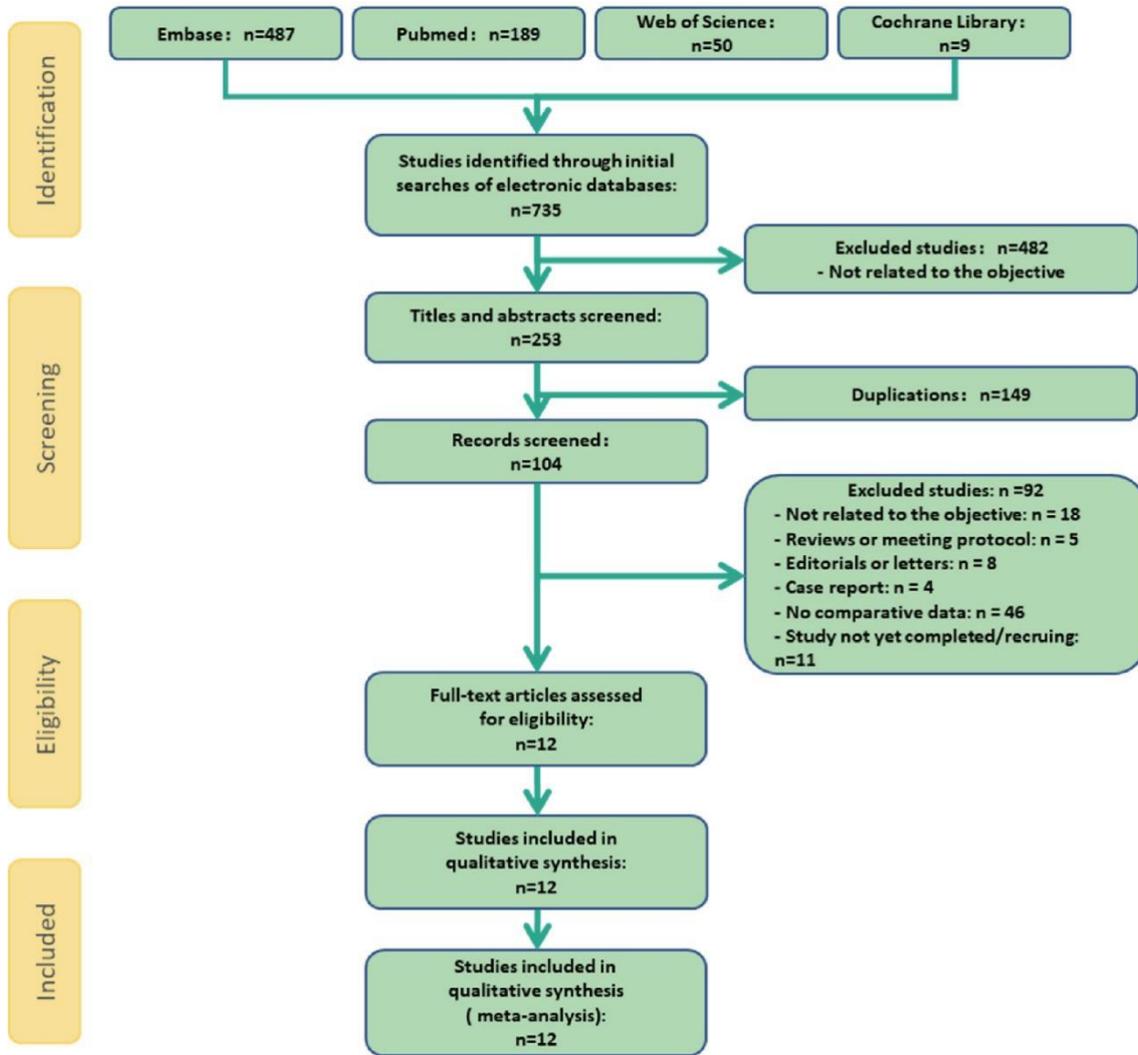
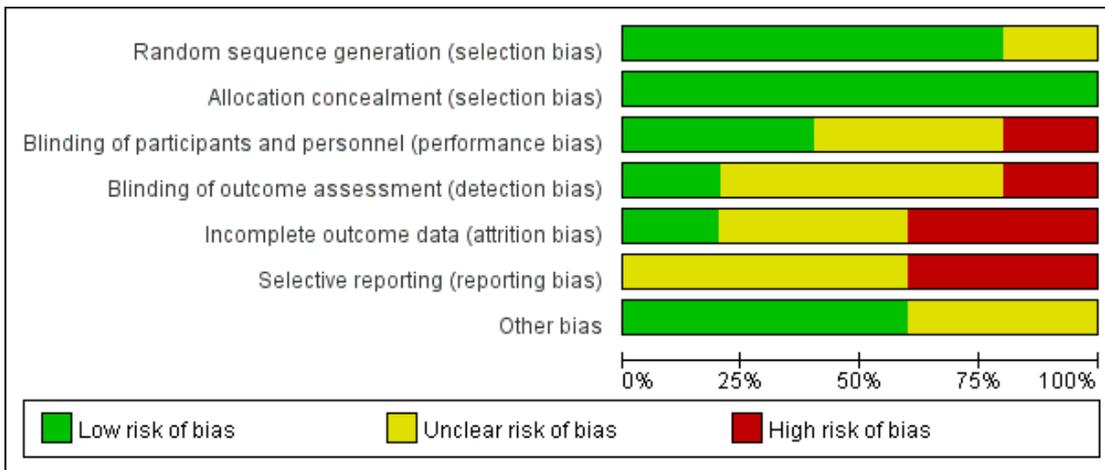


Supplemental materials



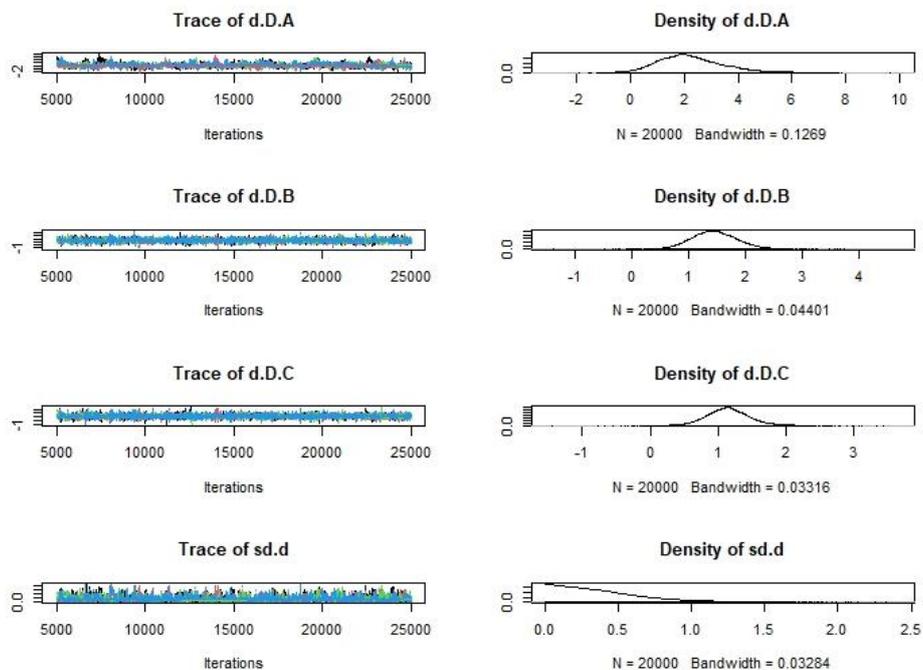
Supplemental Figure 1 The preferred reporting items for systematic reviews and Meta-Analyses (PRISMA) flow diagram.



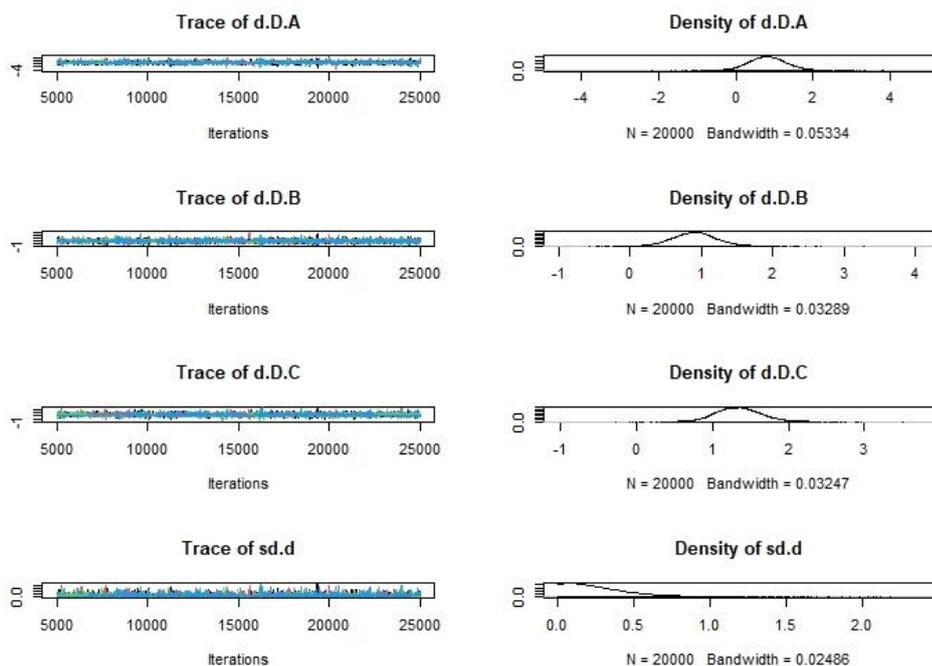
| | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|----------|---|---|---|---|--|--------------------------------------|------------|
| Shi 2022 | + | + | + | ? | + | - | + |
| Sun 2019 | + | + | ? | + | - | - | ? |
| Wei 2019 | + | + | + | ? | ? | ? | + |
| Wei 2023 | + | + | ? | - | - | ? | + |
| Yu 2014 | ? | + | - | ? | ? | ? | ? |

Supplemental Figure 2 Summarized risk of the included randomized controlled trials and Potential risk of bias of each included randomized controlled trials.

A

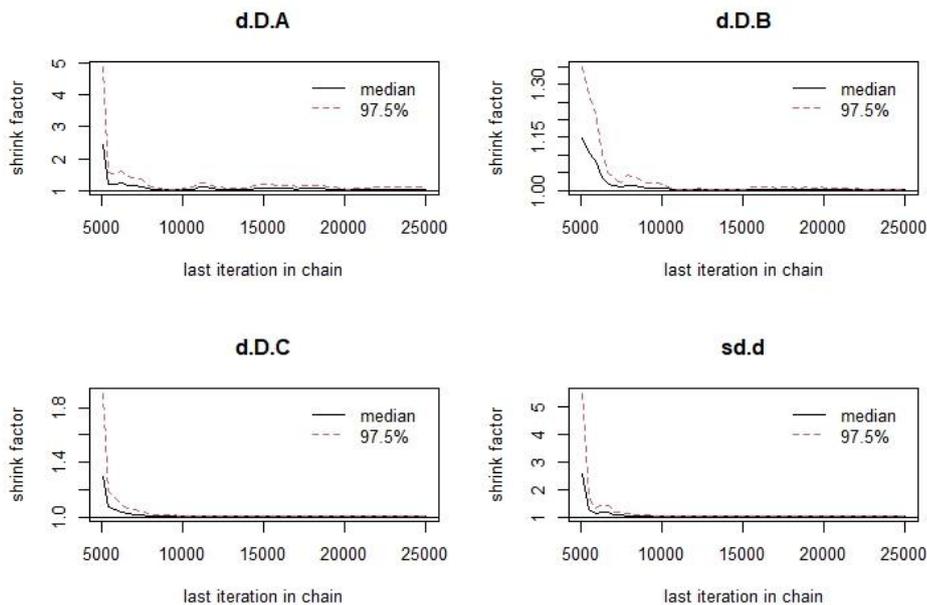


B

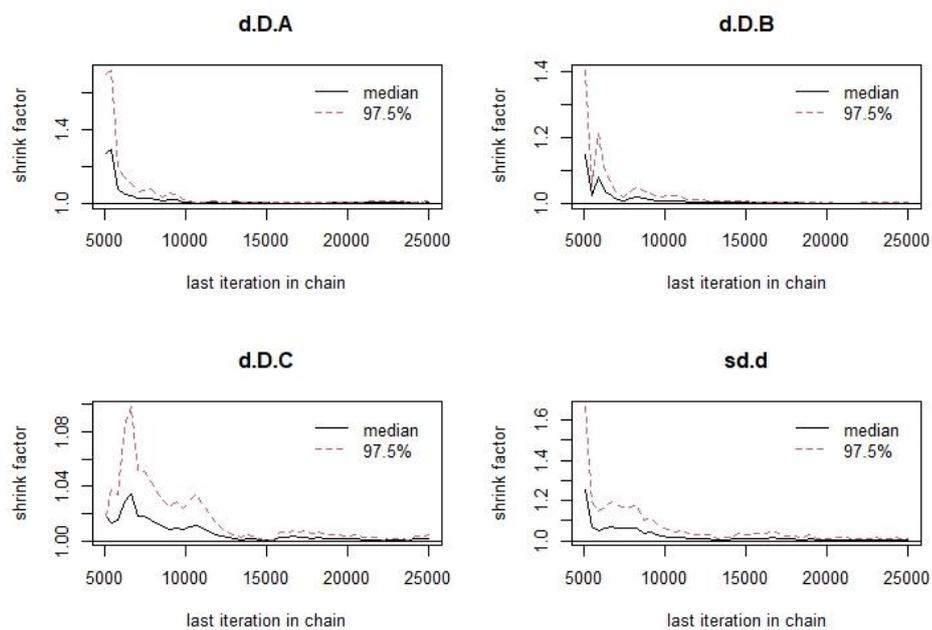


Supplemental Figure 3 Assessment of heterogeneity and transitivity with the trace and density plots. The trace and density plots for overall survival (A) and disease-free survival (B). d.D.A: Consistency models comparing D and A; d.D.B: Consistency models comparing D and B; d.D.C: Consistency models comparing D and C; sd.d: Consistency models comparing D and D; A: stereotactic body radiation therapy; B: intensity-modulated radiation therapy 3D; C: 3-dimensional conformal radiation therapy; D: Surgery.

A



B



Supplemental Figure 4 Assessment of heterogeneity and transitivity with the Brooks-Gelman-Rubin diagnostic plot. The Brooks-Gelman-Rubin diagnostic plot for overall survival (A) and disease-free survival (B). d.D.A: consistency models comparing D and A; d.D.B: consistency models comparing D and B; d.D.C: consistency models comparing D and C; sd.d: consistency models comparing D and D; A: stereotactic body radiation therapy; B: intensity-modulated radiation therapy 3D; C: 3-dimensional conformal radiation therapy; D: Surgery.

Supplemental Table 1 The preferred reporting items for systematic reviews and Meta-Analyses (PRISMA) checklist

| Section and Topic | Item # | Checklist item | Location where item is reported |
|--------------------------|---------------|--|--|
| TITLE | | | |
| Title | 1 | Identify the report as a systematic review. | 1 |
| ABSTRACT | | | |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. | NA |
| INTRODUCTION | | | |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | 5-6 |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | 5-6 |
| METHODS | | | |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | 7 |
| Information sources | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | 6 |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | 6 |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | 7 |

| | | | |
|-------------------------------|-----|--|---------|
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | 8 |
| Data items | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | Table 1 |
| | 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | Table 1 |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | 8-9 |
| Effect measures | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | 8-9 |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for | 8-9 |

each synthesis (item #5)).

| | | | |
|---------------------------|-----|---|--------------|
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | 8-9 |
| | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | 8-9 |
| | 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | 8-9 |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | 8-9 |
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | 8-9 |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | 8-9 |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | 8-9 |
| RESULTS | | | |
| Study selection | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | Figure 1 |
| | 16b | Cite studies that might appear to meet the | Supplemental |

| | | | |
|-------------------------------|-----|--|------------------------|
| | | inclusion criteria, but which were excluded, and explain why they were excluded. | Table 2 |
| Study characteristics | 17 | Cite each included study and present its characteristics. | Table 1 |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | Supplementary Figure 1 |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | Table 1 |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | 10-11 |
| | 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | 10-11 |
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results. | 10-11 |
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | 10-11 |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | 10-11 |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | 10-11 |

DISCUSSION

| | | | |
|--|-----|--|----|
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | 12 |
| | 23b | Discuss any limitations of the evidence included in the review. | 14 |
| | 23c | Discuss any limitations of the review processes used. | 14 |
| | 23d | Discuss implications of the results for practice, policy, and future research. | 15 |
| OTHER INFORMATION | | | |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | 6 |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | NA |
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. | NA |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | 16 |
| Competing interests | 26 | Declare any competing interests of review authors. | 17 |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | 16 |

NA: Not applicable.

Supplemental Table 2 Inclusion criteria and exclusion criteria of participants in the included randomized controlled trials

| Study | Inclusion criteria | Exclusion criteria |
|-------------------------|--|---|
| Liu 2020 ^[1] | <p>1)HCC confirmed by postoperative histology.</p> <p>2)without neoadjuvant treatment before the first hepatectomy.</p> <p>3)a complete removal of tumor confirmed by postoperative pathology.</p> <p>4) Child-Pugh class A5, A6, or B7.</p> <p>5) Eastern Cooperative Oncology Group performance status 0 or 1.</p> <p>6) with postoperative imaging follow-up of more than 2 months</p> | Not reported |
| Shi 2022 ^[2] | <p>Adults who were diagnosed with HCC in BCLC stage 0 or A, pathologically proved MVI in the surgical specimen, and received marginal resection</p> | <p>BCLC-B stage;</p> <p>MVI negative;</p> <p>Macroscopic vascular invasion;</p> <p>Preoperative treatment;</p> <p>Tumor rupture;</p> <p>Refusal</p> |
| Sun 2019 ^[3] | <p>(1) Age 20-70 years old, the HCC was resectable (single tumor <10 cm in diameter or multiple lesions confined to one hemiliver); No evidence of extrahepatic metastasis;</p> <p>(2) an Eastern Cooperative Oncology Group performance status score of 0 or 1, and liver function of ChildPugh Class A or B;</p> <p>(3) white cell count (WBC)>4*10⁹/L,and Platelets >10*10⁹/L; No apparent abnormality of the heart, lung, and</p> | Not reported |

kidney; No HCV, HIV and syphilis infection;

(4) complete removal of all hepatic tumor and PVTT on intraoperative ultrasound (US).

(1) age ranging from 20 to 70 years;

(2) HCC

diagnosed by biopsy or by the noninvasive criteria according to the European Association for the Study of Liver guidelines.

(3) hepatitis B Surface Antigen (HBsAg) positivity;

(4) a solitary tumor with a maximum diameter ≤ 5 cm and was assessed to be resectable

using the Criteria in the Appendix, Supplemental Digital Content 2,

(5) preoperative clinical parameters in predicting a high risk of MVI presence on subsequent histopathological study

(i) HCC without any adjuvant and neoadjuvant treatments except for postoperative radiotherapy;

(ii) macroscopically complete removal of tumour and no residual tumours demonstrated by intraoperative ultrasonography;

(iii) Child-Pugh class A;

(iv) Eastern Cooperative Oncology Group Performance Status ≤ 1 ;

(v) absence of distant metastasis from the primary HCC or prior second tumour

The eligibility criteria included pathological diagnosis of HCC after hepatectomy with narrow pathological margins (< 1 cm), age > 18 years, and recovery from surgery with an Eastern Cooperative Oncology Group performance status score of 0 or 1.

(1) a history of other malignancy in the past five years;

(2) any previous antitumor treatment for HCC within one year;

(3) hepatitis C virus (HCV) or human immunodeficiency virus (HIV) co-infection

Not reported

Wei 2023^[4]

Wang 2015^[5]

Long 2023^[6]

Patients were also excluded if they had severe disease with a history of heart attack, severe arrhythmia, or

| | | |
|--------------------------|--|--|
| | <p>(1) male and female aged < 75 years;</p> <p>(2) primary HCC treated with curative surgical liver resection; (3) surgical margin less than 10 mm but microscopically free of tumor,</p> <p>(4) No presence of macro-vascular invasion but MVI were proven by postoperative pathology; (5) not more than two lesions, double primary tumor proven by postoperative pathology without intra or extrahepatic metastasis;</p> <p>(6) no tumor fracture and hemorrhage before and during resection;</p> <p>(7) Preoperative liver function was Child-Pugh A degree and Postoperative liver function recovered to ChildPugh A degree in 4 weeks; (8) previous hepatitis B virus (HBV) infection confirmed by serological detection;</p> <p>(9) No severe cardiopulmonary or metabolic system dysfunction.</p> | <p>mental illness.</p> <p>(1) postoperative intra or extrahepatic metastases within 4 weeks;</p> <p>(2) postoperative liver failure or severe complications/adverse events within 4 weeks;</p> <p>(3) had simultaneous malignant tumor/diseases;</p> <p>(4) RT was performed as preoperative or intraoperative adjuvant treatment;</p> <p>(5) TACE was performed as postoperative adjuvant treatment;</p> <p>(6) sensitivity to radiation therapy.</p> |
| Wang 2020 ^[7] | | |
| Wei 2019 ^[8] | <p>The key inclusion criteria were age 18 to 70 years, HCC diagnosed by biopsy or by the noninvasive criteria of the European Association for the Study of Liver guidelines,² the primary HCC being resectable, and Cheng's type II/III PVTT (ie, PVTT that involved the right- or left-side branch or main trunk of the portal vein)</p> | <p>The key exclusion criteria were a history of other malignancy in the past 5 years, any previous antitumor treatment of HCC within 1 year, and hepatitis C virus (HCV) or HIV</p> |

| | | |
|--------------------------|--|---|
| | | infection. |
| Rong 2020 ^[9] | The key inclusion criteria specified a central HCC with no preoperative radiotherapy and a resectable lesion that could be completely removed, at the same time retaining a sufficient residual liver tissue to maintain adequate function | Patients with presence of distant metastasis, a hepatectomy margin more than 1 cm or undergone palliative resection with tumor residual were excluded from the trial. |
| | 1) had to be 18–75 years old; | 1) had a history of preoperative therapy; |
| | 2) have the presence of PVTT type I or II (PVTT not having reached the main trunk of the portal vein); | 2) had other malignant tumors or extrahepatic metastases; |
| | 3) have Child–Pugh stage A or B liver function; | |
| | 4) been diagnosed with a resectable tumor; | |
| Bai 2016 ^[10] | 5) been diagnosed with HCC based on postoperative pathology | 3) PVTT location expanded to the main trunk or more; |
| | | 4) patients with HCC recurrence within 1 month. |
| | 1) centrally located HCC with no preoperative RT; | 1) patients with presence of distant metastasis; |
| | 2) resectable lesion that could be completely removed, at the same time retaining a sufficient residual liver tissue to maintain adequate function; | 2) resection margin ≥ 1 cm; |
| | 3) compensated cirrhosis or no cirrhosis; | 3) palliative resection with tumor residual; |
| Yu 2014 ^[11] | 4) Child-Pugh liverfunction class A; | 4) non-HCC confirmed by postoperative pathology |
| | 5) Eastern Cooperative Oncology Group Performance Status of 0 or 1 | |
| Wang | 1) primary lesion treated with curative surgical liver | Not reported |

- resection (microscopically surgical margin free of tumor);
- 2) MVI were proven by postoperative pathology but without macro-vascular invasion;
- 3) no tumor rupture and hemorrhage before and during resection;
- 4) no liver failure or severe complications/ adverse events after surgery within 1 month;
- 5) no postoperative death within 3 months;
- 6) preoperative liver function was Child-Pugh A degree;
- 7) absence of previous or simultaneous malignant tumor/diseases;
- 8) patients with continuous follow-up records until death or censored time.

Supplemental Table 3 Characteristics of included clinical trials in the network meta-analysis

| Study (year) | Country | Center (S/M) | Study period | Study design | Radiotherapy | Main outcome | PSM (Y/N) | NOS score |
|--------------|---------|--------------|----------------|---------------|--------------|--------------|-----------|-----------|
| Liu 2020 | CN | S | 2014.4-2016.12 | Retrospective | SBRT | OS, DFS | N | M |
| Shi 2022 | CN | S | 2015.8-2016.12 | RCT | SBRT | OS, DFS | N | H |
| Sun 2019 | CN | S | 2013.7-2016.6 | RCT | IMRT | OS, DFS | N | H |
| Wei 2023 | CN | S | 2003-2013 | RCT | IMRT | OS, DFS | N | H |
| Wang 2015 | CN | S | 2007-2011 | Retrospective | IMRT | OS, DFS | N | M |
| Long | CN | S | 2008.1-2016.3 | Prospective | IMRT | OS, | Y | H |

| | | | | | | | | | |
|--------------|----|---|----------------|---------------|--------|--|------------|---|---|
| 2023 | | | | | | | DFS | | |
| Wang 2020 | CN | S | 2015.7-2018.12 | Prospective | IMRT | | OS, DFS | N | M |
| Wei 2019 | CN | M | 2016.1-2017.12 | RCT | 3D-CRT | | OS, DFS | N | H |
| Rong 2020 | CN | S | 2007.7-2012.3 | Prospective | 3D-CRT | | OS, DFS | N | M |
| Bai 2016 | CN | S | 2009-2010 | Retrospective | 3D-CRT | | OS, DFS | N | M |
| Yu 2014 | CN | M | 2007.7- 2012.3 | RCT | 3D-CRT | | OS, DFS | N | H |
| Wang 2017 | CN | S | 2008.7-2015.12 | Retrospective | 3D-CRT | | OS, DFS | N | M |

CN: China; S: Single center; M: Multicenter; RCT: Random control trial; SBRT: Stereotactic body radiotherapy; IMRT: Intensity modulated radiotherapy; 3D-CRT: 3-dimensional conformal radiation therapy; OS: Overall survival; DFS: Disease-free survival; PSM: Propensity score matching; NOS: Newcastle-Ottawa Scale for cohort studies; N: No; Y: Yes; M: Middle; H: High.

REFERENCES

- Liu L**, Shui Y, Yu Q, Guo Y, Zhang L, Zhou X, Yu R, Lou J, Wei S, Wei Q. Narrow-Margin Hepatectomy Resulted in Higher Recurrence and Lower Overall Survival for R0 Resection Hepatocellular Carcinoma. *Front Oncol* 2020; **10**: 610636 [PMID: 33552983 DOI: 10.3389/fonc.2020.610636]
- Shi C**, Li Y, Geng L, Shen W, Sui C, Dai B, Lu J, Pan M, Yang J. Adjuvant stereotactic body radiotherapy after marginal resection for hepatocellular carcinoma with microvascular invasion: A randomised controlled trial. *Eur J Cancer* 2022; **166**: 176-184 [PMID: 35303509 DOI: 10.1016/j.ejca.2022.02.012]
- Sun J**, Yang L, Shi J, Liu C, Zhang X, Chai Z, Lau WY, Meng Y, Cheng SQ. Postoperative adjuvant IMRT for patients with HCC and portal vein tumor thrombus: An open-label randomized controlled trial. *Radiother Oncol* 2019; **140**: 20-25 [PMID: 31176205 DOI: 10.1016/j.radonc.2019.05.006]
- Wei X**, Jiang Y, Feng S, Lu C, Huo L, Zhou B, Meng Y, Lau WY, Zheng Y, Cheng S. Neoadjuvant

intensity modulated radiotherapy for a single and small (≤ 5 cm) hepatitis B virus-related hepatocellular carcinoma predicted to have high risks of microvascular invasion: a randomized clinical trial. *Int J Surg* 2023; **109**: 3052-3060 [PMID: 37352528 DOI: 10.1097/JS9.0000000000000574]

5 **Wang WH**, Wang Z, Wu JX, Zhang T, Rong WQ, Wang LM, Jin J, Wang SL, Song YW, Liu YP, Ren H, Fang H, Wang WQ, Liu XF, Yu ZH, Li YX. Survival benefit with IMRT following narrow-margin hepatectomy in patients with hepatocellular carcinoma close to major vessels. *Liver Int* 2015; **35**: 2603-2610 [PMID: 25939444 DOI: 10.1111/Liv.12857]

6 **Long L**, Chen B, Wang H, Zhao Y, Wu F, Wang L, Rong W, Wu J, Li Y, Wang W. Survival benefit of radiotherapy following narrow-margin hepatectomy in patients with hepatocellular carcinoma: A propensity score-matched analysis based on phase II study. *Radiother Oncol* 2023; **180**: 109462 [PMID: 36634853 DOI: 10.1016/j.radonc.2022.109462]

7 **Wang L**, Wang W, Rong W, Li Z, Wu F, Liu Y, Zheng Y, Zhang K, Siqin T, Liu M, Chen B, Wu J. Postoperative adjuvant treatment strategy for hepatocellular carcinoma with microvascular invasion: a non-randomized interventional clinical study. *BMC Cancer* 2020; **20**: 614 [PMID: 32611327 DOI: 10.1186/s12885-020-07087-7]

8 **Wei X**, Jiang Y, Zhang X, Feng S, Zhou B, Ye X, Xing H, Xu Y, Shi J, Guo W, Zhou D, Zhang H, Sun H, Huang C, Lu C, Zheng Y, Meng Y, Huang B, Cong W, Lau WY, Cheng S. Neoadjuvant Three-Dimensional Conformal Radiotherapy for Resectable Hepatocellular Carcinoma With Portal Vein Tumor Thrombus: A Randomized, Open-Label, Multicenter Controlled Study. *J Clin Oncol* 2019; **37**: 2141-2151 [PMID: 31283409 DOI: 10.1200/JCO.18.02184]

9 **Rong W**, Yu W, Wang L, Wu F, Zhang K, Chen B, Miao C, Liu L, An S, Tao C, Wang W, Wu J. Adjuvant radiotherapy in central hepatocellular carcinoma after narrow-margin hepatectomy: A 10-year real-world evidence. *Chin J Cancer Res* 2020; **32**: 645-653 [PMID: 33223759 DOI: 10.21147/j.issn.1000-9604.2020.05.09]

10 **Bai T**, Chen J, Xie ZB, Wu FX, Wang SD, Liu JJ, Li LQ. The efficacy and safety of postoperative adjuvant transarterial embolization and radiotherapy in hepatocellular carcinoma patients with portal vein tumor thrombus. *Onco Targets Ther* 2016; **9**: 3841-3848 [PMID: 27390524 DOI: 10.2147/OTT.S104307]

11 **Yu W**, Wang W, Rong W, Wang L, Xu Q, Wu F, Liu L, Wu J. Adjuvant radiotherapy in centrally located hepatocellular carcinomas after hepatectomy with narrow margin (< 1 cm): a prospective randomized study. *J Am Coll Surg* 2014; **218**: 381-392 [PMID: 24559953 DOI: 10.1016/j.jamcollsurg.2014.02.011]

10.1016/j.jamcollsurg.2013.11.030]

12 **Wang L**, Wang W, Yao X, Rong W, Wu F, Chen B, Liu M, Lin S, Liu Y, Wu J. Postoperative adjuvant radiotherapy is associated with improved survival in hepatocellular carcinoma with microvascular invasion. *Oncotarget* 2017; **8**: 79971-79981 [PMID: 29108379 DOI: 10.18632/oncotarget.20402]