Neoadjuvant radiotherapy for resectable hepatocellular carcinoma with vascular invasion: A systematic review and meta-analysis

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Abstract. Advances in conformal and image-guided external-beam radiotherapy have expanded its application in hepatocellular carcinoma (HCC); however, the benefit of neoadjuvant radiotherapy before resection for HCC with vascular invasion remains uncertain. A systematic review and meta-analysis were conducted comparing neoadjuvant radiotherapy plus hepatectomy vs. hepatectomy alone in resectable HCC with vascular invasion. Databases were searched through August 1, 2024. Primary outcomes were overall survival (OS) and disease-free survival (DFS). A total of four studies (n=362) were included. In the overall pooled analysis, neoadjuvant radiotherapy was not associated with a statistically significant improvement in 1-year OS [risk ratio (RR) 1.62; 95% confidence interval (CI) 0.71-3.69] or 2-year OS (RR 2.64; 95% CI 0.57-12.27), with considerable heterogeneity (I^2 97 and 94%, respectively). Similarly, 1-year DFS was not significantly different between groups (RR 2.68; 95% CI 0.50-14.43; I^2 95%). In subgroup analyses by vascular invasion type, patients with portal vein tumor thrombus (PVTT) showed a higher 1-year and 2-year OS compared with surgery alone, and two studies reporting time-to-event outcomes suggested lower recurrence and mortality; however, these findings are based on a small number of studies and should be interpreted with caution. Reported radiotherapy-related toxicities were generally manageable. Overall, current evidence is limited and heterogeneous; neoadjuvant radiotherapy may benefit selected patients with resectable HCC and PVTT, but adequately powered multicenter randomized trials with standardized protocols are needed.

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Introduction

Primary liver cancer is a major global health burden, ranking sixth in incidence (4.3% of new cases) and third in cancer mortality (7.8% of deaths) (1). Among pathological subtypes, hepatocellular carcinoma (HCC) accounts for 75-85% of primary liver cancers (2). Surgical resection remains the main curative option, yet <30% of patients are eligible at initial diagnosis (3), and even after resection the 5-year recurrence rate can reach 70%, with vascular invasion being a key driver of postoperative recurrence (4,5). Vascular invasion includes macrovascular invasion and microvascular invasion (MVI); macrovascular invasion is frequently manifested as portal vein tumor thrombus (PVTT), with a reported incidence of 44.0-66.2% in China (6). PVTT is an independent adverse prognostic factor in HCC (3,7,8), and untreated HCC with PVTT is associated with an markedly poor overall survival (OS) of only 2.4-4.0 months, which further worsens when the main portal vein trunk is involved (9,10). Clinically, surgery is generally preferred for type I/II PVTT, whereas type III PVTT may undergo upfront surgery or surgery following radiotherapy to control tumor progression (11). Notably, evidence suggests PVTT may be more radiosensitive than the primary tumor (12). In parallel, MVI is a notable invasive feature characterized by cancer cell nests within endothelial-lined vascular lumina, predominantly involving portal vein branches, and is notably associated with intrahepatic/distant metastasis, early postoperative recurrence (within 1 year) and poor prognosis (13,14). These challenges have driven increasing interest in neoadjuvant strategies to improve resectability and reduce recurrence; neoadjuvant radiotherapy has been adopted as one acceptable neoadjuvant approach for HCC (15), yet whether it can meaningfully improve outcomes in resectable HCC with vascular invasion remains uncertain.

The radiation therapy modalities for HCC primarily include internal and external radiation therapy (16). The present meta-analysis primarily focused on external radiation therapy due to its economic advantages and widespread

use (17). External radiation therapy involves the use of radiation sources located outside the patient's body, which are directed toward the tumor site by radiation therapy equipment. This radiation damages the DNA of tumor cells, thereby inducing tumor cell death. The main techniques employed include three-dimensional conformal radiation therapy (3DCRT), intensity-modulated radiation therapy, image-guided radiation therapy and stereotactic body radiation therapy. Advancements in radiotherapy technology have addressed the high incidence of radiation-induced liver disease, which was previously common with conventional radiotherapy techniques, such as whole liver irradiation and mobile strip irradiation, making radiotherapy a notable treatment option for HCC (18,19). The introduction of the latest spiral computed tomography-guided radiotherapy equipment has further underscored the growing importance of radiotherapy in the treatment of patients with HCC (20).

Neoadjuvant radiotherapy holds considerable potential in reducing tumor size, alleviating preoperative tumor burden, eliminating small metastases, improving the rate of curative resection, reducing postoperative recurrence and prolonging OS time. Furthermore, the effectiveness of neoadjuvant radiotherapy can serve as a prognostic and predictive indicator, aiding clinicians in making informed decisions regarding neoadjuvant therapy (21). The present meta-analysis aimed to systematically review and synthesize the existing clinical evidence on neoadjuvant radiotherapy for resectable HCC with vascular invasion, in order to characterize its current clinical application, safety and possible role in multimodal treatment strategies and to inform future clinical research.

Materials and methods

Search strategy. The PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.elsevier.com/products/embase), Cochrane Library (https://www.cochrane.org/about-us), China National Knowledge Infrastructure (https://www.cnki.net/), Wanfang (https://med.wanfangdata.com.cn/) and VIP (https://www.cqvip.com/) databases were systematically searched to comprehensively cover the relevant Chinese and English literature. Studies on neoadjuvant radiotherapy for resectable HCC with vascular invasion were retrieved from these databases up to August 1, 2024.

To maximize the inclusion of unpublished and up-to-date data, abstracts and reports from the American Society of Clinical Oncology (https://www.emerson.com/en-us/automation/asco) and European Society for Medical Oncology (https://www.esmo.org/) conferences were also searched up to August 1, 2024. The following medical subject heading combinations were used for the computer-assisted search: ('hepatocellular carcinoma' or 'liver cancer' or 'HCC') and ('liver resection' or 'surgical resection') and ('preoperative' or 'neoadjuvant radiotherapy') and ('vascular invasion'). The detailed search strategies for each database are provided in Table SI. Additionally, manual searches were performed by referencing key articles to identify other relevant studies.

Study selection. Following the preliminary search, two authors independently screened the titles and abstracts of the identified articles to determine their relevance. Subsequently, the two authors independently reviewed the full texts based on predefined inclusion and exclusion criteria. Any disagreements were resolved by a third author.

Inclusion and exclusion criteria. The inclusion criteria for the present study were as follows: i) Patients with resectable HCC (aged between 18 and 70 years) who underwent liver resection, with or without neoadjuvant radiotherapy; ii) studies comparing OS and disease free survival (DFS); iii) a median follow-up time of >6 months; and iv) patients with resectable HCC who had not received any prior radiation therapy.

The exclusion criteria for the present study were as follows: i) A history of other malignant tumors and antitumor treatments within the past 5 years; ii) patients with HCC who received treatments other than radiotherapy prior to surgery; iii) patients with unresectable HCC; iv) conference abstracts, reviews, case reports, letters, editorials, comments or any research other than peer-reviewed original research articles; and v) duplicate studies or data reported by the same institution or hospital. In cases of duplicate populations, studies with broader institutional representation or a larger number of patients were selected.

Quality assessment. The quality of the data from randomized controlled trials (RCTs) was evaluated using the Cochrane Collaboration (https://www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2) tool to assess the risk of bias. For non-randomized studies, the Newcastle-Ottawa Scale (NOS) was used for quality evaluation (22). This assessment considered three aspects: The method of case and control group selection, the comparability between the two groups and the exposure assessment method. The higher the evaluation score, the higher the study quality. The NOS score ranges from 0 to 9, with studies scoring >7 considered high-quality. The quality assessment was conducted by two independent reviewers, and any disagreements between them were resolved by a third reviewer.

Data extraction. A singular author independently extracted the following data from all included studies: Authors, countries, study design, neoadjuvant radiotherapy details, patient characteristics, treatment efficacy and clinical outcomes of surgery. Data such as risk ratio (RR) and 95% confidence interval (CI) for OS and DFS were also calculated. The second author cross-checked the data, and in the case of discrepancies, a third author was invited to discuss the matter, resolve differences and reach a consensus.

Statistical analysis. The analysis included OS, DFS and tumor responses. For time-to-event outcomes, hazard ratios (HRs) are generally the preferred effect measure. However, HRs for OS/DFS were not consistently reported across all included studies. Therefore, for the primary synthesis survival probabilities were extracted at prespecified time points (1-year and 2-year OS; 1-year DFS) from Kaplan-Meier curves and pooled risk ratios (RRs) as a pragmatic, consistent measure across studies. The RR values of each study were summarized using random-effects model, as determined by Review Manager (RevMan version 5.4; Cochrane Collaboration). According to the Cochrane Collaboration guidelines,

heterogeneity was assessed using the Q-statistic and I^2 index, with significant heterogeneity defined as a P<0.05 and an I^2 index >50%. Due to the expected heterogeneity of intervention effects from multiple studies from different populations and geographical locations, a random effects model was used for analysis. To explore the sources of heterogeneity, sensitivity analysis (RevMan, Cochrane Collaboration; version 5.4) and random-effects regression model analysis (STATA, StataCorp LP; version 17.0) were performed. Additionally, exploratory subgroup analysis and HR analysis were conducted to assess potential differences in the prognosis of neoadjuvant radiotherapy for various types of HCC vascular invasion.

Evidence quality assessment. The quality of evidence for the primary outcome measures (1-year OS, 2-year OS and 1-year DFS) was graded using GRADEpro GDT web (https://gradepro.org). The assessment considered five factors that could downgrade the evidence, namely, risk of bias, imprecision, inconsistency, indirectness and publication bias, as well as three factors that could upgrade the evidence, namely, large effect size, dose-response relationship and absence of confounding. Evidence quality was classified into four levels: i) High: Future research is unlikely to change the confidence in the estimate of effect. ii) Moderate: Future research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate. iii) Low: Future research is likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate. iv) Very low: Any estimate of effect is uncertain.

Results

Retrieval results and study characteristics. According to the search strategy, a total of 372 articles were retrieved. After removing duplicates and reviewing the titles and abstracts, a comprehensive and detailed evaluation was conducted on the remaining 8 articles.

Overall, 2 of the 8 articles lacked a control group; one study focused on tumor response after neoadjuvant radiotherapy, without a control group, the other study compared its results with those of previous articles, which did not meet the inclusion criteria, and was therefore excluded. Another article was a systematic review that included different research subjects, and its inclusion year had not been updated. Another record was a master's thesis, although its research direction meets the inclusion criteria of this study, it was ultimately excluded after discussion due to its lack of rigorous peer review. The flowchart of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (https://prisma.es/) (Fig. 1) illustrates the entire evaluation process, from the initial search to the final selection of studies.

Ultimately, 362 patients from 4 studies were included in the meta-analysis, 2 of which were randomized controlled trials (RCTs) (23-26). The publication period ranged from 2007 to 2023. The sample comprised 362 cases, including 172 in the neoadjuvant radiotherapy group and 190 in the surgery-only group. Among the 4 studies on vascular invasion, one focused on HCC with MVI, and 3 studied HCC with PVTT. The Cochrane Collaboration tool was used to assess the risk of bias, and the data quality of the RCTs was rated as 'A'. The risk of bias graphs and summaries are provided in Figs. 2 and 3. The NOS scores for the two non-randomized studies were 7 and 4, respectively. The feature tables of the included studies are shown in Tables I and II. Additionally, the GRADE evidence profile is presented in Table III. The 1-year OS was rated as low quality, whereas 2-year OS and 1-year DFS were rated as very low quality. For these outcomes, downgrading was mainly driven by concerns regarding risk of bias and inconsistency, both of which were judged as serious; in addition, imprecision was also judged as serious for 2-year OS and 1-year DFS. These downgrades were mainly attributable to the predominance of retrospective or non-randomized studies, limited reporting of patient selection, baseline comparability, allocation and follow-up procedures, and clinical heterogeneity across studies in patient characteristics and treatment protocols; for 2-year OS and 1-year DFS, the small number of studies and limited sample sizes further contributed to imprecision. Publication bias was considered likely for the OS outcomes and undetected for 1-year DFS. By contrast, the evidence for PVTT recurrence was rated as high quality, with no serious concerns identified across the GRADE domains.

Primary outcomes. Based on the survival curves provided by the 4 studies, the 1- and 2-year OS rates of the neoadjuvant radiotherapy group and the surgery alone group were extracted. The meta-analysis results (Fig. 4) showed significant heterogeneity between the studies (I^2=97% for 1-year OS and 94% for 2-year OS; P<0.00001), so a random-effects model was used for aggregation. Given the considerable heterogeneity, the pooled estimates should be interpreted as an average effect across clinically diverse studies and are not sufficiently robust for definitive inference. The random-effects meta-analysis did not show a statistically significant difference in OS at 1 year (RR, 1.62; 95% CI, 0.71-3.69; P=0.25) or 2 years (RR, 2.64; 95% CI, 0.57-12.27; P=0.21). A total of 3 studies reported the 1-year DFS rates for both groups. The meta-analysis revealed significant heterogeneity (I^2=95%; P<0.00001), so a random-effects model was used for aggregation. The pooled RR for DFS was 2.68 (95% CI, 0.50-14.43; P=0.25; Fig. 5), indicating that neoadjuvant radiotherapy cannot significantly improve DFS compared with surgery alone.

Subgroup analyses. According to the type of vascular invasion, the 4 studies were divided into subgroups, namely, HCC with PVTT and HCC with MVI, for further analysis (Fig. 6). In the PVTT subgroup, neoadjuvant radiotherapy significantly improved 1-year OS (RR, 1.88; 95% CI, 1.52-2.32; P<0.00001) and 2-year OS (RR, 2.95; 95% CI, 1.55-5.62; P=0.001) rates compared with surgery alone. In the MVI subgroup, the difference in 1-year and 2-year OS rates between patients treated with neoadjuvant radiotherapy was not statistically significant. Further analysis was conducted in the subgroups of resectable HCC with PVTT (Fig. 7). In the PVTT subgroup, meta-analysis of two studies revealed that neoadjuvant radiotherapy significantly reduced the recurrence rate (HR, 0.42; 95% CI, 0.31-0.58; P<0.00001) and mortality rate (HR, 0.34; 95% CI, 0.24-0.48; P<0.00001) compared with surgery alone.

Sensitivity analyses and further exploration. To assess the robustness of the findings, a stratified sensitivity analysis was

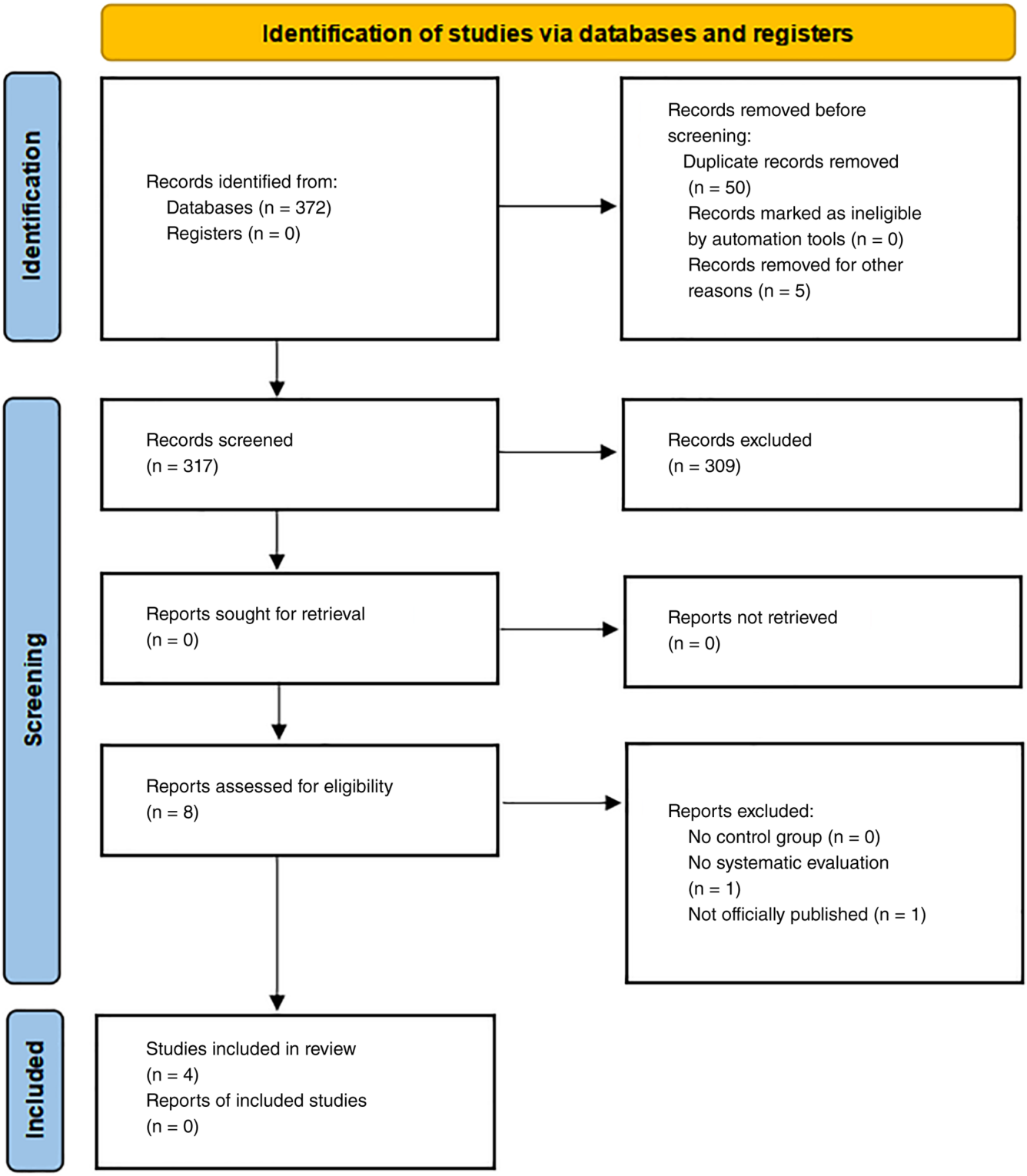

Figure 1. Preferred reporting items for systematic reviews and meta-analysis flow diagram for the current review and meta-analysis of outcomes following treatment with neoadjuvant radiotherapy for hepatocellular carcinoma with vascular invasion.

conducted. After excluding studies with small sample sizes (n<50), the pooled effect sizes were recalculated. Heterogeneity decreased to 0 and 53% for 1- and 2-year OS, respectively. The pooled effect sizes for 1- and 2-year OS were 1.81 (95% CI, 1.43-2.29; P<0.00001) and 5.13 (95% CI, 0.74-35.43; P=0.10), respectively (Fig. 8). Therefore, the sensitivity analysis not only confirmed the stability of the results but also indicated that heterogeneity primarily stemmed from differences in sample sizes.

Subsequently, a random-effects meta-regression model (STATA 17.0) was applied to further explore the sources of heterogeneity. Additional analyses with radiotherapy techniques, radiation doses, types of vascular invasion and liver function as covariates were conducted, as shown in Table IV.

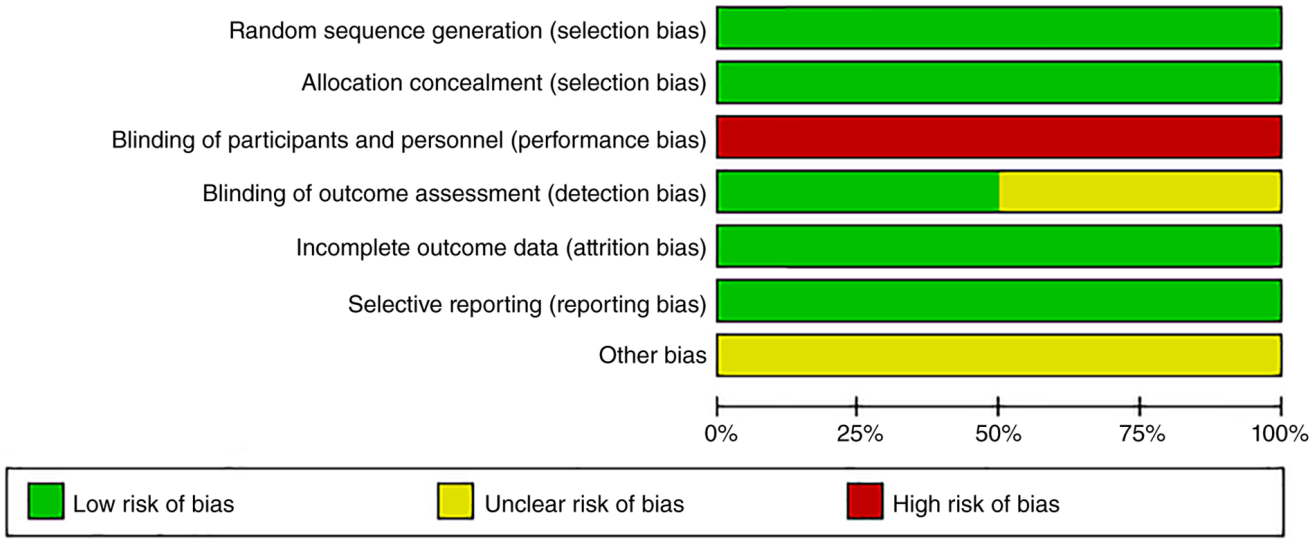

Figure 2. Risk of bias graph for randomized controlled trials.

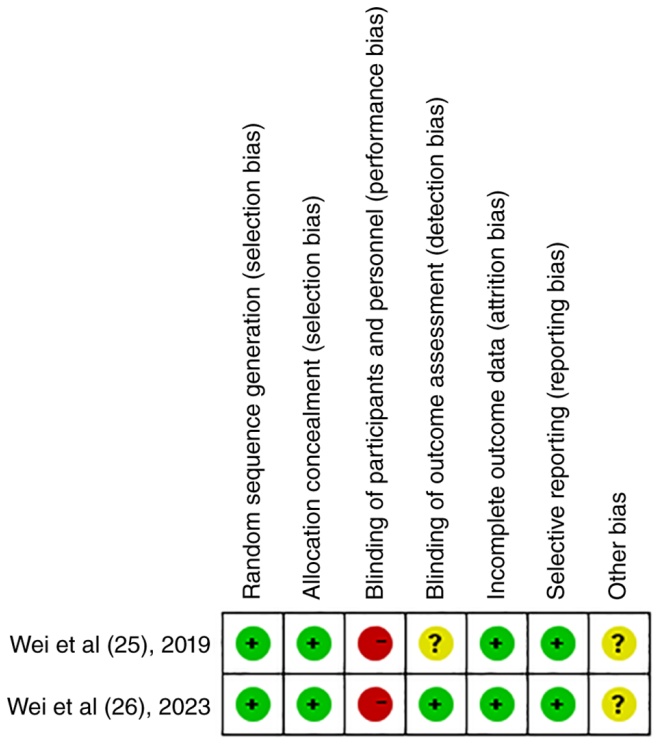

Figure 3. Risk of bias summary for randomized controlled trials. The green circle represents low risk of bias; the yellow circle represents unclear risk of bias; the red circle represents high risk of bias.

The results demonstrated that 3DCRT significantly reduced heterogeneity (P<0.05) by minimizing dose variation due to its precision. The heterogeneity in the PVTT subgroup was significantly lower than in the MVI subgroup (P<0.001), which is consistent with the findings from the subgroup analysis shown in Fig. 6.

Response rate and safety assessment. A total of 4 studies described tumor responses following neoadjuvant radiotherapy. Kamiyama *et al* (23) reported that 53.3% of patients (8 cases) achieved complete necrosis of a tumor thrombus after neoadjuvant radiotherapy. A total of 3 studies, including 157 patients in the neoadjuvant radiotherapy group, and ultimately 155 patients underwent surgery. The following postoperative results were reported: 30 patients showed pathological partial remission, 114 patients exhibited stable disease and 11 patients showed disease progression, while none exhibited pathological complete remission.

Overall, the complications and adverse events associated with neoadjuvant radiotherapy were relatively mild. In the study by Kamiyama *et al* (23), 1 patient experienced severe nausea and vomiting, while the remaining patients had no serious adverse reactions. A total of 2 patients in the neoadjuvant radiotherapy group experienced liver function deterioration and 4 patients had disease progression or extrahepatic metastasis in the study by Li *et al* (24). In the study by Wei *et al* (25), 2 patients had grade 3 liver toxicity, and 7 patients experienced disease progression or extrahepatic metastasis. In the study by Wei *et al* (26), 2 cases showed grade 3 liver toxicity and 4 cases showed grade 3 to 4 thrombocytopenia. No patients canceled surgery due to radiation therapy toxicity.

Discussion

At present, radiation therapy is utilized as adjuvant therapy for small liver cancer (single tumor with a maximum diameter of ≤3 cm and no invasion of blood vessels or surrounding tissues), palliative treatment for patients with HCC and distant metastasis, bridging therapy during the liver transplantation waiting period, and in combination with surgery or intervention for patients with HCC to achieve optimal therapeutic outcomes. In Western countries, sorafenib is one of the preferred treatment options for HCC with vascular invasion (27). However, HCC with PVTT or MVI not only shows limited efficacy with sorafenib but also presents a higher incidence of severe toxicity reactions, such as grade 3-4 hand-foot skin reaction, severe diarrhea, hypertension requiring medical intervention, profound fatigue and severe hepatic dysfunction (28). The effectiveness of neoadjuvant radiotherapy in treating resectable

Table I. Characteristics of the studies that fulfilled the inclusion criteria in the meta-analysis.

First author, year	Country of publication	Study design	Quality	Neoadjuvant RT	Number of patients	Patients who underwent surgery	Median follow-up time, months	1-year OS rate, %	2-year OS rate, %	1-year DFS rate, %	(Refs.)
Kamiyama *et al*, 2007	Japan	Cohort	NOS4	Yes	15	15	19.4	86.2	NA	NA	(23)
				No	28	28	9.1	39.0	NA	NA	
Li *et al*, 2016	China	Cohort	NOS7	Yes	45	39	8.4	69.0	20.4	33.0	(24)
				No	50	50	8.4	35.6	0.0	2.3	
Wei *et al*, 2019	China	RCT	A	Yes	82	73	15.2	75.2	27.4	33.0	(25)
				No	82	82	10.8	43.1	9.4	14.9	
Wei *et al*, 2023	China	RCT	A	Yes	30	27	68.0	96.3	88.9	86.7	(26)
				No	30	30	68.0	100.0	93.3	90.0	

RT, radiotherapy; OS, overall survival; DFS, disease-free survival; NOS, Newcastle Ottawa Scale; RCT, randomized controlled trial; NA, not available.

HCC with vascular invasion remains uncertain. The present systematic review and meta-analysis synthesized prospective evidence on neoadjuvant external-beam radiotherapy followed by hepatectomy vs. hepatectomy alone in resectable HCC with vascular invasion. The most notable finding is that, in the overall pooled analysis, neoadjuvant radiotherapy was not associated with a statistically significant improvement in fixed time-point OS or DFS. Notably, these pooled estimates were accompanied by substantial between-study heterogeneity, which limits the strength and generalizability of any overall conclusion.

The high heterogeneity deserves particular emphasis because it affects not only statistical interpretation but also the clinical meaning of the pooled results. First, the included studies enrolled patients with different forms of vascular invasion, principally PVTT and predicted MVI, which are biologically and clinically distinct entities rather than interchangeable manifestations of the same disease process. Second, the studies differed in design and methodological rigor, including both randomized and prospective non-randomized cohorts, thereby introducing variation in baseline comparability and susceptibility to bias. Third, there was likely clinical heterogeneity in tumor burden, extent of vascular invasion, liver functional reserve, radiotherapy protocols and perioperative management, all of which may modify treatment effect. Under these circumstances, the pooled estimates should not be interpreted as a precise average treatment effect applicable to all patients with resectable HCC and vascular invasion. Rather, they represent a summary across clinically heterogeneous populations in whom the role of neoadjuvant radiotherapy is unlikely to be uniform.

The absence of a statistically significant benefit in the primary pooled outcomes should therefore not be viewed simply as evidence of 'no effect', but as evidence that the currently available prospective data are insufficiently consistent and too limited in size to establish a reliable OS advantage. At the same time, the combination of non-significant primary results and marked heterogeneity argues strongly against broad claims of efficacy. In other words, the present evidence does not support routine use of neoadjuvant radiotherapy for the overall population of resectable HCC with vascular invasion. Any potential benefit appears to depend markedly on patient selection, particularly the biological type of vascular invasion. This point is reinforced by the subgroup analyses. Patients with PVTT showed higher 1- and 2-year OS rates with neoadjuvant radiotherapy, and the limited studies reporting time-to-event outcomes suggested lower postoperative recurrence and mortality. However, these findings should be interpreted cautiously as they are based on a small number of studies, and subgroup analyses in the setting of marked overall heterogeneity are inherently exploratory. Nonetheless, the PVTT signal is clinically plausible and warrants focused discussion because it may reflect a true difference in therapeutic susceptibility between macroscopic and microscopic vascular disease.

A central interpretation issue is that vascular invasion encompasses biologically distinct entities. PVTT is macroscopic tumor extension within the portal venous system and is identifiable on imaging, allowing the thrombus to be explicitly targeted in the radiotherapy volume alongside the primary

Table II. Comparison of clinicopathological characteristics between the neoadjuvant RT and surgery alone groups.

	Kamiyama *et al* (23), 2007		Li *et al* (24), 2016		Wei *et al* (25), 2019		Wei *et al* (26), 2023	
Characteristics	Neoadjuvant RT (n=15)	Surgery alone (n=28)	Neoadjuvant RT (n=45)	Surgery alone (n=50)	Neoadjuvant RT (n=82)	Surgery alone (n=82)	Neoadjuvant RT (n=30)	Surgery alone (n=30)
Age, years	53.5±8.3	56.1±9.6	50 (33-66)	47 (25-69)	52.8±10.3	50.5±10.1	49 (39-70)	52 (36-70)
Sex (male/female), n	13/2	25/3	43/2	42/8	67/15	74/8	22/8	23/7
ECOG performance status (0/1/2), n	NA	NA	38/5/2	37/10/3	64/15/3	67/14/1	20/5/5	17/8/5
Child-Pugh stage (A/B/C), n	15/0/0	24/4/0	40/5/0	42/8/0	79/3/0	80/2/0	28/2/0	28/2/0
HBsAg (+/-), n	10/5	18/10	37/8	44/6	75/7	76/6	30/0	30/0
Cirrhosis (yes/no), n	9/6	11/17	29/16	30/20	13/69	14/68	18/12	20/10
Tumor number (S/M), n	9/6	12/16	42/3	40/10	73/9	69/13	NA	NA
Microvascular invasion (yes/no), n	NA	NA	30/9	33/17	50/13	75/7	20/9	23/7
Differentiation (I and II/III and IV), n	5/10	18/10	30/9	45/5	14/59	8/74	4/25	8/22

Values are expressed as n, the mean ± standard deviation or median (range). RT, radiotherapy; ECOG, Eastern Cooperative Oncology Group; HBsAg, hepatitis B virus surface antigen; S, single; M, multiple; NA, not available.

Table III. Grading of recommendations assessment, development and evaluation evidence profile.

Outcome	Studies (patients)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Quality	Importance
1-year OS	4 (n=362)	Serious	Serious	Not serious	Not serious	Likely	Low	Critical
2-year OS	4 (n=362)	Serious	Serious	Not serious	Serious	Likely	Very low	Critical
1-year DFS	3 (n=301)	Serious	Serious	Not serious	Serious	Undetected	Very low	Critical
PVTT recurrence	3 (n=287)	Not serious	Not serious	Not serious	Not serious	Undetected	High	Important

OS, overall survival; DFS, disease-free survival; PVTT, portal vein tumor thrombus.

tumor. From a clinical standpoint, reducing thrombus burden preoperatively could plausibly improve the technical feasibility of resection, increase the probability of complete removal of both the intrahepatic lesion and the portal vein tumor thrombus, and reduce early postoperative recurrence driven by residual macroscopic disease. One radiobiological hypothesis is that intravascular tumor thrombi may experience a microenvironment different from intra-parenchymal microscopic invasion, potentially affecting radiosensitivity (29,30); nevertheless, this remains speculative, and the included clinical studies did not contain mechanistic correlates to confirm this explanation. Therefore, while PVTT-targeted radiotherapy is biologically plausible, the observed PVTT subgroup signal should not be over-interpreted as proof of a specific mechanism.

By contrast, MVI represents microscopic tumor emboli within small vessels and is typically confirmed pathologically after resection. Although postoperative adjuvant radiotherapy can improve OS or recurrence-free survival in cases of HCC with concomitant MVI (31,32), MVI-directed neoadjuvant radiotherapy in practice relies on preoperative risk prediction rather than direct visualization, introducing two challenges. First, misclassification of MVI risk can dilute any true benefit, particularly when only a subset of patients actually harbor histologic MVI. Second, a target volume designed around the visible primary tumor may not encompass diffuse microscopic extension beyond the gross tumor boundary, which is the defining feature of MVI. The single included randomized trial addressing predicted high-risk MVI (26) reported no statistically significant difference in OS or DFS between neoadjuvant radiotherapy and surgery alone, and OS in both arms was high, suggesting a relatively favorable baseline prognosis in this cohort. Under these circumstances, any marginal gain from preoperative irradiation may be difficult to detect and could be offset by practical considerations such as treatment-related

Table IV. Random effects meta-regression model analysis results.

Covariate	Classification standard	1-year OS P-value	2-year OS P-value
Radiation therapy techniques	3DCRT vs. no 3DCRT	0.020	0.030
Radiotherapy dose	≥40 vs. <40 Gy	0.280	0.260
Vascular invasion type	PVTT vs. MVI	<0.001	<0.001
Liver function (Child-Pugh)	A vs. B/C	0.350	0.380

PVTT, portal vein tumor thrombosis; MVI, microvascular invasion; OS, overall survival; 3DCRT, three-dimensional conformal radiation therapy; Gy, Gray.

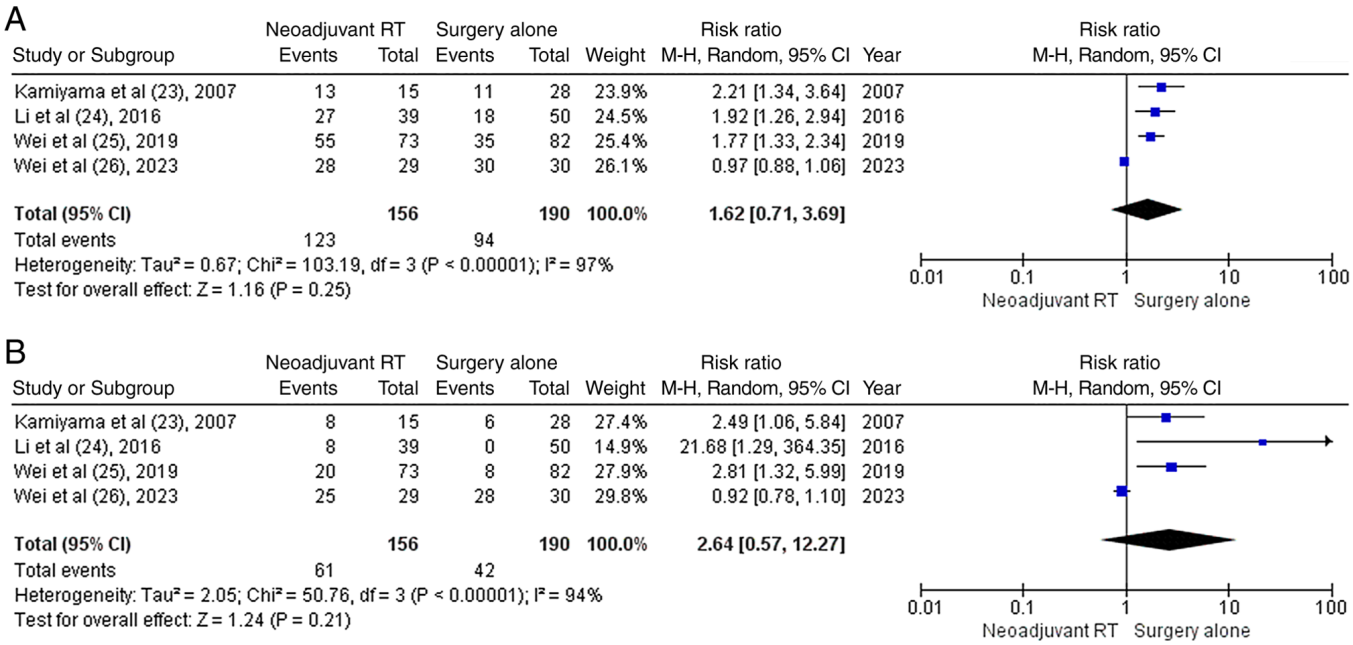

Figure 4. Pooled risk ratios of (A) 1- and (B) 2-year overall survival in the comparison of the neoadjuvant radiotherapy group and the surgery alone group. RT, radiotherapy; CI, confidence interval; M-H, Mantel-Haenszel.

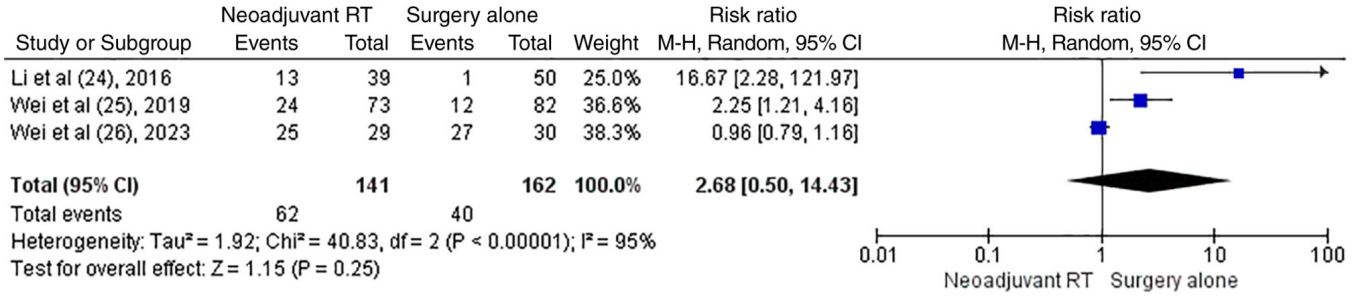

Figure 5. Pooled risk ratios of 1-year disease-free survival in the comparison of the neoadjuvant radiotherapy group and the surgery alone group. RT, radiotherapy, CI, confidence interval, M-H, Mantel-Haenszel.

delay to surgery, perioperative liver function impact or competing risks of recurrence that are not mitigated by a localized preoperative field. Collectively, the present evidence does not support routine neoadjuvant radiotherapy for resectable disease with predicted MVI, but it highlights the need for improved risk stratification and endpoint selection if this question is revisited in future trials.

Potential biological risks should be interpreted with caution. Although preclinical data suggest that irradiation may influence invasion-related pathways, including matrix metalloproteinase activity and epithelial mesenchymal transition, these observations are context-dependent and have not been clinically validated in this setting (33,34). The included studies did not systematically report translational biomarkers,

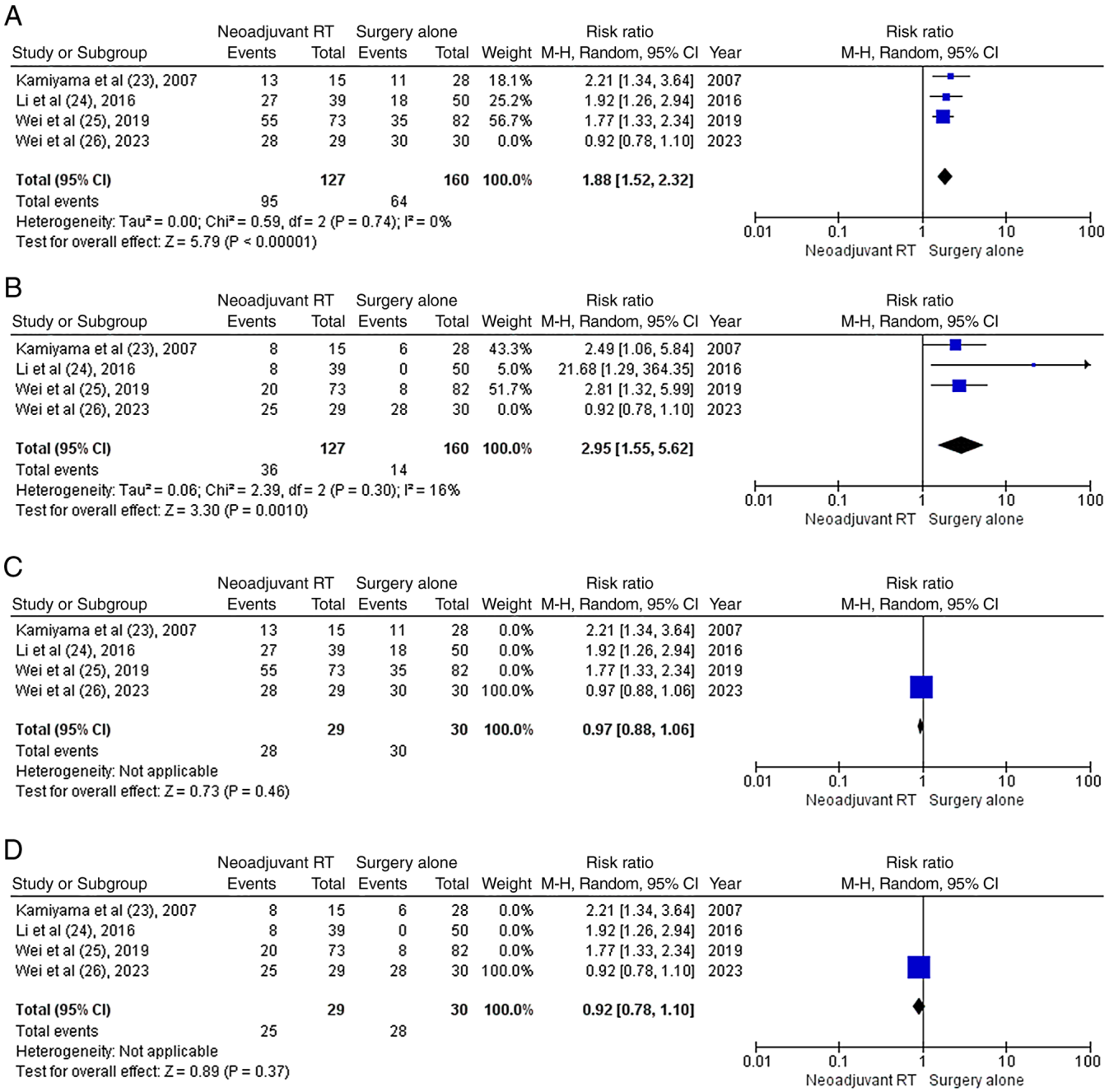

Figure 6. Pooled risk ratios of (A) 1- and (B) 2-year OS in the subgroup analysis of HCC with PVTT. Pooled risk ratios of (C) 1- and (D) 2-year OS in the subgroup analysis of HCC with MVI. OS, overall survival; PVTT, portal vein tumor thrombosis; MVI, microvascular invasion; RT, radiotherapy; HCC, hepatocellular carcinoma; CI, confidence interval; M-H, Mantel-Haenszel.

recurrence patterns or postoperative treatments sufficient to assess whether radiotherapy altered invasive or metastatic behavior. Thus, this concern remains theoretical within the current evidence base. Future trials should incorporate prospective characterization of recurrence dynamics and relevant translational endpoints to better define both benefit and risk.

Safety and feasibility remain central to the potential adoption of neoadjuvant radiotherapy in HCC. In the included studies, neoadjuvant radiotherapy was generally described as tolerable, and most treated patients proceeded to surgery, supporting feasibility in carefully selected candidates (23-26). Nevertheless, toxicity reporting was inconsistent across trials and follow-up was limited in some cohorts, which constrains inference regarding rare but clinically consequential events such as radiation-induced liver disease, postoperative hepatic decompensation and late biliary or vascular complications (17,35,36). Given the high prevalence of underlying cirrhosis and the narrow hepatic functional reserve in numerous patients with HCC (37), future studies should standardize reporting of radiotherapy technique, hepatic dose-volume parameters, perioperative morbidity and longitudinal liver function to better define the therapeutic window.

The present findings should be interpreted cautiously given the limited number of prospective studies and the substantial heterogeneity across populations and

Table V. Evidence-informed clinical implications and research recommendations.

Suggested content	Quality of evidence	Recommendation level	(Refs.)
Neoadjuvant radiotherapy improves OS/DFS in patients with PVTT	Medium	Research-based recommendation	Kamiyama *et al* (23), 2007; Li *et al* (24), 2016; Wei *et al* (25), 2019
Neoadjuvant radiotherapy improves DFS in patients with MVI	High	Unconventional recommendation	Wei *et al* (26), 2023

OS, overall survival; DFS, disease-free survival; PVTT, portal vein tumor thrombus; MVI, microvascular invasion; NA, not applicable.

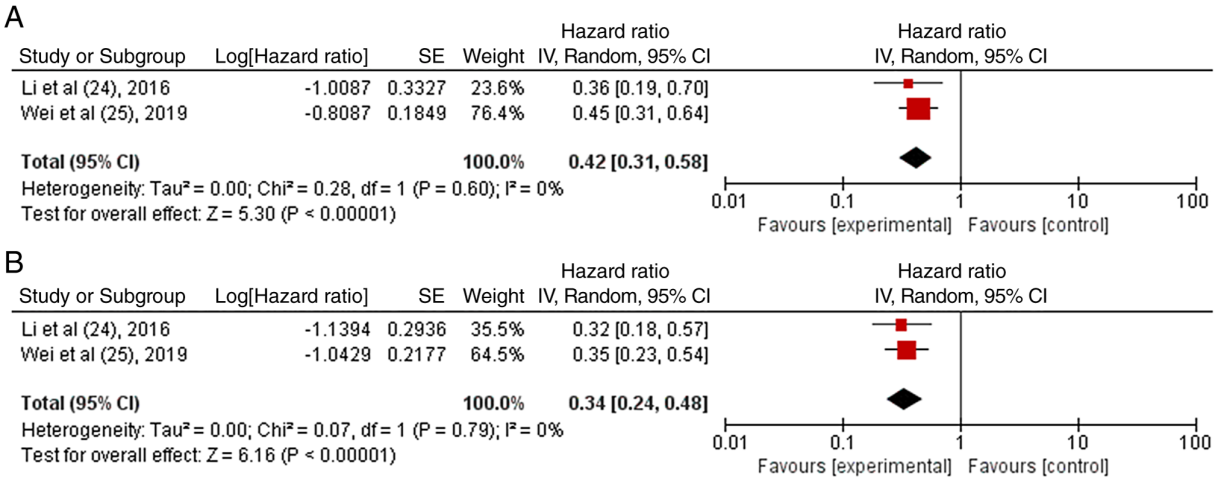

Figure 7. Pooled hazard ratio of (A) recurrence, and (B) mortality in the comparison of the neoadjuvant radiotherapy group and the surgery alone group. CI, confidence interval; SE, standard error; M-H, Mantel-Haenszel.

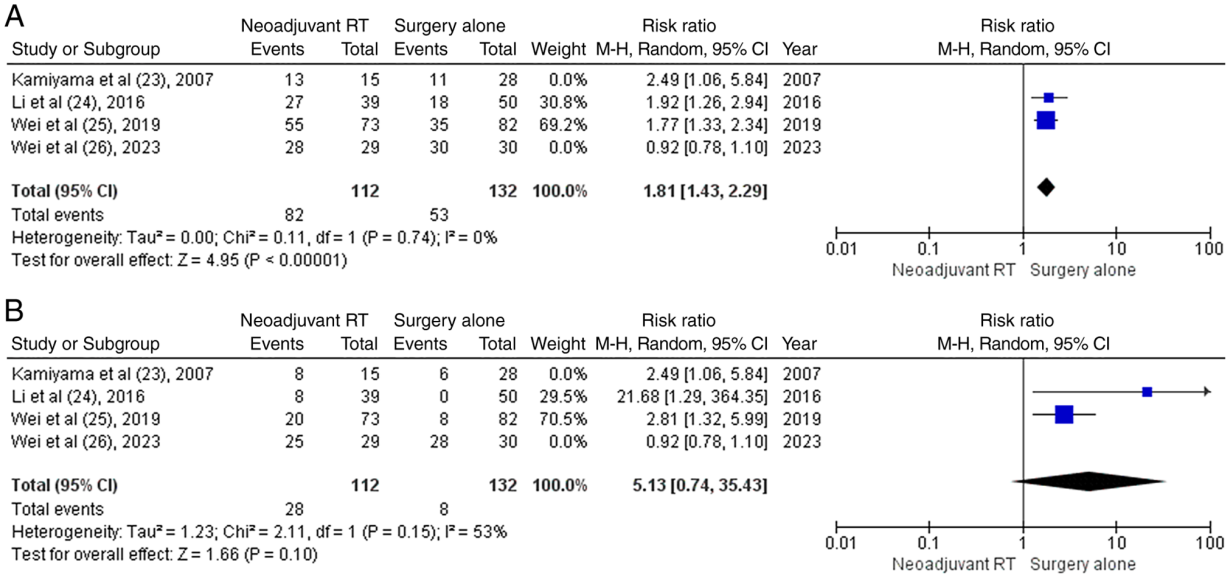

Figure 8. Sensitivity analysis of (A) 1- and (B) 2-year overall survival between the neoadjuvant radiotherapy group and the surgery alone group. RT, radiotherapy; CI, confidence interval; M-H, Mantel-Haenszel.

radiotherapy approaches. Therefore, the following points are intended as evidence-informed clinical implications and research-oriented considerations, rather than prescriptive practice recommendations. For patients with resectable HCC and PVTT, the available prospective evidence suggests that neoadjuvant radiotherapy may be considered in carefully

selected candidates within multidisciplinary decision-making and, whenever feasible, within clinical trials. In the included studies, radiotherapy was delivered predominantly using conformal techniques targeting the primary tumor and PVTT, with dose fractionation schedules commonly ranging 45-50 Gy over 15-25 fractions (38). Tumor response was typically asessed several weeks after radiotherapy using HCC-appropriate response criteria (such as modified RECIST/RECIST 1.1) (39), and subsequent surgical plans were individualized based on radiographic response, liver function reserve and technical resectability. For resectable HCC with predicted MVI, current evidence does not demonstrate a clear survival or recurrence benefit from neoadjuvant radiotherapy; thus, routine use cannot be recommended outside research settings, and any consideration should be restricted to well-designed trials with rigorous risk stratification. Consistent with this evidence profile, Table V summarizes the present evidence-aligned implications and research priorities, emphasizing the need for adequately powered multicenter trials with standardized radiotherapy protocols, time-to-event endpoints, and comprehensive reporting of both efficacy and safety outcomes.

Several limitations constrain the strength and generalizability of the present conclusions. The evidence base is small (n=4), includes only two randomized trials and contains heterogeneity in populations and radiotherapy approaches. Moreover, because the present study was based on published aggregate data rather than individual patient data, propensity score matching could not be performed. The considerable heterogeneity for overall OS/DFS indicates that pooled estimates represent average effects across settings that may differ in tumor burden, PVTT extent, surgical candidacy criteria and adjuvant therapies. Furthermore, the present primary synthesis relied on fixed time-point survival probabilities extracted from Kaplan-Meier curves, which is less informative than HRs for time-to-event outcomes and may contribute to imprecision. This strategy was used as a pragmatic alternative when standard HR-based synthesis was not possible. It is acknowledged that such RR estimates represent a secondary approximation of time-to-event outcomes after dichotomization at fixed time points and thus reflect time-point-specific cumulative risk rather than the full survival process. Accordingly, these estimates should be interpreted with caution and should not be considered fully interchangeable with HRs. Finally, all included studies were conducted in Asian populations, where hepatitis B-related HCC predominates (40), potentially limiting generalizability to regions with different etiologic profiles and treatment pathways.

In summary, current prospective evidence does not demonstrate a statistically significant survival advantage of neoadjuvant radiotherapy for the overall population of resectable HCC with vascular invasion but suggests a potential benefit in carefully selected patients with PVTT. For resectable disease with predicted MVI, the available evidence does not support routine use outside research settings. Prospective, rigorously designed multicenter trials are warranted to determine whether neoadjuvant radiotherapy targeting PVTT can improve long-term outcomes. Such studies should incorporate stratification according to the type and extent of vascular invasion, standardized radiotherapy protocols, and time-to-event endpoints with sufficient follow-up. The studies should also aim to identify the patient subgroups most likely to derive benefit while ensuring careful assessment of hepatic function and perioperative safety.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YS and YL were responsible for literature search, data collection, data analysis, statistical analysis, manuscript preparation, manuscript editing and manuscript revision. HY, QY, DZ and XH were responsible for data collection, manuscript editing, manuscript revision and final review. YS and YL confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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