05$. All the data analyses were performed with R (version 4.1.2).

## Results

### Study search and selection

Database searching yielded a total of 5257 records, with 5087 excluded after reviewing the titles and abstracts (Fig. 1). For the remaining articles, 144 were further excluded because they did not meet the inclusion criteria. Finally, 36 studies were included in the meta-analysis (11, 14, 15, 24–30, 37–62).

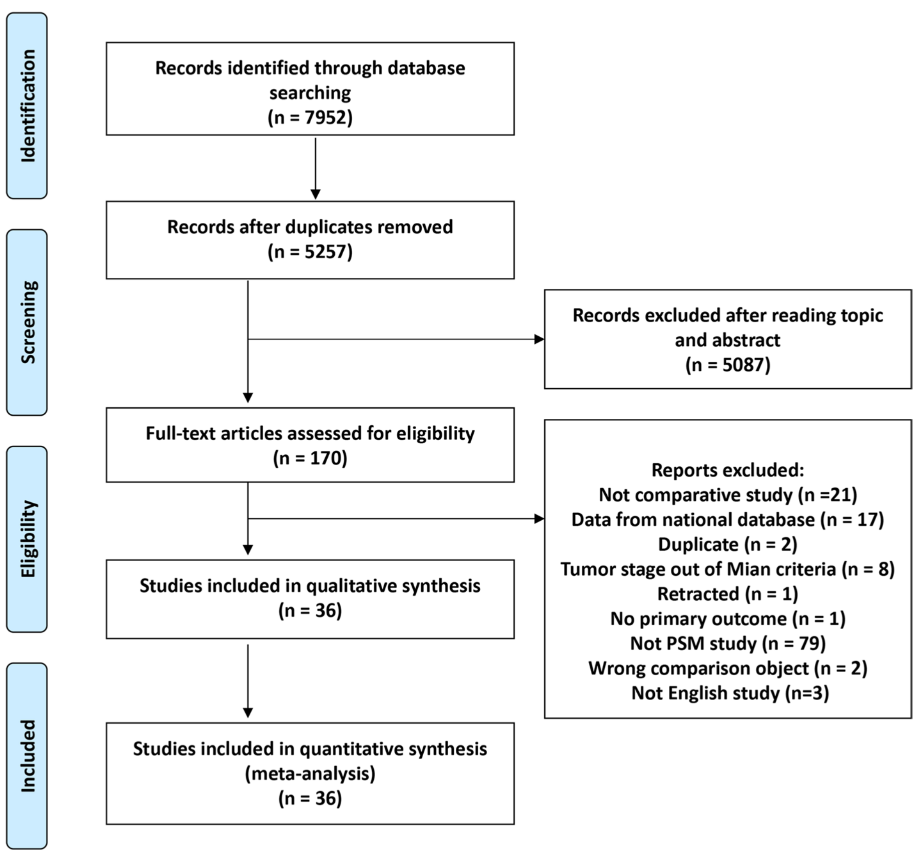


**Fig. 1** Flow chart of study selection

### Study characteristics

The included 36 studies consisted of 6 RCTs and 30 PSM studies consisting of 38 datasets, involving a total of 7384 patients, with 3694 patients treated with LR and 3690 patients treated with RFA. These studies were conducted in China ($n=20$), Korea ($n=10$), Japan ($n=2$), Italy ($n=3$), and France and Italy (multicenter study) ($n=1$). The quality of the included studies was assessed, and the results are shown in Supplementary materials S2 and S3.

Patient characteristics are shown in Table 1. Although all patients were eligible for BCLC 0/A, the inclusion criteria for tumor size and number varied among the included studies. Four studies involving 524 patients included BCLC 0 patients, and another four involving 638 patients included patients with single tumors ≤ 3 cm. Three studies compared RFA with NAR, and one compared RFA with AR. Six studies reported the comparison between RFA with laparoscopic hepatectomy (LH).

### OS, DFS, and recurrence

The pooled analysis demonstrated that ES-HCC patients with a low level of heterogeneity undergoing RFA had significantly worse OS than those undergoing LR (*HR*, 1.22; 95% *CI*, 1.13–1.31; $P<0.01$; $I^2=32\%$) (Fig. 2). In addition, ES-HCC patients with a moderate level of heterogeneity undergoing RFA had significantly worse DFS than those undergoing LR (*HR*, 1.56; 95% *CI*, 1.39–1.74; $P<0.01$; $I^2=50\%$) (Fig. 2).

As shown in Supplementary S4, the survival and DFS rates were better in the LR group except for 1-year survival rates. A few studies reported that overall recurrence rate and 3- and 5-year recurrence rates were much higher in the RFA group (*OR*, 9.34; 95% *CI*, 1.54–56.59; $P<0.01$; $I^2=91$; *OR*, 4.78; 95% *CI*, 2.29–9.98; $P<0.01$; $I^2=67\%$, respectively).

### Sensitivity analysis and publication bias

The sensitivity analysis showed that the results of OS and DFS were robust (Supplementary materials S5). Funnel plots of OS and DFS combined with Begg's and Egger's tests indicated no significant publication bias (Supplementary materials S6).

### Meta-regression and subgroup analysis

Meta-regression indicated that published year, sample size, study design, region, inclusion criteria, the proportion of solitary tumor, and modality of RFA significantly affected the results (Supplementary materials S7). Details of the subgroup analysis are shown in Table 2 and Supplementary material S8. The cumulative result of RCTs indicated no significant difference between RFA and LR in OS or DFS, while the cumulative result of PSM studies showed that LR is superior to RFA in both OS and DFS. For patients with BCLC 0 HCC, RFA and LR have comparable effects on OS and DFS. When the single tumor diameter increased

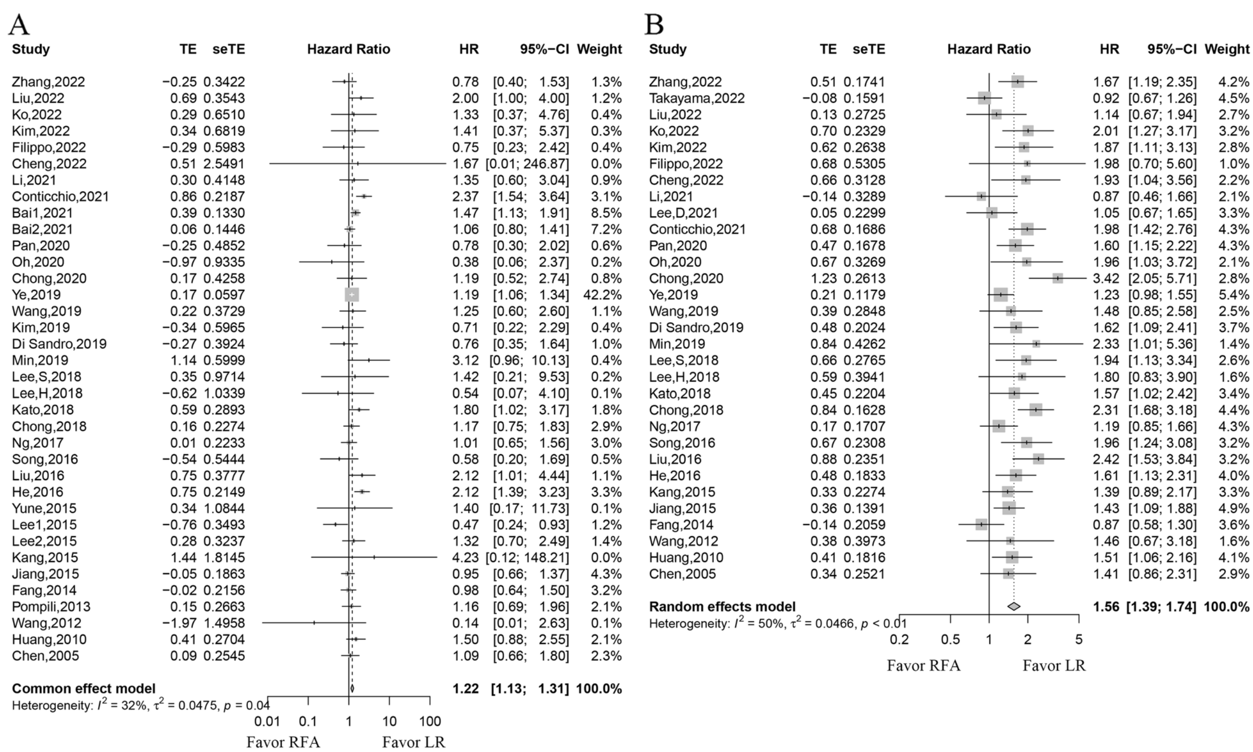


**Fig. 2** Forest plot for hazard ratios of overall survival (OS) and disease-free survival (DFS). **A** forest plot for OS. **B** Forest plot for DFS

**Table 2** Subgroup analysis of overall survival and disease-free survival

| Subgroup | No. of datasets | HR | 95% *CI* | $I^2$ | Model |
|---|---|---|---|---|---|
| OS | | | | | |
| Single tumor ≤ 2 cm | 4 | 1.40 | 0.93–2.11 | 0% | Fixed |
| Single tumor ≤ 3 cm | 8 | 1.19 | 0.90–1.58 | 0% | Fixed |
| Single tumor ≤ 5 cm | 17 | 1.17 | 1.05–1.29 | 0% | Fixed |
| LH | 6 | 1.33 | 0.87–2.03 | 0% | Fixed |
| NAR | 3 | 1.81 | 1.05–3.10 | 0% | Fixed |
| PSM | 31 | 1.24 | 1.14–1.34 | 38% | Fixed |
| RCT | 5 | 1.09 | 0.86–1.37 | 0% | Fixed |
| Sample size < 100 | 23 | 1.14 | 0.95–1.36 | 0% | Fixed |
| Sample size > 100 | 13 | 1.26 | 1.03–1.53 | 63% | Random |
| Asia | 32 | 1.2 | 1.11–1.30 | 22% | Fixed |
| Europe | 4 | 1.24 | 0.70–2.20 | 69% | Random |
| China | 21 | 1.21 | 1.11–1.31 | 21% | Fixed |
| Published after 2015 | 26 | 1.26 | 1.16–1.37 | 33% | Fixed |
| Published on or before 2015 | 10 | 1.03 | 0.86–1.24 | 14% | Fixed |
| Surgical margin > 1 cm | 4 | 1.25 | 0.93–1.68 | 35% | Fixed |
| Ablation margin > 0.5 cm | 9 | 1.29 | 1.09–1.53 | 0% | Fixed |
| Ablation margin > 1 cm | 6 | 1.12 | 0.67–1.86 | 54% | Random |
| RFS | | | | | |
| Single tumor ≤ 2 cm | 3 | 1.51 | 0.85–2.69 | 70% | Random |
| Single tumor ≤ 3 cm | 8 | 1.45 | 1.11–1.90 | 66% | Random |
| Single tumor ≤ 5 cm | 15 | 1.55 | 139–1.73 | 30% | Fixed |
| LH | 7 | 1.78 | 1.32–2.39 | 59% | Random |
| NAR | 2 | 1.48 | 1.09–2.02 | 0% | Fixed |
| PSM | 25 | 1.64 | 1.51–1.78 | 35% | Fixed |
| RCT | 6 | 1.15 | 0.98–1.35 | 38% | Fixed |
| Sample size < 100 | 20 | 1.68 | 1.50–1.88 | 33% | Fixed |
| Sample size > 100 | 11 | 1.42 | 1.20–1.67 | 62% | Random |
| Asia | 28 | 1.54 | 1.36–1.73 | 52% | Random |
| Europe | 3 | 1.83 | 1.43–2.34 | 0% | Fixed |
| China | 19 | 1.54 | 1.34–1.77 | 54% | Random |
| Published after 2015 | 25 | 1.63 | 1.43–1.86 | 53% | Random |
| Published on or before 2015 | 6 | 1.52 | 1.41–1.64 | 3% | Fixed |
| Surgical margin > 1 cm | 4 | 1.69 | 1.38–2.06 | 8% | Fixed |
| Ablation margin > 0.5 cm | 7 | 1.42 | 1.22–1.66 | 0% | Fixed |
| Ablation margin > 1 cm | 5 | 1.56 | 1.31–1.86 | 3% | Fixed |

*HR* hazard ratio, *OS* overall survival, *LH* laparoscopic hepatectomy, *NAR* nonanatomic resection, *PSM* propensity score match, *RCT* randomized controlled trial, *DFS* disease-free survival

to 3 cm, the OS between the RFA and LR groups was similar, while the DFS was better in the LR group. When the single tumor diameter increased to 5 cm, the OS and DFS were better in the LR group. Four studies explicitly reported resection marigin is > 1 cm, subgroup analysis showed similar OS between two groups but better DFS in the LR group. Nine studies and six studies explicitly reported ablation margins are > 0.5 cm and > 1 cm, respectively. Subgroup analysis showed that when ablation margin is > 0.5 cm, LR was superior to RFA on OS; however, the advantage of LR disappeared when ablation margin is larger than 1 cm. LR was better than RFA in DFS, whether the ablation margin was larger than 0.5 cm or 1 cm. For OS, the inconsistency was also found in other subgroups, including the subgroup of sample size < 100 or > 100, Asia or Europe, and published before or after 2015. Besides, subgroup analysis also showed that LR was superior to RFA on DFS. RFA can be performed with ultrasound, CT guidance, or open or laparoscopic surgery. The modalities of RFA were various among included studies. Subgroup analysis showed that patients receiving RFA performed with ultrasound guidance had worse OS and DFS compared with LR. After mixing a percentage of patients with CT-guided RFA into ultrasound-guided RFA, OS and DFS were similar between the two groups.

#### Morbidity and hospital stay

The incidences of postoperative overall and major complications were statistically lower in the RFA group than in the LR group (*OR*, 0.32; 95% *CI*, 0.21–0.50; $P<0.01$; $I^2=57\%$; *OR*, 0.26; 95% *CI*, 0.11–0.62; $P<0.01$; $I^2=60\%$, respectively) (Fig. 3). The length of hospital stay was 5.75 days shorter in the RFA group than in the LR group (Fig. 4).

## Discussion

In this meta-analysis, meta-analysis showed that ES-HCC patients undergoing LR had better OS and DFS than those undergoing RFA. However, ES-HCC is a complex conceptual set of HCC with different diameters (0–5 cm) and different numbers (1–3 tumors). Additionally, details related to hepatectomy (including anatomic hepatectomy, laparoscopic hepatectomy, tumor resection margin) and radiofrequency ablation (including radiofrequency ablation guidance, ablation margin, and ablation equipment) will affect

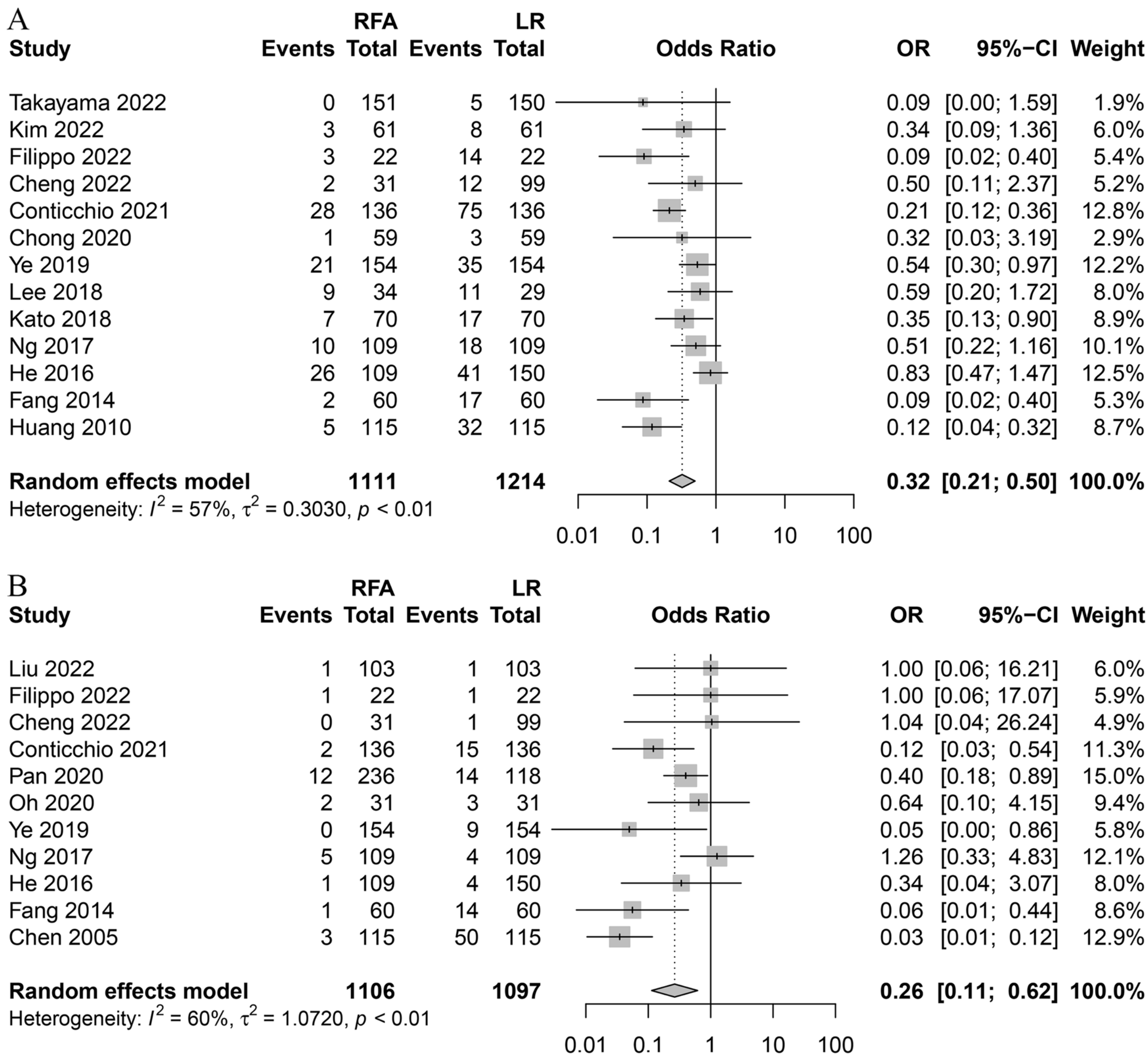


**Fig. 3** Forest plot for overall and major complications. **A** Forest plot for total complication. **B** Forest plot for major complication

| Study | RFA Total | RFA Mean | RFA SD | LR Total | LR Mean | LR SD | MD | 95%−CI | Weight |
|---|---|---|---|---|---|---|---|---|---|
| Zhang 2022 | 67 | 3.96 | 2.5600 | 67 | 8.93 | 2.4600 | −4.97 | [ −5.82; −4.12] | 6.7% |
| Takayama 2022 | 151 | 11.05 | 6.7365 | 150 | 17.35 | 8.2340 | −6.30 | [ −8.00; −4.60] | 6.2% |
| Kim 2022 | 61 | 5.10 | 2.2000 | 61 | 8.90 | 12.9000 | −3.80 | [ −7.08; −0.52] | 4.7% |
| Filippo 2022 | 22 | 2.36 | 2.3589 | 22 | 7.36 | 7.3589 | −5.00 | [ −8.23; −1.77] | 4.8% |
| Cheng 2022 | 31 | 3.06 | 2.2500 | 99 | 6.05 | 4.5700 | −2.99 | [ −4.19; −1.79] | 6.5% |
| Conticchio 2021 | 136 | 2.91 | 2.9127 | 136 | 15.67 | 38.7643 | −12.76 | [−19.29; −6.22] | 2.5% |
| Pan 2020 | 236 | 3.70 | 2.9836 | 118 | 5.35 | 2.2516 | −1.65 | [ −2.21; −1.09] | 6.8% |
| Chong 2020 | 59 | 2.70 | 1.3000 | 59 | 4.60 | 1.2000 | −1.90 | [ −2.35; −1.45] | 6.9% |
| Ye 2019 | 154 | 2.38 | 0.8900 | 154 | 8.90 | 3.3300 | −6.52 | [ −7.06; −5.98] | 6.8% |
| Di Sandro 2019 | 91 | 3.35 | 3.3521 | 91 | 8.35 | 3.7665 | −5.00 | [ −6.04; −3.96] | 6.6% |
| Kato 2018 | 70 | 4.14 | 4.1418 | 70 | 12.70 | 10.9710 | −8.55 | [−11.30; −5.81] | 5.2% |
| Ng 2017 | 109 | 5.43 | 5.4311 | 109 | 10.07 | 10.0741 | −4.64 | [ −6.79; −2.49] | 5.8% |
| Song 2016 | 78 | 10.35 | 10.3525 | 78 | 15.35 | 15.3525 | −5.00 | [ −9.11; −0.89] | 4.0% |
| He 2016 | 147 | 5.09 | 3.5000 | 147 | 11.42 | 4.2400 | −6.33 | [ −7.22; −5.44] | 6.7% |
| Fang 2014 | 60 | 4.30 | 1.5000 | 60 | 11.80 | 3.1000 | −7.50 | [ −8.37; −6.63] | 6.7% |
| Huang 2010 | 115 | 6.92 | 3.4600 | 115 | 15.36 | 4.2100 | −8.44 | [ −9.44; −7.44] | 6.6% |
| Chen 2005 | 71 | 9.18 | 3.0600 | 90 | 19.70 | 5.6100 | −10.52 | [−11.88; −9.16] | 6.4% |
| **Random effects model** | **1658** | | | **1626** | | | **−5.75** | **[ −7.02; −4.47]** | **100.0%** |

Heterogeneity: $I^2 = 97\%$, $\tau^2 = 6.1006$, $p < 0.01$

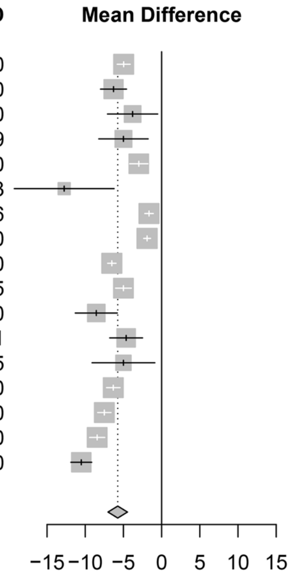


**Fig. 4** Forest plot for hospital stay

the survival of patients with HCC. Subgroup analysis showed that RFA and LR can provide similar OS and RFS for very early stage HCC (single tumor and the diameter less or equal to 2 cm). Additionally, when the tumor was single and less or equal to 3 cm, or the ablation margin wa larger than 1 cm, the OS provided by RFA and LR was similar, although the RFS was still better in LR. The incidence of postoperative complications was significantly lower, and hospitalization was significantly shorter among ES-HCC patients undergoing RFA.

The primary advantage of RFA over LR is less invasiveness. RFA causes minor damage to the surrounding healthy liver parenchyma, thus maximally preserving the liver remnant [37]. As a result, the complication rates were much lower, and the length of hospital stay was much shorter.

The main reason for the inferiority of RFA to LR in long-term survival is the higher local recurrence rate related to incomplete ablation [38]. The efficacy of RFA could be affected by several factors, including tumor number, tumor size, tumor location, RFA mode, RFA method, the level of regional medical care, and the experience of doctors [6, 39–42]. The insufficient ablation led to a high local recurrence rate [39]. On the other hand, LR could remove both the tumor and its micro neoplastic embolus by radically resecting primary cancer and adjacent liver parenchymal to guarantee a negative margin [43, 44]. In the subgroup analysis, we found that RFA can achieve similar OS to LR when the ablation margin was lager than 1 cm. Hence, the complete removal of the primary tumor and potential micrometastasis by LR might explain cothe superior long-term prognosis of early-stage HCC patients in the LR group.

Several meta-analyses have been available to compare the effects of RFA versus LR for HCC. Xu et al. performed a meta-analysis of five RCTs comparing survival outcomes of patients with small HCC who underwent LR or RFA [31]. RFA led to decreased overall survival compared with LR at 5 years, but the trial sequential analysis indicated that additional trials were necessary to confirm this conclusion. Additionally, time-to-event outcomes are most appropriately analyzed using HR [34]. Another recently published network meta-analysis by Zhang et al., which included RCTs and PSM studies, showed that LR is superior to RFA in OS and DFS [45]. The results are consistent with ours. However, their meta-analysis did not include one RCT and several PSM studies newly published in 2022. As far as we know, our meta-analysis is the most updated, with a maximum number of high-quality studies being included. More than 11,000 ES-HCC patients from 5 countries in the east and west were included to make the results more reliable and clinically meaningful. Moreover, sensitivity, subgroup, and meta-regression analyses provided ample evidence supporting our conclusion. The most important is that we focused on special subgroups which previous meta-analysis not did, including tumor number, tumor size, surgical margin, ablation margin, and even different guidance for RFA. Recently, a study based on Surveillance, Epidemiology, and End Results Program

(SEER) database promped that RFA is an inferior option for solitary hepatocellular carcinoma ≤ 5 cm without cirrhosis [46]. This is an interesting and important finding because it lets us know that for HCC patients without cirrhosis, surgery is far a more suitable treatment than RFA. Because of insufficient data of liver cirrhosis in most of included studies and the proportion of liver cirrhosis of those studies reported, this data ranged from 2.2 to 94.1%, and we cannot confirm this view of the recent study. More well-designed studies are needed to verify this conclusion.

It should be noted that there are limitations for this study. First, we included both RCTs and PSM studies. Although the propensity score matching method could reduce baseline differences between groups, the deviations could not be eliminated compared with RCTs. Second, tumor heterogeneity could not be avoided. Although all the cases were ES-HCC, tumor number and size varied among patients in the included studies. Hence, we conducted a subgroup analysis; however, we found no significant difference between the two groups in OS among patients with a single tumor size of < 3 cm. However, extended subgroup analysis based on tumor number and tumor size is limited due to limited data. Third, the proportion of open LR or LH, anatomic or non-anatomic LR, are also inconsistent among included articles. Furthermore, with the development of RFA technology, various RFA techniques were used in different studies at different times. The influence of such heterogeneity has not been determined.

## Conclusion

In conclusion, this meta-analysis showed that LR provided better OS and DFS for patients with early-stage HCC. However, RFA and LR probably had similar effects on OS in patients with solitary HCC less than 3 cm or when the ablation margin was larger than 1 cm which need more studies to confirm. The effects of different modalities of RFA on long-term survival are needed for further assessment.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12957-024-03330-8.

**Additional file 1** PRISMA checklist

**Additional file 2 Supplementary material: Supplementary material S1**: Search strategy. **Supplementary material S2** NOS score for PSM studies. **Supplementary material S3** Risk bias of RCTs. **Supplementary material S4** 1-,3-,and 5-year survival rate, disease-free survival rate, and recurrence rate. **Supplementary material S5** Forest plot for sensitivity analysis of overall survival and disease-free survival. **Supplementary material S6** Funnel plot for overall survival and disease-free survival. **Supplementary material S7** Meta-regression. OS, overall survival; DFS, disease-free survival; RFA, radiofrequency ablation. **Supplementary material S8** Subgroup analysis for OS and DFS based on modality of RFA


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### Authors' contributions

L.H. and J.L. extracted the data and assessed the quality of included studies. L.H. and A.W. analysised the data and prepared the figures. L.H. and X.S. prepared the tables. L.H. and Y.Q. wrote the manuscript. All authors reviewed the manuscript.

### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.


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### References


1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49.
2. Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology. 2018;67(1):358–80.
3. EASL Clinical Practice Guidelines. management of hepatocellular carcinoma. J Hepatol. 2018;69(1):182–236.
4. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet. 2018;391(10127):1301–14.
5. Lee DH, Lee JM, Lee JY, Kim SH, Yoon JH, Kim YJ, et al. Radiofrequency ablation of hepatocellular carcinoma as first-line treatment: long-term results and prognostic factors in 162 patients with cirrhosis. Radiology. 2014;270(3):900–9.
6. Shiina S, Tateishi R, Arano T, Uchino K, Enooku K, Nakagawa H, et al. Radiofrequency ablation for hepatocellular carcinoma: 10-year outcome and prognostic factors. Am J Gastroenterol. 2012;107(4):569–77 quiz 78.
7. N'Kontchou G, Mahamoudi A, Aout M, Ganne-Carrié N, Grando V, Coderc E, et al. Radiofrequency ablation of hepatocellular carcinoma: long-term results and prognostic factors in 235 Western patients with cirrhosis. Hepatology. 2009;50(5):1475–83.
8. Livraghi T, Meloni F, Di Stasi M, Rolle E, Solbiati L, Tinelli C, et al. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: Is resection still the treatment of choice? Hepatology. 2008;47(1):82–9.
9. Ikeda K, Kobayashi M, Kawamura Y, Imai N, Seko Y, Hirakawa M, et al. Stage progression of small hepatocellular carcinoma after radical therapy: comparisons of radiofrequency ablation and surgery using the Markov model. Liver Int. 2011;31(5):692–9.
10. Peng ZW, Lin XJ, Zhang YJ, Liang HH, Guo RP, Shi M, et al. Radiofrequency ablation versus hepatic resection for the treatment of

hepatocellular carcinomas 2 cm or smaller: a retrospective comparative study. Radiology. 2012;262(3):1022–33.
11. Pompili M, Saviano A, de Matthaeis N, Cucchetti A, Ardito F, Federico B, et al. Long-term effectiveness of resection and radiofrequency ablation for single hepatocellular carcinoma ≤3 cm Results of a multicenter Italian survey. J Hepatol. 2013;59(1):89–97.
12. Tohme S, Geller DA, Cardinal JS, Chen HW, Packiam V, Reddy S, et al. Radiofrequency ablation compared to resection in early-stage hepatocellular carcinoma. HPB (Oxford). 2013;15(3):210–7.
13. Yang HJ, Lee JH, Lee DH, Yu SJ, Kim YJ, Yoon JH, et al. Small single-nodule hepatocellular carcinoma: comparison of transarterial chemoembolization, radiofrequency ablation, and hepatic resection by using inverse probability weighting. Radiology. 2014;271(3):909–18.
14. Jiang L, Yan L, Wen T, Li B, Zeng Y, Yang J, et al. Comparison of outcomes of hepatic resection and radiofrequency ablation for hepatocellular carcinoma patients with multifocal tumors meeting the Barcelona-Clinic Liver Cancer stage A classification. J Am Coll Surg. 2015;221(5):951–61.
15. Kang TW, Kim JM, Rhim H, Lee MW, Kim YS, Lim HK, et al. Small hepatocellular carcinoma: radiofrequency ablation versus nonanatomic resection–propensity score analyses of long-term outcomes. Radiology. 2015;275(3):908–19.
16. Ueno M, Hayami S, Shigekawa Y, Kawai M, Hirono S, Okada K, et al. Prognostic impact of surgery and radiofrequency ablation on single nodular HCC 5 cm: cohort study based on serum HCC markers. J Hepatol. 2015;63(6):1352–9.
17. Mohkam K, Dumont PN, Manichon AF, Jouvet JC, Boussel L, Merle P, et al. No-touch multibipolar radiofrequency ablation vs. surgical resection for solitary hepatocellular carcinoma ranging from 2 to 5cm. Journal of Hepatology. 2018;68(6):1172–80.
18. Hsiao CY, Hu RH, Ho CM, Wu YM, Lee PH, Ho MC. Surgical resection versus radiofrequency ablation for Barcelona Clinic Liver Cancer very early stage hepatocellular carcinoma: long-term results of a single-center study. Am J Surg. 2020;220(4):958–64.
19. Ogiso S, Seo S, Eso Y, Yoh T, Kawai T, Okumura S, et al. Laparoscopic liver resection versus percutaneous radiofrequency ablation for small hepatocellular carcinoma. HPB. 2021;23(4):533–7.
20. Yun WK, Choi MS, Choi D, Rhim HC, Joh JW, Kim KH, et al. Superior long-term outcomes after surgery in Child-Pugh class a patients with single small hepatocellular carcinoma compared to radiofrequency ablation. Hep Intl. 2011;5(2):722–9.
21. Lai EC, Tang CN. Radiofrequency ablation versus hepatic resection for hepatocellular carcinoma within the Milan criteria–a comparative study. Int J Surg. 2013;11(1):77–80.
22. Chu HH, Kim JH, Kim PN, Kim SY, Lim YS, Park SH, et al. Surgical resection versus radiofrequency ablation very early-stage HCC (</=2 cm single HCC): a propensity score analysis. Liver Int. 2019;39(12):2397–407.
23. Lin CH, Ho CM, Wu CH, Liang PC, Wu YM, Hu RH, et al. Minimally invasive surgery versus radiofrequency ablation for single subcapsular hepatocellular carcinoma </= 2 cm with compensated liver cirrhosis. Surg Endosc. 2020;34(12):5566–73.
24. Pan YX, Long Q, Yi MJ, Chen JB, Chen JC, Zhang YJ, et al. Radiofrequency ablation versus laparoscopic hepatectomy for hepatocellular carcinoma: a real world single center study. Eur J Surg Oncol. 2020;46:548–59 (**(4 Pt A)**).
25. Takayama T, Hasegawa K, Izumi N, Kudo M, Shimada M, Yamanaka N, et al. Surgery versus radiofrequency ablation for small hepatocellular carcinoma: a randomized controlled trial (SURF trial). Liver cancer. 2022;11(3):209–18.
26. Lee HW, Lee JM, Yoon JH, Kim YJ, Park JW, Park SJ, et al. A prospective randomized study comparing radiofrequency ablation and hepatic resection for hepatocellular carcinoma. Ann Surg Treat Res. 2018;94(2):74–82.
27. Ng KKC, Chok KSH, Chan ACY, Cheung TT, Wong TCL, Fung JYY, et al. Randomized clinical trial of hepatic resection versus radiofrequency ablation for early-stage hepatocellular carcinoma. Br J Surg. 2017;104(13):1775–84.
28. Fang Y, Chen W, Liang X, Li D, Lou H, Chen R, et al. Comparison of long-term effectiveness and complications of radiofrequency ablation with hepatectomy for small hepatocellular carcinoma. J Gastroenterol Hepatol. 2014;29(1):193–200.
29. Huang J, Yan L, Cheng Z, Wu H, Du L, Wang J, et al. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. Ann Surg. 2010;252(6):903–12.
30. Chen MS, Li JQ, Zheng Y, Guo RP, Liang HH, Zhang YQ, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Ann Surg. 2006;243(3):321–8.
31. Xu XL, Liu XD, Liang M, Luo BM. Radiofrequency ablation versus hepatic resection for small hepatocellular carcinoma: systematic review of randomized controlled trials with meta-analysis and trial sequential analysis. Radiology. 2018;287(2):461–72.
32. Knobloch K, Yoon U, Vogt PM. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and publication bias. J Craniomaxillofac Surg. 2011;39(2):91–2.
33. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343: d5928.
34. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007;8:16.
35. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205–13.
36. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–60.
37. Lau WY, Lai EC. The current role of radiofrequency ablation in the management of hepatocellular carcinoma: a systematic review. Ann Surg. 2009;249(1):20–5.
38. Feng K, Yan J, Li X, Xia F, Ma K, Wang S, et al. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. J Hepatol. 2012;57(4):794–802.
39. Chen J, Peng K, Hu D, Shen J, Zhou Z, Xu L, et al. Tumor location influences oncologic outcomes of hepatocellular carcinoma patients undergoing radiofrequency ablation. Cancers (Basel). 2018;10(10):378.
40. Schullian P, Johnston E, Laimer G, Putzer D, Eberle G, Amann A, et al. Frequency and risk factors for major complications after stereotactic radiofrequency ablation of liver tumors in 1235 ablation sessions: a 15-year experience. Eur Radiol. 2021;31(5):3042–52.
41. Kim TH, Lee JM, Lee DH, Joo I, Park SJ, Yoon JH. Can "no-touch" radiofrequency ablation for hepatocellular carcinoma improve local tumor control? Systematic review and meta-analysis Eur Radiol. 2023;33(1):545–54.
42. Hocquelet A, Aubé C, Rode A, Cartier V, Sutter O, Manichon AF, et al. Comparison of no-touch multi-bipolar vs. monopolar radiofrequency ablation for small HCC. J Hepatol. 2017;66(1):67–74.
43. Chen ZH, Zhang XP, Feng JK, Li LQ, Zhang F, Hu YR, et al. Actual long-term survival in hepatocellular carcinoma patients with microvascular invasion: a multicenter study from China. Hepatol Int. 2021;15(3):642–50.
44. Hu H, Qi S, Zeng S, Zhang P, He L, Wen S, et al. Importance of microvascular invasion risk and tumor size on recurrence and survival of hepatocellular carcinoma after anatomical resection and non-anatomical resection. Front Oncol. 2021;11: 621622.
45. Zhang YL, Qin YL, Dong P, Ning HF, Wang GZ. Liver resection, radiofrequency ablation, and radiofrequency ablation combined with transcatheter arterial chemoembolization for very- early- and early-stage hepatocellular carcinoma: a systematic review and Bayesian network meta-analysis for comparison of efficacy. Front Oncol. 2022;1212:991944.
46. Dong SC, Bai DS, Wang FA, Jin SJ, Zhang C, Zhou BH, et al. Radiofrequency ablation is an inferior option to liver resection for solitary hepatocellular carcinoma ≤ 5 cm without cirrhosis: a population-based study with stratification by tumor size. Hepatobiliary Pancreat Dis Int. 2023;22(6):605–14.

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