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ORIGINAL ARTICLE

Which is the best combination of surgery for hepatocellular carcinoma with hepatic/portal vein thrombosis in China: a network meta-analysis of randomized controlled trials

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Summary

Purpose: *To assess the efficacy and safety of different perioperative regimens using network meta-analysis for hepatocellular carcinoma (HCC) with hepatic/portal vein thrombosis. The interested modalities included neoadjuvant three-dimensional conformal radiotherapy (3D-CRT), post-operative intensity modulated radiation therapy (IMRT). post-operative transarterial chemoembolization (TACE) and surgery alone.*

Methods: *PubMed and Cochrane Library electronic databases were systematically searched for eligible studies published up to November 2020. Data related to treatment efficacy including overall survival (OS), and disease-free survival (DFS) were extracted and compared using a Bayesian approach. Adverse events (AEs) were assessed and compared.*

Results: *Four studies published between 2005 and 2020 involving a total of 422 patients were enrolled in this network meta-analysis. The comparison showed that surgery with IMRT ranked relatively higher in prolonging OS in advanced HCC patients, followed by neoadjuvant 3DCRT and surgery plus TACE. Postoperative IMRT appeared better choice in terms of DFS. The rate of AEs did not significantly differ*

Conclusions: *Adjuvant IMRT showed more favorable treatment responses compared with other regimens in HCC patients with hepatic/portal vein thrombosis.*

Key words: *IMRT, 3D-CRT, TACE, advanced, HCC, network meta-analysis*

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second most frequent cause of cancer-related death globally [1]. 70-80% of HCC patients are diagnosed at an advanced stage and their prognosis is extremely poor, with survival limited to about only several months [2].

HCC with multiple tumors more than 5 cm or tumor involving a major branch of the portal or hepatic veins were considered as advanced stage (according to the UICC TMM staging system and the BCLC staging system). Guidelines in Europe and America recommend conservative methods rather than surgery as treatments [2], while experts from Southeast Asian countries hold different opinions [3]. Kokudo et al [4] have compared surgical and non-surgical treatments in advanced-stage HCC patients and found surgery yields better survival outcomes. Two meta-analyses conducted by Liang et al [5] and Zhang et al [6] also suggest similar trending. Some suggest a multidisciplinary therapy including transcatheter arterial chemoembolization (TACE), and radiotherapy (RT) should also be

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considered to achieved more satisfactory results [7-11]. Relevant studies have reported that pre-operative TACE showed good tumor response than surgery alone [12]. Other researchers indicated that patients could gain more benefits by adding RT before or after surgery [10,13]. Therefore, the purpose of this network meta-analysis was to evaluate the efficacy and safety of these regimens in terms of OS and DFS and severe adverse events (AEs) and determine which is the best combination of surgery in HCC patients with hepatic/portal vein thrombosis.

Methods

Literature search

We conducted this network meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. A systematic literature search of PubMed and Cochrane Library from November 2005 through November 2020 was performed. The search strategy was based on combinations of the following keywords: ("liver neoplasm" [MeSH terms]) OR ("hepatocellular carcinoma" [MeSH terms]) AND [all fields]) AND ((advanced [Mesh]) OR ("Portal vein tumor thrombus" or "PVTT") OR ("hepatic vein"). In addition, we manually examined the titles of all references within the selected articles to identify other potentially appropriate articles. Two authors (QW and TZ) evaluated the titles and abstracts independently. Disagreements were discussed until consensus was reached. Letters to the editor, case reports, nonrandomized trials, animal studies, editorials, and posters were excluded. The language was also restricted to English.

Study selection criteria

The selected studies had to meet the following criteria: 1) included patients with pathologically proven HCC with PVTT or hepatic vein invasion; 2) The primary liver tumor being resectable and regimens were mainly focused on perioperative treatments, and surgery alone was used as control group; 3) detailed data on method, characteristics of patient population, the rate of all grade and grade 3-4 AEs, and overall survival; 4) compared at least two arms that consisted of the abovementioned interested regimens; 5) Design-Only randomized clinical trials (RCTs).

Data extraction and quality assessment

Two authors (QW and TZ) independently reviewed and screened all eligible studies based on the study selection criteria detailed above. The following data were extracted and summarized in a standardized table, including the study's first author; characteristics of the population; and inclusion of patients, interventions, sample size, numbers randomized trials to each arm (Table 1). The assessment of primary outcome in this study was OS and DFS. AEs rates were the secondary outcome we measured and compared.

Methodological quality and risk of bias assessment

The quality of the included studies was assessed using the Cochrane risk of bias tool (Version 5.1.0) [14]. Each study was evaluated independently by two authors explicitly with the following judgement system: low risk of bias, high risk of bias, or unclear (either lack of information or uncertainty for bias).

Statistics

We conducted a network meta-analysis to compare the outcomes among the 4 studies for advanced HCC, which included direct (ie, head-to-head) and indirect treatment comparisons. We extracted the OS and DFS data directly from the studies to hazard ratios (HRs) with 95% confidence intervals (95% CIs). We utilized the GEMTC package v 0.8-7 in R version 4.0.2 to perform a Bayesian analysis. The fixed effects model and consistency models were used to calculate ORs and 95% credibility intervals due to its relatively lower deviance information criterion (DIC). OS and PFS data were expressed as HR, with corresponding 95% CIs. We utilized the Addis version 1.16.5 to analyze AE rates using relative risk (RR), with corresponding 95% CIs. We used non-informative prior distributions and over-dispersed initial values with a scale of 0–5, in four chains to fit the model. This yielded 150,000 iterations, including 20,000 tuning iterations and a thinning interval of 10 for each chain.

This method was also used to generate distribution parameters for the model. Convergence of iterations was assessed using the Gelman–Rubin–Brooks statistic [14]. According to posterior probabilities, we were able to rank probabilities for each intervention. Due to the absence of head-to-head clinical trials, it was not possible to conduct consistency testing. The apparent heterogeneity within the study population meant that we should not combine the two postoperative TACE studies for pooled analysis, and therefore we opted to analyze each study separately. Indirect comparisons were performed for different regimens, such as Neoadjuvant 3DCRT versus postoperative IMRT. The adjusted indirect comparison was calculated using Bayesian methods embedded in the following formula: ln(HR)=[ln(UL – HR) + ln(LL – HR)]/2; seln(HR)

Table 1. Clinical baseline characteristics of the included studies

First author	*Primary tumor & PVTT type*	*BCLC/UICC stage*	*Total number*	*Arm (regimen/control)*
Wei	Resectable; TypeII/III PVTT	Stage C/IIIb	151	Neo3DCRT+Surgery /Surgery
Sun	Resectable; TypeI-IV PVTT	Stage C/IIIb	52	Surgery+IMRT/Surgery
Peng	Resectable; TypeI-IV PVTT	Stage C/IIIb	104	Surgery+TACE/Surgery
Zhong	Resectable; TypeI-IV PVTT	Stage B-C/IIIa-IIIb	115	Surgery+TACE/Surgery

=[ln(UL–HR)–ln(LL–HR)]/(1.96×2); RR was calculated as follows; log(HR)=[log(UL – HR) + log(LL – HR)]/2; selog(HR)=[log(UL – HR) – log(LL – HR)]/ (1.96×2); HR <1 or RR <1 to identify treatment superiority.

Results

Study selection and patient characteristics

A total of four trials involving 422 patients were included [13,15-18]. The complete trial selection process is provided in Figure 1. Three trials provided complete OS, PFS, and AE data. Detailed studies and participant characteristics are also provided (Table 1).

Structure of network meta-analysis (NMA) and risk of bias

The network plot of treatment regimens used in the analysis is provided as Figure 2. We compared four treatment regimens, that is, neoadjuvant 3D-CRT, postoperative IMRT, postoperative TACE and surgery alone which was used as control. All four studies were randomized control studies. The included populations were not discernibly different. The results of the risk of bias are shown in Figure 3.

NMA results for OS, PFS

When compared with surgery alone, the results suggested that postoperative IMRT significantly prolonged OS (HR 0.44; CI 0.24–0.82), followed with neoadjuvant 3DCRT (HR 0.51; 0.34-0.76) and postoperative TACE(HR 0.64; CI 0.47-0.88). Each of the included interventions [IMRT (HR 0.36;0.20-0.66), 3DCRT (HR0.63; 0.46-0.86), TACE (HR0.62; 0.42-0.92)] was significantly superior to surgery alone in terms of DFS. Further indirect comparisons of the interventions suggested IMRT ranked relatively higher than 3DCRT and TACE in terms of OS and DFS but without statical significance (Figure 4).

The results of SUCRA curve for each treatment in terms of OS demonstrated the same results i.e. that Postoperative IMRT was the best regimen (SUCRA 0.8325) followed by neoadjuvant 3D-cRT (0.7236) and TACE (SUCRA 0.4412). Surgery alone was the worst (SUCRA 0.0026) regimen for advanced-stage HCC patients. Meanwhile, associated PFS measures were ranked from high to low, as follows: IMRT (SUCRA 0.9592), TACE (0.5274), 3DCRT (0.5097), surgery alone (0.0037).

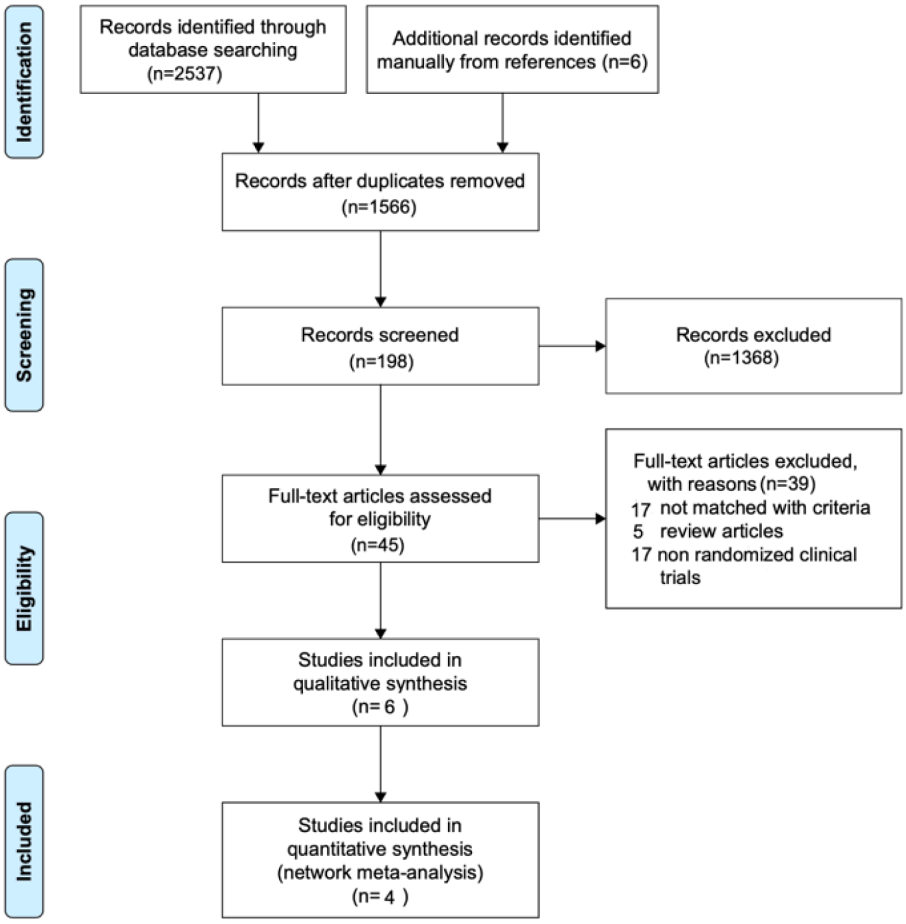

Figure 1. Flowchart of study identification and selection process.

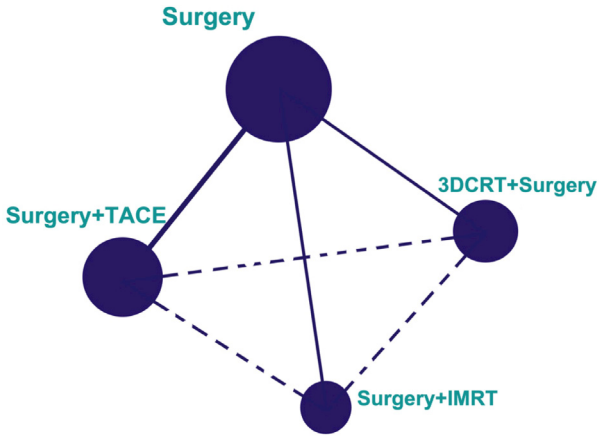

Figure 2. Network maps of comparing interventions. Each circular node represents a type of treatment. The circle size is proportional to the total number of patients (under the drug name). The width of lines is proportional to the number of studies performing head-to-head comparisons in the same study, and the dotted line is the indirect comparison shown in this NMA.

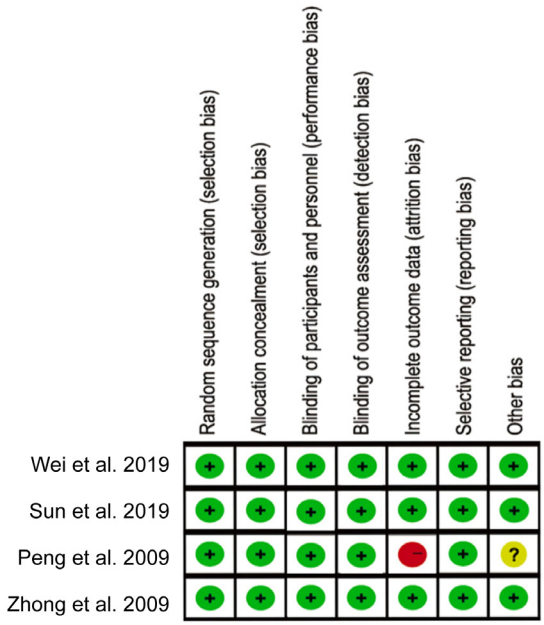

Figure 3. The risk of bias of included studies.

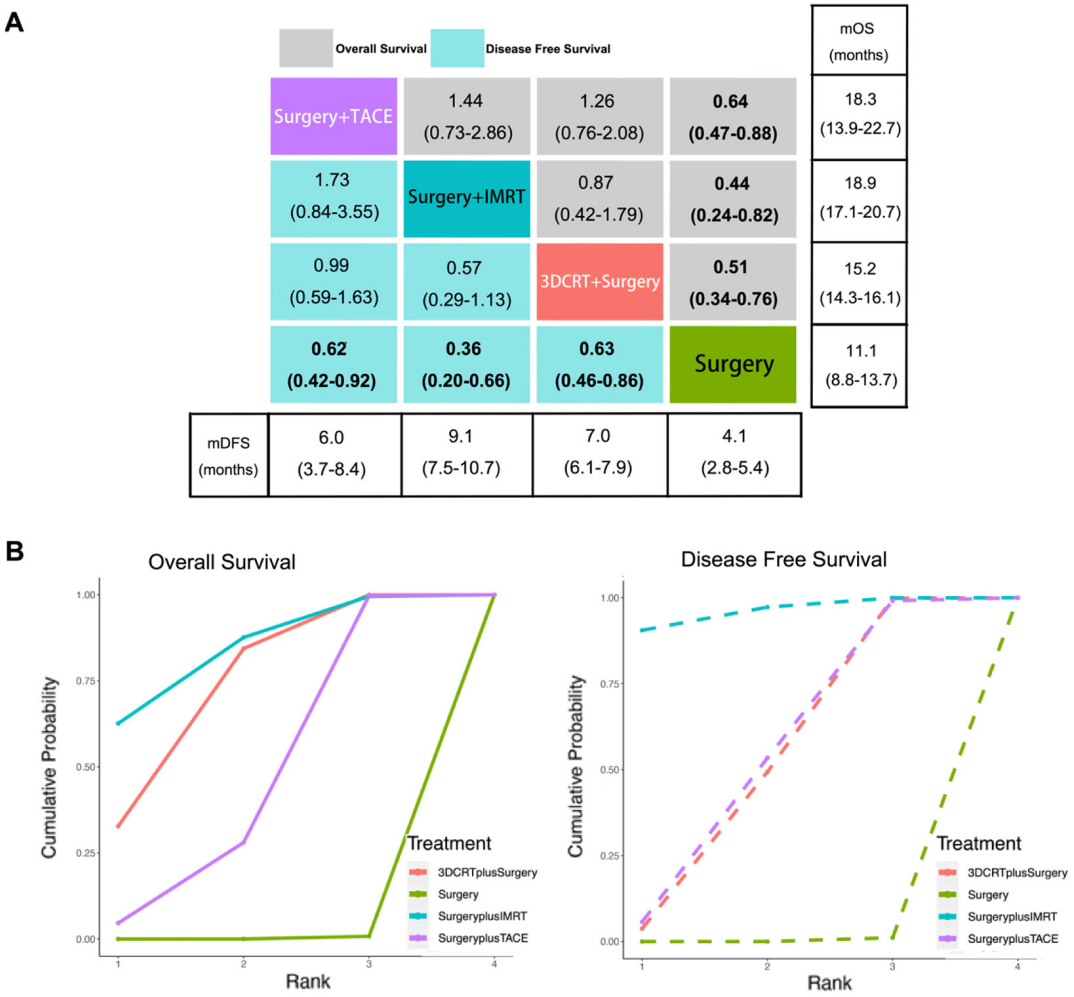

Figure 4. OS and PFS comparisons and ranking curves of efficacy. **A:** Each cell of the block contains the pooled HR and 95% credibility intervals for OS and PFS; significant results are in bold. **B:** Cumulative ranking probability of each regimens, higher in the area under curve indicates better treatment option. HR: hazard ratio; mOS: median overall survival; mPFS: median progression-free survival; OS: overall survival; PFS: progression-free survival

Indirect comparisons and descriptive analysis of ORR

Among AEs with incidence >10%, ALT increase occurred in all the trials of these four interventions. Leukocyte count decrease was the most common side effect of neoadjuvant 3DCRT, whereas TACE commonly manifested with nausea and vomiting. A detailed overview of treatment-related AEs is provided in Table 2. The results from indirect comparisons suggested no significant difference with regard to grade 3-4 AEs among the interventions (Figure 6A). Figure 6B also showed that for grade 3-4 AEs, safety ranking of IMRT was superior, followed by TACE and 3DCRT.

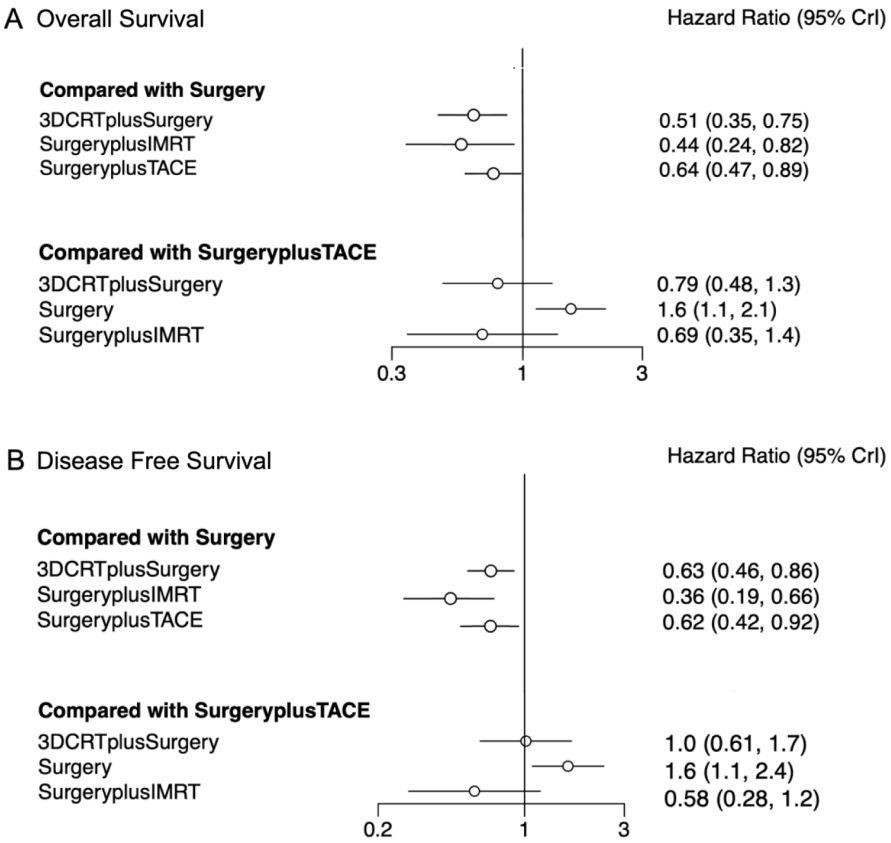

Figure 5. Forest plots depicting the direct and indirect results of head-to-head comparisons. CrI: credible intervals.

Table 2. Toxicity spectrum for every intervention based on any grade and grade 3–4 adverse events. The rate of adverse events in each drug.

Adverse events	*Any grade of adverse events*	*3-4 grade adverse events*
Intra-abdominal hemorrhage	NeoRT(2.7)	RT&T(3.1)
Liver failure	NeoRT(2.7)	NeoRT(2.7)
Anemia	NeoRT(3.7)	
Leukocyte count decreased	NeoRT(91),TACE(3.6),RT&T(15.6)	
Platelet count decreased	NeoRT(12.3)	
Fatigue	IMRT(15.4)	IMRT(15.4)
Anorexia	IMRT(11.5)	IMRT(11.5)
Nausea/Vomiting	TACE(54.4), IMRT(7.7),NeoRT(14.6),RT&T(54.7)	IMRT(7.7)
ALT increase	NeoRT(21.9),TACE(42.6), IMRT(11.5),RT&T(23.4)	NeoRT(2.4), IMRT(11.5),TACE(8.8)
Bilirubin increase	NeoRT(15), IMRT(7.7),TACE(35.1)	NeoRT(2), IMRT(7.7)
Gastroduodenitis	IMRT(3.8)	IMRT(3.8)
Duodenal ulcer	IMRT(3.8)	IMRT(3.8),RT&T(7.8)

The number in parentheses represents the incidence of each adverse event for each regimen. NeoRT: Neoadjuvant 3DCRT+Surgery; TACE: Surgery+TACE; IMRT: Surgery+IMRT;RT&T: 3DCR+TACE

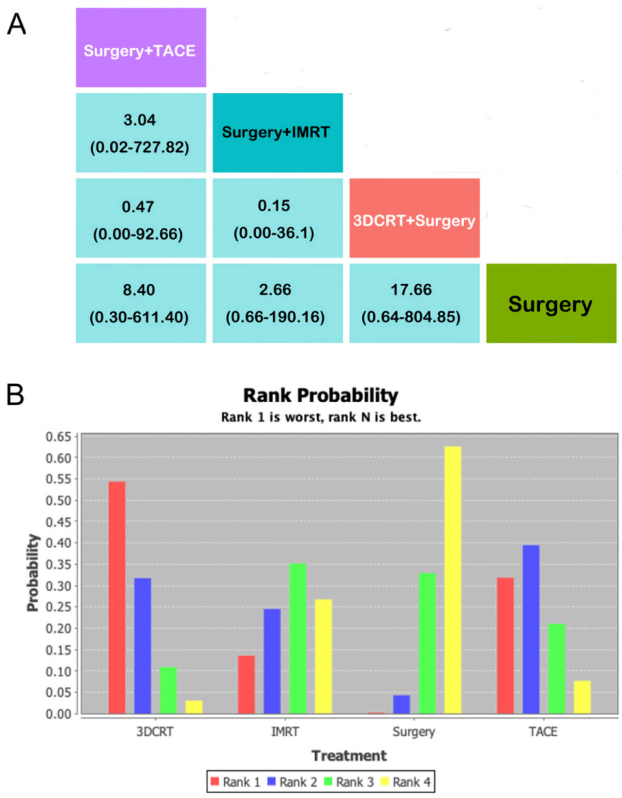

Figure 6. A: Comparisons and **B:** rank probability of any grade and 3–4 grade AEs(Rank 1 is worst, rank N is best). AE: adverse event.

Discussion

HCC with hepatic or portal vein thrombosis has a well-known poor prognosis. Many western experts refuse to operate them due to high tumor recurrence or insufficient liver capacity. However, unlike alcohol-related cirrhosis or HCV infection which forms the leading cause in western liver cancer, HCC in Southeast countries were mainly caused by chronic hepatitis B virus infection and usually have a good liver reserve function. Surgery remains the preferred treatment option among them [3,19]. When combined with some other local control regimens, they have shown promising results in recent years [19]. Preoperative small-dose RT has been reported to downstage some types of III PVTT patients, reduce recurrence rate without increasing surgical risks, and reduce postoperative hepatic failure rates [10]. Adjuvant TACE after surgery has been reported to reduce recurrence rates and prolong survival of PVTT patients but can only increase the 1-year survival rate [16,20]. The current challenge is to better understand the best combination of surgery in order to provide better survival benefits, while minimizing toxicity.

To the best of our knowledge, this is the first network meta-analysis to compare the efficacy and safety of the treatment regimens in HCC patient with hepatic/portal vein invasion. We collected the direct and indirect comparative data and assessed the median survival rate, and severe AEs in advanced HCC patients undergoing different treatment modalities. The pooled results demonstrated that postoperative IMRT group, TACE and neoadjuvant 3DCRT group all have shown significantly better OS outcomes rather than the surgery alone group. However, there was no statistical significance in OS when these regimens were compared with one another. In terms of AEs during the treatment period, the rate of grade 3-4 AEs was not significantly different between the four treatments, although the fewest were associated with IMRT. The SUCRA results indicated that IMRT is a better option for advanced-stage HCC patients, followed by 3DCRT and TACE in regards of OS, while TACE ranked slightly better than 3DCRT but still lower than IMRT in terms of DFS.

Rapid development in radiotherapy technology, including IMRT, breath-holding techniques, and knowledge of liver partial volume, all limit radiation exposure to the liver parenchyma surrounding the tumor and allows high dose of radiation deliver to HCC tumors precisely and without excessive hepato-toxicity [21]. Hou et al [22] compared 3DCRT and IMRT for advanced HCC patients and found IMRT was more effective treatment that provides more survival benefit than 3DCRT, which strongly supports our results. In recent years, an increasing number of studies have explored the role of TACE in the management of advanced-stage HCC patients. Some studies have demonstrated the safety of TACE in the presence of adequate collateral circulation around the occluded portal vein [16,18]. However, researches compared TACE or RT as a more effective adjuvant regimens are still lacking. The network meta-analysis is a useful method for integrating information from both direct and indirect treatment comparisons in a network of studies using novel statistical methods [23]. Quantitative comparison of the efficacy and safety of various competing treatments could be made in a single analysis. In clinical practice, some 'head-to-head' comparison can't be made due to some ethical reasons, and our study provides the opportunity and the results of this study may also serve as a reference for optimizing the design of future trials.

Our study has certain limitations. First, the inclusion criteria for the included studies might lead to bias. The extend of vascular invasion vary among studies, the population involved in

neoadjuvant 3DCRT group was type II-III PVTT, while other studies involve type I-IV PVTT, and subgroup analysis could not be achieved due to lack of information. Second, all four studies were conducted in big medical centers in Southeast countries, and the operations were carried out by experienced doctors, thus the results might not be suitable in a wider range of patient population. Third, only four trials were included into the final network meta-analysis, and authors characterize hepatocellular carcinoma as an orphan disease in terms of scientific evidence. Only few RCT or meta-analyses of individual data have been conducted, none of them including more than 1000 patients. The evidence of our conclusion is relatively weakened due to the inadequate clinical data and small combined effect size. We still need more RCTs to enroll in for further in-depth statistical analyses and a more convincible results to get published.

Conclusion

This network meta-analysis provided evidence that the combination of TACE, 3DCRT or IMRT with surgery improved survival and achieved better outcome. Future RCTs are needed to confirm the advantages of combined therapy of interested modalities over those modalities used alone for HCC patients with hepatic/portal vein thrombosis.

Author contributions

QW, YC and TZ contributed to data extraction. YH, SD, TY, MD, YX, ZZ contributed to manuscript revision. QW and YC contributed equally to the article thus should be assigned as co first-authors.

Conflict of interests

The authors declare no conflict of interests.

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