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Neoadjuvant therapy for resectable hepatocellular carcinoma with portal vein tumor thrombus: an updated systematic review with meta-analysis

Weidong Lin[1*], Kunpeng Wang[1], Chenyi Pan[1] and Lei Ma[1]

Abstract

Objective This study aimed to compare survival outcomes of neoadjuvant therapy followed by surgery (Neo + Surgery) with surgery alone (Surgery) in patients with resectable hepatocellular carcinoma (HCC) and portal vein tumor thrombus (PVTT).

Methods A comprehensive search of online databases was performed from January 1990 to May 2025. Relative outcomes of RFS and OS were synthesized. The perioperative outcomes were analyzed. A single-arm meta-analysis and subgroup analysis were conducted.

Results Eight studies involving 1024 participants (417 in the Neo + surgery group vs. 607 in the Surgery group) were included. The Neo + surgery group showed a significant advantage over the Surgery group in terms of the overall hazard ratio (HR) for RFS (HR = 0.42, 95% CI: 0.33 to 0.52, $P < 0.001$) and OS (HR = 0.47, 95% CI: 0.39 to 0.56, $P < 0.001$). The pooled proportion of complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), severe adverse events (AEs) rate, and surgical contraindication rate were 9.1% (95% CI: 1.6%-20.9%, $P = 0.0028$), 36.9% (95%CI: 25.4%-49.1%, $P < 0.001$), 43.5% (95%CI: 26.8%-61.0%, $P < 0.001$), 6.3% (95% CI: 1.7%-12.9%, $P < 0.001$), 18.4% (95% CI: 5.3%-36.3%, $P < 0.001$), and 15.9% (95%CI: 8.8%-24.5%, $P < 0.001$), respectively. No significant differences were observed between the Neo + surgery group and the Surgery group regarding perioperative outcomes.

Conclusion The meta-analysis confirms that Neo + Surgery is superior to Surgery in terms of RFS and OS for patients with resectable HCC and PVTT. Our findings suggest that neoadjuvant therapy may offer clinical benefit and should be considered in selected patients with resectable HCC and PVTT.

Keywords Hepatocellular carcinoma, Portal vein tumor thrombus, Neoadjuvant therapy, Overall survival, Recurrence-free survival

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Introduction

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related death and ranks sixth incidence of malignant tumors worldwide [1]. HCC is frequently characterized by the invasion of the portal vein and the development of tumor thrombi, even in cases involving small tumors [2]. Portal vein tumor thrombus (PVTT) is a major prognostic factor associated with poor survival in HCC patients [3]. The Barcelona Clinic Liver Cancer (BCLC) staging recommends systemic therapy as the sole treatment option for HCC patients with PVTT [4]. However, surgical resection may improve prognosis and confer a chance for long-term survival in selected patients with resectable HCC and PVTT [5–10]. Consequently, surgical resection remains a viable and potentially optimal therapeutic option, as endorsed by the Japanese Society of Hepatology (JSH) consensus statements and the Chinese National Liver Cancer (CNLC) consensus guidelines in appropriately selected cases [11, 12], although it is not recommended by BCLC staging, in which systemic therapy is recommended as the sole treatment. Nevertheless, the long-term postoperative outcomes remain unsatisfactory due to the high incidence of recurrence and metastasis in patients with resectable HCC and PVTT [13, 14]. Large-scale retrospective studies have shown that the postoperative recurrence rate can reach up to 80.2%, while the 5-year overall survival (OS) rate is only 25.7% following liver resection in this patient population [15, 16].

Neoadjuvant therapy, an effective strategy for reducing tumor burden to facilitate surgical intervention and/or decrease postoperative recurrence, has demonstrated survival benefits in various solid-organ malignancies, including non-small cell lung cancer, ovarian cancer, colorectal cancer, and breast cancer [17–20]. In recent years, neoadjuvant therapy has emerged as a promising strategy to reduce postoperative recurrence and improve long-term survival in the management of HCC. Owing to its highly aggressive nature, HCC frequently invades blood vessels and gives rise to micrometastases surrounding the primary tumor. Additionally, a substantial proportion of patients are diagnosed at an advanced stage, rendering them ineligible for surgical resection. Consequently, neoadjuvant therapy represents a potentially valuable approach to enhance survival and reduce recurrence by downstaging tumor to enable surgical resection and eliminating micrometastases around the primary lesion [21]. Several studies have demonstrated that neoadjuvant therapy followed by surgery was associated with a lower recurrence rate and improved survival as compared to surgery alone in advanced HCC patients, including those with PVTT [22–25]. A recent randomized controlled trial (RCT) has demonstrated that neoadjuvant radiotherapy provided significantly better postoperative survival outcomes than surgery alone for patients with resectable HCC and PVTT [26]. However, it remains unclear whether neoadjuvant therapy followed by surgery (Neo + Surgery) provides superior survival benefits compared to surgery alone (Surgery) in resectable HCC with PVTT. Therefore, we conducted this meta-analysis to compare the survival benefit between Neo + surgery and Surgery in the treatment of patients with HCC and PVTT.

Methods

Literature search and selection

We registered our study protocol with PROSPERO(ID: CRD42024568694) (https://www.crd.york.ac.uk/PROSPERO/view/CRD42024568694). A comprehensive literature search was performed in PubMed, Embase, Web of Science, and the Cochrane Library for studies published from January 1990 to May 2025. The initial search was completed on July 31, 2024, and the final search was conducted on May 3, 2025. We used the term "hepatocellular carcinoma" for Medical Subject Headings term and relevant keywords. The search strategy for each database was presented in Suppl Table 1. The reference lists of eligible studies and relevant systematic reviews were also manually screened to identify additional records. Two independent reviewers (L.W.D. and M.L.) screened the retrieved literature and manually reviewed relevant articles.

All included studies were assessed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [27]. The inclusion criteria were: (1) population: patients with HCC and PVTT; (2) intervention: neoadjuvant therapy followed by surgery versus surgery alone; (3) outcomes: at least one of the following: recurrence-free survival (RFS), disease-free survival (DFS), or overall survival (OS); (4) study design: RCTs or observational studies (cohort or case-control studies).

Studies were excluded if they met any of the following criteria: (1) including patients with non-HCC diagnoses, such as intrahepatic cholangiocarcinoma or recurrent HCC; (2) involved HCC patients with extrahepatic metastasis; (3) were conferences abstracts, case reports, non-comparative studies, and non-English publications; or (4) had fewer than 10 participants in studies either the control or experimental group.

Data extraction and quality assessment

Data extraction and quality assessments were independently performed by two reviewers (L.W.D. and W.K.P.). Extracted data included study characteristics (first author, publication year, country, number of patients, study design, and follow-up duration); patient demographics (age, sex, tumor characteristics, and type of PVTT);

intervention details (neoadjuvant therapy regimens and surgical procedure); and survival outcomes (RFS and OS). RFS was defined as the time from surgery to recurrence or the development of a new tumor, regardless of intrahepatic or extrahepatic location. OS was defined as the time from surgery to death or last follow-up. Hazard ratios (HRs) and 95% confidence intervals (CIs) for both intervention arms were extracted. When not directly reported, HRs and risk ratios (RRs) were estimated from the Kaplan-Meier curves using Engauge Digitizer or a combination of Engauge Digitizer and HR calculation spreadsheet described by Tierney et al. [28]. Standard deviations (SDs) was estimated using the method proposed by Hozo SP et al. [29].

The quality of the included studies was assessed using different tools according to study design: RCTs were evaluated using the Cochrane Handbook for Systematic Reviews of Interventions [30]; prospective non-randomized studies were assessed using the Methodological Index for Non-Randomized Studies (MINORS) [31]; and retrospective cohort studies were evaluated using the modified Newcastle-Ottawa Scale (NOS) [32]. Any disagreements were resolved through discussion with a third reviewer (P.C.Y.).

Statistical analysis

The pooled RR with 95% CIs was calculated for dichotomous outcomes, while log-transformed HR was incorporated into a generic inverse variance meta-analysis. The pooled weighted mean difference (WMD) with 95% CIs was estimated for continuous outcomes. Single-arm meta-analyses were conducted for the Neo + surgery group.

Heterogeneity among studies was evaluated using the Cochran chi-square test and I^2 statistic, with $I^2 > 50\%$ indicating significant heterogeneity. A random-effects model was applied when heterogeneity was significant ($I^2 > 50\%$), whereas a fixed-effects model was used when heterogeneity was low ($I^2 \leqq 50\%$).

Potential publication bias was evaluated using the funnel plots and Egger's test. $P < 0.05$ (two-sided) was considered statistical significance. Certainty of evidence was appraised with GRADE across risk of bias, inconsistency, indirectness, imprecision, and publication bias; and summarized in a Summary of Findings table. All statistical analyses were performed by using STATA version 14.0 (Stata Corporation, College Station, TX, USA).

Results

Study selection and quality assessment

According to the aforementioned search protocol, a total of 5748 articles were identified through online databases from January 1, 1990, to May 3, 2025. An additional two citations were retrieved by manually searching the reference lists of included and relevant review articles. After removing duplicates, 5182 records remained for screening. Of those, 5127 were excluded based on titles and abstract screening. The full texts of the remaining 55 articles were assessed, and 47 were excluded for various reasons. Ultimately, eight full-text studies involving 1024 participants (417 in the Neo + surgery group vs. 607 in the Surgery group) were included in this meta-analysis (Fig. 1) [22, 26, 33–38]. The characteristics, quality assessment scores, and demographic information of the included studies are presented in Tables 1 and 2. Details of neoadjuvant therapy and surgical procedure are summarized in Table 3.

Recurrence-free survival

Six studies were included in the analysis of the overall HR of RFS and revealed a significant benefit in the Neo + surgery group compared to the Surgery group (HR = 0.42, 95% CI: 0.33 to 0.52, $P < 0.001$) (Fig. 2). Certainty of evidence (GRADE) for RFS was rated LOW, with no serious concerns for inconsistency, indirectness, imprecision, and publication bias, as shown in Suppl Table 2.

Overall survival

Eight studies evaluated overall HR of OS, showing a significant advantage in the Neo + surgery group compared to the Surgery group (HR = 0.47, 95% CI: 0.39 to 0.56, $P < 0.001$) (Fig. 3). Certainty of evidence (GRADE) for OS was rated LOW, with no serious concerns for inconsistency, indirectness, imprecision, and publication bias, as shown in Suppl Table 2.

Tumor response rate and AEs rate of neoadjuvant therapy

Seven studies reported the tumor response rate of neoadjuvant therapy based on mRECIST [39], six studies described adverse events (AEs) of grade $\geqq 3$, and three prospective trials reported the surgical contraindication rate. Single-arm meta-analysis was performed based on these outcomes. The pooled proportions for complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), severe AEs rate, and surgical contraindication rate were 9.1% (95% CI: 1.6%-20.9%, $P = 0.0028$), 36.9% (95%CI: 25.4%-49.1%, $P < 0.001$), 43.5% (95%CI: 26.8%-61.0%, $P < 0.001$), 6.3% (95% CI: 1.7%-12.9%, $P < 0.001$), 18.4% (95% CI: 5.3%-36.3%, $P < 0.001$), and 15.9% (95% CI: 8.8%-24.5%, $P < 0.001$), respectively (Suppl Fig. 2A-F).

Surgery-related outcomes

A comparative analysis of surgery-related outcomes, including intraoperative blood loss, perioperative blood transfusion rates, mortality, and postoperative complications, indicated no significant differences between the

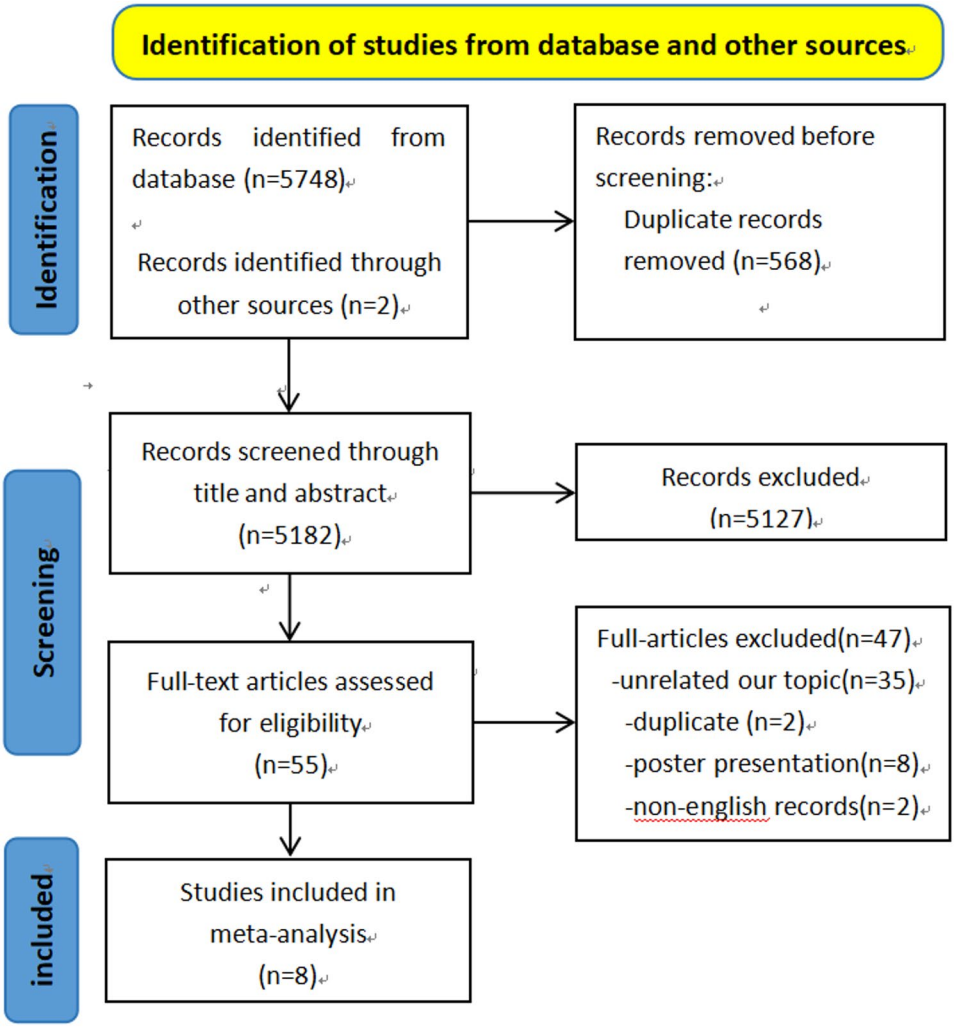


Fig. 1 Flowchart of study selection

Table 1 Characteristics and quality assessment of the included studies

Studies	Year	Country	Intervention	Study Period	Study Type	Quality Assessment
Kamiyama et al. [33]	2007	Japan	Neo + Surgery vs. Surgery	1990–2006	Retrospective cohort	8#
Li et al. [22]	2016	China	Neo + Surgery vs. Surgery	2010–2013	Non-RCT	20Δ
Zhang et al. [34]	2016	China	Neo + Surgery vs. Surgery	2006–2011	Non-RCT	22Δ
Chong et al. [35]	2018	South Korea	Neo + Surgery vs. Surgery	2005–2014	Retrospective cohort	7#
Wei et al. [26]	2019	China	Neo + Surgery vs. Surgery	2016–2017	RCT	*
Cao et al. [36]	2023	China	Neo + Surgery vs. Surgery	2015–2021	Retrospective cohort	8#
Hu et al. [37]	2023	China	Neo + Surgery vs. Surgery	2017–2021	Retrospective cohort	8#
Hou et al. [38]	2024	China	Neo + Surgery vs. Surgery	2015–2022	Retrospective cohort	8#

Non-RCT indicates nonrandomized controlled trial; RCT indicates randomized controlled trial

Retrospective cohort was evaluated by using Newcastle-Ottawa Quality Assessment Scale(NOS)

Δ Non-RCT was evaluated by using Methodological Index for Non-randomized Studies (Minors)

* RCT was evaluated by using Cochrane handbook systematic reviews of interventions, which was shown in Supplementary Fig. 1

Table 2 Demographics of the included studies

Studies	No.of Patients	Age(Mean)	Sex (male%)	Hepatitis	Tumor number (Single%)	Tumor size (Mean, cm)	Type of PVTTΔ	Period of Follow-up (Mean, mo)
				HBV HCV			VP1/2 VP3/4	
Kamiyama et al. [33]	15/28	53.5/56.1	86.7/89.3	7/16 2/3	60.0/42.9	6.47/11.0	0 15/28	83
Li et al. [22]	45/50	50/47	95.6/84	37/44 NA	93.3/80.0	10/9	0 45/50	8.4
Zhang et al. [34]	115/205	47.9/46.8	89.6/94.6	105/194 3/2	61.7/58.5	9.1/9.9	46/91 69/114	NA
Chong et al [35]	26/18	50.0/48.7	84.6/77.8	22/15 0/0	NA	4.4/6.4	12/14 14/4	13
Wei et al. [26]	82/82	52.8/50.5	81.7/90.2	75/76 0/0	89.0/84.1	39.0%/51.2%#	0 82/82	15.2/10.8
Cao et al. [36]	36/64 (25/25*)	56/55	84.0/84.0	27/33 5/3	58.3/65.6	8.92/7	4/13 32/51	21.6/53.2
Hu et al. [37]	65/55 (43/43*)	47.4/50.0	80.6/90.7	58/51 0/1	69.2/67.3	9.50/9.17	21/30 44/25	33.8/38.7
Hou et al. [38]	33/105 (29/58*)	50.7/53.3	90.9/89.5	31/99 1/5	78.7/80.9	6.1/28.6#	14/59 19/46	26

Δ Type of PVTT is stratified according to PVTT classification of Japan Society of Hepatology

* indicates after propensity score matching

# indicates the proportion of tumors larger than 10 cm

* AR indicates anatomic resection, *NA* not applicable

Table 3 Neoadjuvant therapy and surgical characteristics of the included studies

Studies	Regimens of Neo-therapy	Details of Neo-therapy	Type of hepatectomy (Major %)	AR*(%)	R0 resection(%)	Type of thrombectomy
						En bloc(%) thrombectomy (%)
Kamiyama et al. [33]	RT	30 Gy in 10 fractions	NA	NA	NA	0 100/100
Li et al. [22]	3DCRT	18 Gy in 6 fractions	59.0/44.0	46.2/48.0	NA	0 100/100
Zhang et al. [34]	TACE	MMC + LBP + EPI(1–2 sessions)	NA	50.6/35.6	97.6/86.3	70.6/35.6 29.4/64.4
Chong et al. [35]	CCRT + HAIC	45 Gy in 25 fractions/HAIC with 5-FU + DDP(3–12 sessions)	92.3/61.1	NA	100/100	NA
Wei et al. [26]	3DCRT	18 Gy in 6 fractions	79.5/70.0	32.9/29.3	98.6/98.8	26.0/20.7 74.0/79.3
Cao et al. [36]	TKI + PD-1	NA	75.0/71.9	NA	100/100	47.3/53.1 52.7/46.9
Hu et al. [37]	HAIC	HAIC with FOLFOX (average times: 3.2)	NA	NA	100/100	NA
Hou et al. [38]	TKI + PD-1 + TACE	NA	45.5/42.9	69.7/62.9	100/100	NA

RT radiotherapy, *3DCRT* three-dimensional conformal radiotherapy, *TACE* transarterial chemoembolization, *CCRT* concurrent chemoradiotherapy, *HAIC* hepatic arterial infusion chemotherapy, *TKI* tyrosine kinase inhibitor, *PD-1* programmed death antibody. *MMP* mitomycin, *LBP* lobaplatin, *EPI* epirubicin, *DDP* cisplatin, *NA* not applicable

Neo + surgery group and the Surgery group (all $P > 0.05$) (Suppl Fig. 3A-D).

Subgroup analysis

Subgroup analysis for types of PVTT

PVTT was categorized into third-order branch (VP1), second-order branch (VP2), first-order branch (VP3), and main trunk/contralateral branch (VP4) according to portal vein tumor thrombosis classification of Japan Society of Hepatology [40]. Two studies (Zhang 2016 and Hu 2023), involving 188 patients (67 in the Neo + surgery group and 121 in the Surgery group), reported outcomes for type VP1/2 in terms of OS and were subsequently analyzed. The Neo + surgery group showed a significantly better OS compared to the Surgery group in the type VP1/2 subgroup (HR = 0.57, 95% CI: 0.37–0.88, P = 0.003). Five studies (Kamiyama 2007, Li 2016, Wei 2019, Cao 2023, and Hu 2023) encompassing 454 participants (218 in the Neo + surgery group and 236 in the Surgery group) described outcomes for type VP3/4 in terms of OS and were evaluated. The Neo + surgery group exhibited a significant OS benefit compared to the Surgery group in the type VP3/4 subgroup (HR = 0.58, 95% CI: 0.36–0.93, P = 0.022) (Fig. 4).

Subgroup analysis for study type

The included studies were stratified by study design into a prospective group (Li 2016, Zhang 2016, and Wei 2019) and a retrospective group (Kamiyama 2007, Chong 2018, Cao 2023, Hu 2023, and Hou 2024). The Neo + surgery group had a significant OS benefit compared with the Surgery group both in the prospective subgroup (HR = 0.43, 95% CI: 0.27–0.71, P = 0.001) and the retrospective subgroup (HR = 0.40, 95% CI: 0.29–0.55, $P < 0.001$) (Fig. 5).

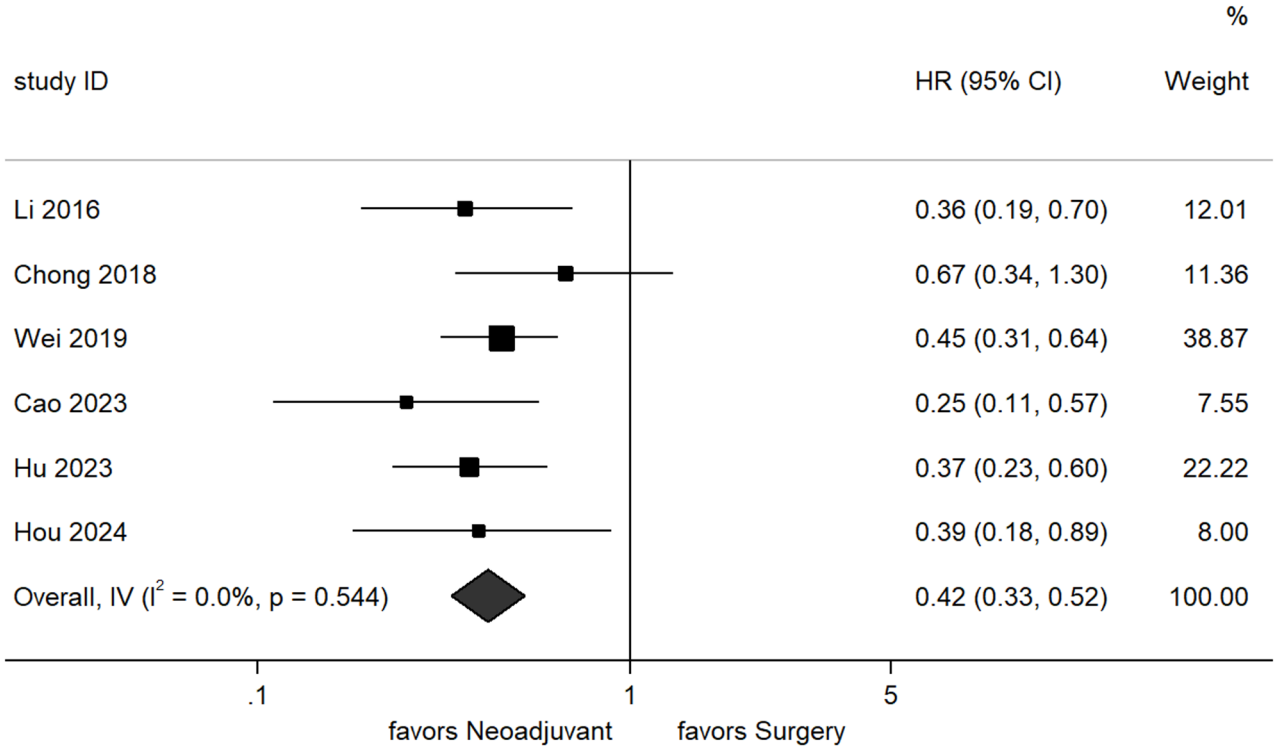


Fig. 2 Forest plot of the results of the meta-analysis comparing RFS of the two groups

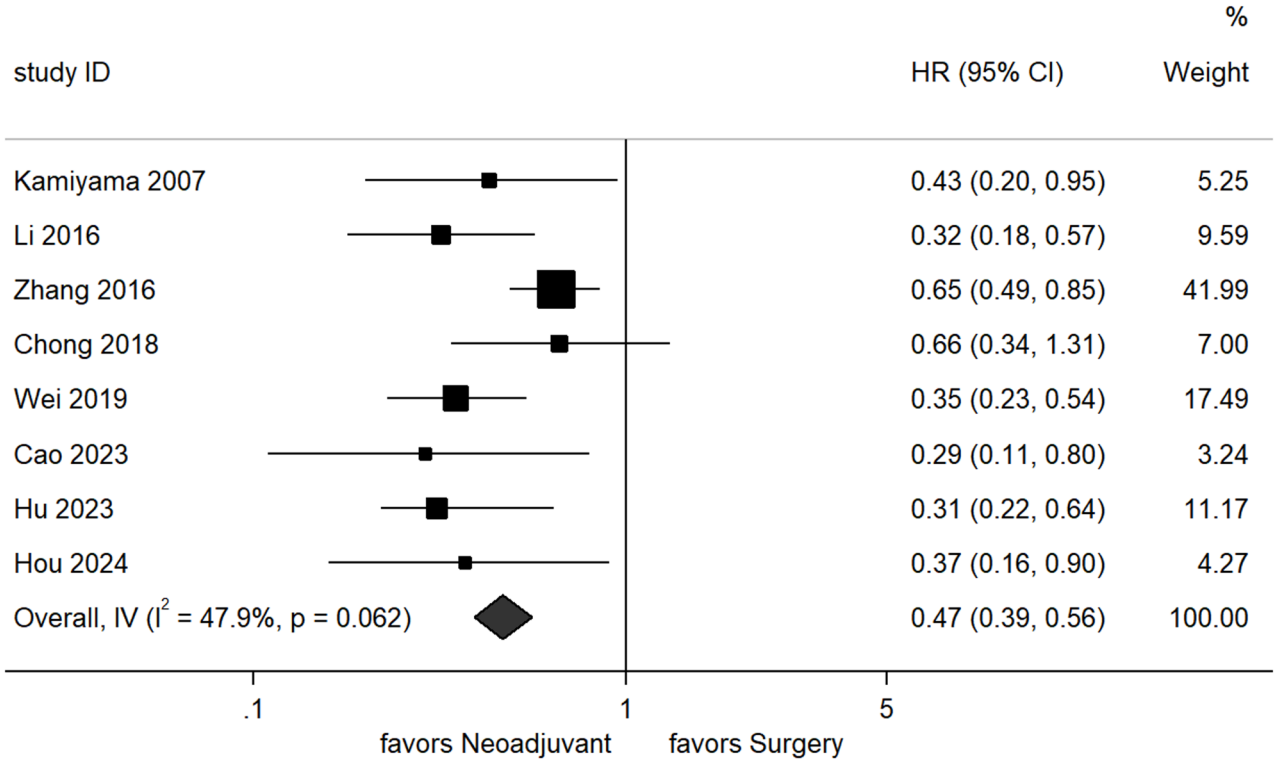


Fig. 3 Forest plot of the results of the meta-analysis comparing OS of the two groups

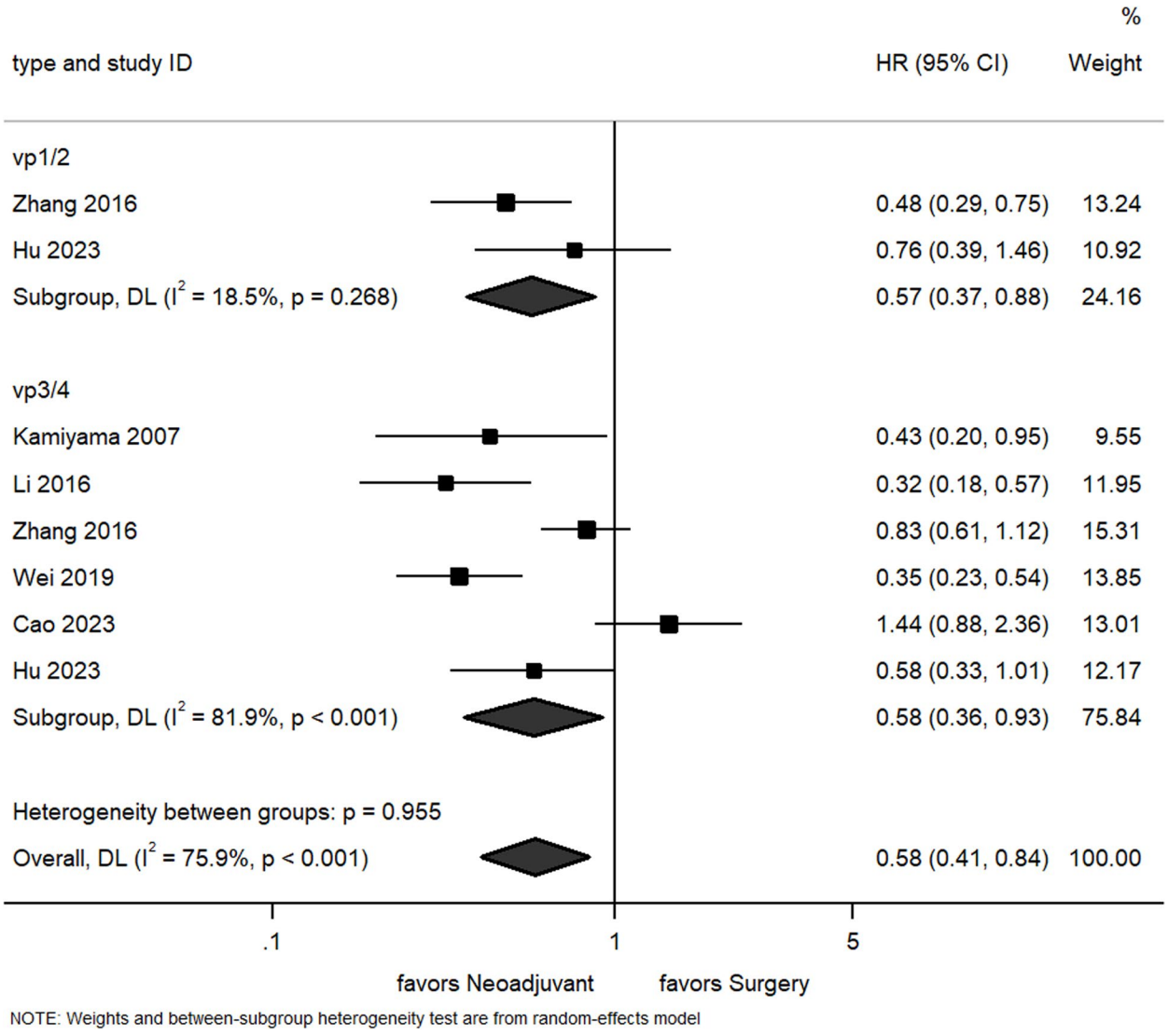


Fig. 4 Forest plot of the results of the subgroup analysis based on vp types

Subgroup analysis for modalities of neoadjuvant therapy

According to the modalities of neoadjuvant therapy, the included studies were categorized into a radiotherapy (RT) group (Kamiyama 2007, Li 2016,and Wei 2019) and a non-RT group (Zhang 2016, Chong 2018, Cao 2023, Hu 2023, and Hou 2024). The Neo + surgery group showed a significant OS benefits compared with the Surgery group, both in the RT (HR = 0.35, 95%CI: 0.26–0.48, $P < 0.001$) and the non-RT subgroups (HR = 0.53, 95%CI: 0.43–0.66, $P < 0.001$) (Fig. 6).

Publication bias and sensitivity analysis

Visual inspection of funnel plots for OS and RFS did not reveal marked asymmetry, and Egger's test was non-significant (all $P > 0.05$), suggesting a low likelihood of publication bias. Sensitivity analyses have confirmed the robustness of the results (Suppl Table 3, Suppl Fig. 4, and Suppl Fig. 5).

Discussion

This meta-analysis incorporated the most recent studies from 2007 to 2024 to compare outcomes of Neo + Surgery versus Surgery in patients with resectable HCC and PVTT. As summarized in Table 1, although only one study was a RCT, the majority of the included studies were of relatively high quality based on quality assessment results. Moreover, most outcomes demonstrated no significant heterogeneity across studies, and sensitivity analyses confirmed that individual research did not disproportionately influence the results. Importantly, in terms of evidence hierarchy, meta-analyses including non-RCTs are not inherently inferior to those limited to RCTs [41].

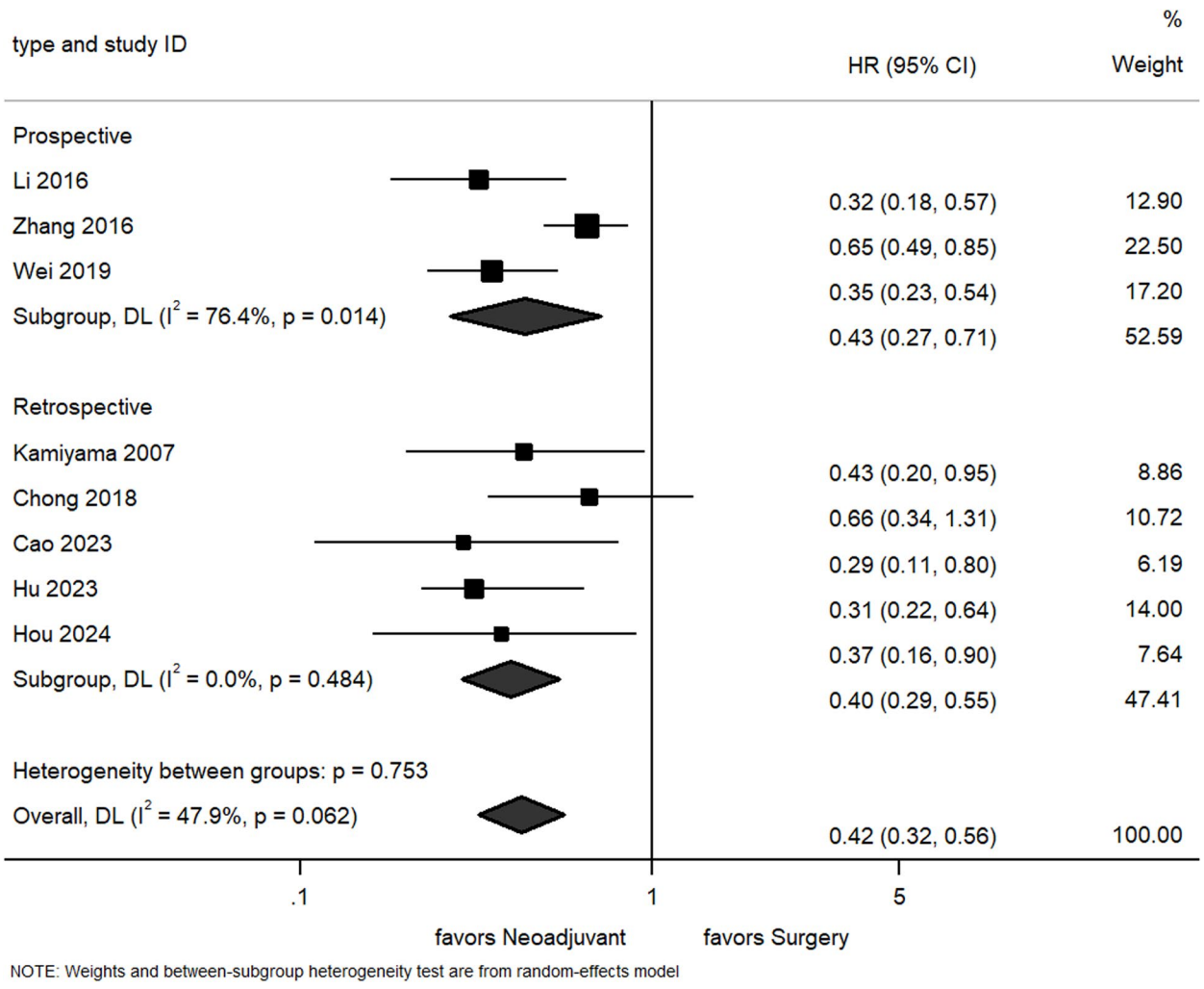


Fig. 5 Forest plot of the results of the subgroup analysis based on study types

A systematic review on neoadjuvant RT for HCC with PVTT was published in 2022 by Wei et al. [42]. Only 3 studies (involving 302 patients) were included, and OS is the sole analytical metric in this review. Moreover, a meta-analysis on this topic was recently published in 2025 by Xuan et al., which included 6 studies comprising 750 participants [43]. However, their analysis focused solely on survival benefits and perioperative outcomes to compare neoadjuvant therapy followed by surgery versus surgery alone. Their results indicated that the Neo + surgery group had significantly better OS (HR = 0.39, 95%CI: 0.30–0.50, $P < 0.001$) and RFS (HR = 0.31, 95%CI: 0.17–0.55, $P < 0.001$) compared to the Surgery group; while the perioperative outcomes were similar between the Neo + surgery group and the Surgery group. In contrast, we not only perform meta-analyses focusing on survival benefits and perioperative outcomes, but also conduct single-arm meta-analyses to comprehensively evaluate the efficacy and safety of different neoadjuvant regimens. Additionally, we perform detailed subgroup analyses to validate the robustness and reliability of our findings. Furthermore, certainty of evidence for primary outcomes was appraised with GRADE. Finally, our study includes more recent publications, which encompass 8 studies with a total of 1024 participants, and provides the most up-to-date evidence on neoadjuvant therapy followed by surgery in patients with resectable HCC and PVTT.

Many studies have demonstrated that hepatic resection with the removal of PVTT improved prognosis for selected patients with HCC and PVTT [44–47]. Moreover, several studies have evaluated liver transplantation as a potential treatment option for HCC patients with PVTT [48, 49]. Therefore, in contrast to Western guidelines such as BCLC staging, surgery, involving liver transplantation, remains a significant treatment option for selected patients with HCC and PVTT in China and Southeast Asia [50, 51]. However, even after surgical excision of tumors along with the PVTT in HCC patients, early recurrence is noted in most cases, and overall prognosis is still poor [13]. As proposed by Mazzotta et al.,

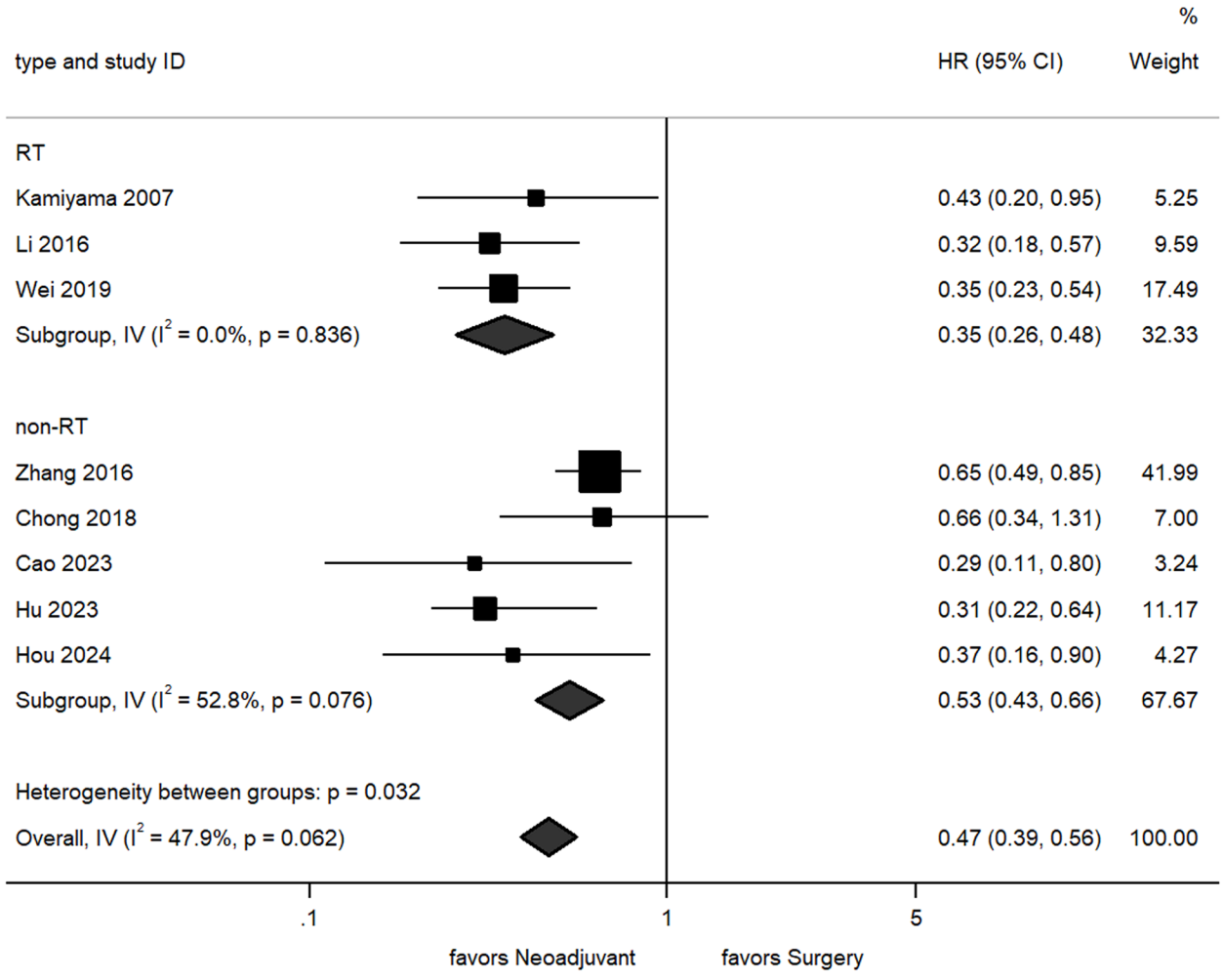


Fig. 6 Forest plot of the results of the subgroup analysis based on modalities of neoadjuvant therapy

the aggressive biology and excessive tumor burden significantly contributed to the poor prognosis in HCC patients with PVTT [52]. Therefore, application of neoadjuvant or adjuvant strategies to minimize recurrence risk is crucial. Recently, the role of neoadjuvant therapy for advanced HCC has been explored widely [21]. However, the outcomes of neoadjuvant therapy for patients with HCC and PVTT remain unclear. The present study demonstrated that Neo + surgery had significantly survival benefits compared to Surgery in resectable HCC with PVTT. Furthermore, several different study types were encompassed in the included studies, which may impact the robustness of the results. Besides five retrospective cohorts, there are two relatively high-quality prospective non-RCTs and one prospective RCT among the included studies. Therefore, we performed subgroup analysis to verify the reliability of our findings based on the study type (the prospective group and the retrospective group). The subgroup analysis indicated that the Neo + surgery group conferred a significant OS advantage over Surgery within both prospective and retrospective groups. These findings suggest that Neo + surgery is superior to Surgery for patients with resectable HCC and PVTT. The Neo + surgery may be a promising treatment strategy for patients with resectable HCC and PVTT.

PVTT was classified into four types (VP1-VP4) according to the Japan Society of Hepatology classification. Anatomical or non-anatomical hepatic resection with en bloc thrombectomy is considered feasible for HCC with PVTT of types VP1 and VP2, but generally not for HCC with PVTT of types VP3 and VP4. Surgical resection offers a more favorable OS benefit for patients with type VP1/2 PVTT, exhibiting 5-year OS rates ranging from 10% to 59%, in contrast to those with type VP3/4 PVTT, who have 5-year OS rates between 0% and 26% [53]. Consequently, it is a reasonable strategy to downstage tumors for facilitating radical resection for patients with type VP3/4 PVTT by neoadjuvant therapy. Notably, patients classified as having type VP3/4 PVTT constitute the majority of participants in the included studies of this meta-analysis, as illustrated in Table 2. We conducted a subgroup analysis based on VP types. The results indicated that the Neo + surgery group showed

a significant OS advantage compared to the Surgery group in both the type VP1/2 subgroup and the type VP3/4 subgroup. The findings suggest that the benefits associated with neoadjuvant treatment may be attributed to various mechanisms, including eradication of micrometastases surrounding the primary tumor, prediction of sensitivity to anticancer regimens, and tumor downstaging to facilitate radical resection in resectable HCC with PVTT. However, it is important to note that only two studies, comprising 188 patients, were included in the type VP1/2 subgroup. Therefore, potential heterogeneity among included studies and the limited sample sizes should be carefully considered when interpreting these results. On the other hand, the results indicate that HCC patients with type VP3/4 PVTT are more likely to benefit from neoadjuvant therapy. Further studies are warranted to better define the outcomes of neoadjuvant therapy for different PVTT types.

It has been demonstrated that various treatment modalities, including TACE, HAIC, and RT, were effective in the management of HCC with PVTT [54]. These modalities result in tumor responses to a certain extent and apply to candidates of neoadjuvant therapy for HCC with PVTT. Tumor response rate is a crucial factor in determining neoadjuvant regimens for HCC with PVTT [21].

We performed a single-arm meta-analysis of tumor response rates based on seven included studies. The results indicated that these modalities achieved an objective response rate(ORR, CR + PR) of 45.96% and a disease control rate(DCR, CR + PR + SD) of 94.7% in the treatment of patients with HCC and PVTT. Additionally, there was no significant difference between the Neo + surgery group and the Surgery group in perioperative outcomes. Furthermore, a major clinical concern remains the surgical contraindication rate caused by either severe AEs during neoadjuvant therapy or tumor progression during the treatment period. Our single-arm meta-analysis revealed the pooled rates of severe AEs and surgical contraindication of 18.4% and 15.9%, respectively. These findings indicate that the current neoadjuvant modalities are effective and relatively safe for HCC with PVTT, and feasible for clinical use.

There is increasing evidence supporting the utility of RT in the management of HCC, particularly in cases with PVTT [55, 56]. Zhang et al. demonstrated that PVTT is more radiosensitive, providing a rationale for the application of radiotherapy in HCC patients with PVTT [57]. Additionally, several studies have confirmed that RT was both effective and safe for managing HCC with PVTT [58, 59]. Furthermore, RCTs have shown that combining RT with surgery yields a significant OS benefit compared to surgery alone for the treatment of HCC patients with PVTT, whether RT is administered as neoadjuvant therapy prior to surgery or as adjuvant therapy postoperatively [26, 60]. Among the included studies, three investigations (Kamiyama 2007, Li 2016, and Wei 2019) utilized RT as a neoadjuvant regimen. However, it remains unclear whether RT outperforms other modalities as a neoadjuvant therapy for HCC with PVTT. To address this, we conducted subgroup analysis based on different neoadjuvant regimens from the included studies (RT group and non-RT group). The results indicated that the Neo + surgery group was superior to the Surgery group both in the RT subgroup and in the non-RT subgroup. These findings suggest that multiple modalities, beyond RT, are effective and feasible options for neoadjuvant therapy in HCC patients with PVTT. However, given the high heterogeneity of HCC and the lack of precise indices or models to predict the efficacy of neoadjuvant therapy [61], further studies are needed to identify individualized and optimal approaches for neoadjuvant treatment in HCC with PVTT.

This meta-analysis has several limitations that warrant consideration. First, most included studies were non-RCTs, which may introduce selection and publication bias. Second, the neoadjuvant therapeutic regimens across the included studies varied, and some information regarding follow-up periods for both groups was invalid, contributing to heterogeneity in the results to some extent. Third, some studies had relatively small sample sizes, which may affect the robustness of statistical analyses and the generalizability of the findings. Finally, the study population is predominantly East Asian, and given the distinct characteristics of HCC between Asian and Western populations, the applicability of these findings to a global context is restricted.

Conclusion

In conclusion, our study demonstrates that Neo + surgery is superior to Surgery in terms of RFS and OS among patients with resectable HCC and PVTT. These findings suggest that neoadjuvant therapy may offer clinical benefit and should be considered in selected patients with resectable HCC and PVTT, particularly in settings where surgery is already established as standard care. Further prospective studies are needed to confirm these findings and establish guideline-level recommendations.

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

Supplementary Material 5.

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Authors' contributions
Study conception and design: Weidong Lin and Kunpeng Wang. Material preparation, data, and retrieval: Weidong Lin, Kunpeng Wang, Chenyi Pan, and Lei Ma. Data analysis and interpretation: Weidong Lin, Kunpeng Wang, Chenyi Pan, and Lei Ma. Statistical analysis: Weidong Lin, Chenyi Pan, and Lei Ma. Manuscript preparation: Weidong Lin and Kunpeng Wang. Manuscript editing: Weidong Lin and Lei Ma. Manuscript review: Weidong Lin, Kunpeng Wang, Chenyi Pan, and Lei Ma. Funding acquisition: Weidong Lin.

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Data availability
All data relevant to the study are included in the article or uploaded as supplementary information.

Declarations

Ethics approval and and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

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