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ORIGINAL ARTICLE

Comparing the efficacy and safety of local-regional treatments for hepatocellular carcinoma with portal/hepatic vein tumor 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 peri-operative regimens using the network meta-analysis for hepatocellular carcinoma (HCC) with portal/hepatic vein tumor thrombosis. The interested modalities included neo-adjuvant three-dimensional radiotherapy (3D-CRT), post-operative intensity modulated radiation therapy (IMRT), post-operative transarterial chemoembolization (TACE), 3DCRT plus TACE and surgery alone.*

Methods: *PubMed and Cochrane Library electronic databases were systematically searched for eligible studies published up to March 2021. 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: *Five studies published between 2009 and 2021 were enrolled in this network meta-analysis. The comparison showed that surgery with IMRT ranks relatively higher in prolonging OS in advanced HCC patients, followed by neoadjuvant 3DCRT and surgery plus TACE. Neoadjuvant 3DCRT and postoperative IMRT appear to be better choices than 3DCRT plus TACE in terms of OS. IMRT, TACE and neoadjuvant 3DCRT group were all superior to surgery alone in terms of DFS. The rate of AEs did not differ significantly.*

Conclusion: *Adjuvant IMRT showed more favorable treatment responses compared to other regimens in HCC patients as a peri-operative regimen.*

Key words: *IMRT, 3DCRT, TACE, hetpatocellular carcinoma, venous thrombosis, 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 limited survival of about only several months [2].

According to the UICC TNM staging system and the BCLC staging system HCC with multiple tumors more than 5 cm or tumor involving a major branch of the portal or hepatic veins are considered as advanced stage. Guidelines in Europe and America recommend conservative methods rather

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than nonpharmacological regimens 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 HCC with portal vein thrombosis 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 researchers suggest that a multidisciplinary therapy including transcatheter arterial chemoembolization (TACE), radiotherapy (RT) should also be considered to achieve more satisfactory results [7-11]. Relevant studies have reported that pre-operative TACE showed good tumor response than surgery alone [12]. Other studies 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 overall survival (OS) and disease-free survival (DFS) and severe adverse events and determine which is the best peri-operative regimen in HCC patients with portal/hepatic vein thrombosis.

Methods

Literature search

This network meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. A systematic literature search of the PubMed and Cochrane Library from November 2005 through August 2021 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]) 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 both English and Chinese.

Study selection criteria

The selected studies had to meet the following criteria: 1) included patients with pathologically proven HCC with portal vein tumor thrombosis (PVTT) or hepatic vein thrombosis; 2) regimens were mainly focused on perioperative treatments, and surgery alone was used as control group; 3) detailed data on methods, characteristics of patient population, the rate of all grade and grade 3-4 adverse events, and OS; 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 included patients, interventions, sample size, and numbers randomized to each arm (Table 1). The primary endpoint was OS and DFS. Adverse events rates were the secondary endpoint that was 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).

We conducted a network meta-analysis to compare the outcomes among the 5 studies for advanced HCC, which included direct (ie, head-to-head) and indirect treatment comparisons. OS and DFS data were extracted directly from the studies with hazard ratios (HRs) and 95% confidence intervals (95% CIs). The Gemtc package v0.8-7 in R version 4.0.2 was utilized to perform a Bayesian analysis. The fixed effects model and consistency models were used to calculate odds ratio (ORs) and 95% credibility intervals due to its relatively lower DIC(8.03),I^2=0.6% and versus the random effects model. OS and PFS data were expressed as HRs, with corresponding 95% CIs. Adverse events rates were assessed using relative risk (RR), with corresponding 95% CIs. Non-informative prior distributions were used and overdispersed initial values with a scale of 0-5, in four chains to fit the model. This yielded 150,000 iterations, includ-

Table 1. Clinical baseline characteristics of the included studies

First author	*Primary tumor & PVTT type*	*BCLC/IICC type*	*Total number*	*Arm (regimen/control)*
Wei	Resectable; Type II/III PVTT	Stage C/IIIb	151	Neo 3DCRT+Surgery/Surgery
Sun	Resectable; Type I-IV PVTT	Stage C/IIIb	52	Surgery+IMRT/Surgery
Peng	Resectable; Type I-IV PVTT	Stage C/IIIb	104	Surgery+TACE/Surgery
Wu	Unknown; Type I-III PVTT	Stage C/IIIb	145	3DCRT+TACE/Surgery
Zhong	Resectable; Type I-IV PVTT	Stage B-C/IIIa-IIIb	115	Surgery+TACE/Surgery

ing 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 its 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 suggested that we should not combine the two postoperative TACE studies for pooled analysis, and therefore we chose to analyze each study separately. Indirect comparisons were performed for different treatment regimens, such as neoadjuvant 3-dimensional conformal radiotherapy (3DCRT) versus 3DCRT plus TACE. The adjusted indirect comparison was calculated using Bayesian methods desrcibed in the following formula: ln(HR)=[ln(UL-HR)+ln(LL-HR)]/2; seln(HR)=[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 was used to identify treatment superiority, using surface under the cumulative ranking curve (SUCRA) for ranking.

Results

Study selection and patient characteristics

A total of five trials involving 567 patients were included [13,15,17,18]. The trial selection process is shown in Figure 1. Five trials provided complete OS data, and four trials provided complete PFS, and adverse events data. Detailed study and participant characteristics depicted in Table 1.

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

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

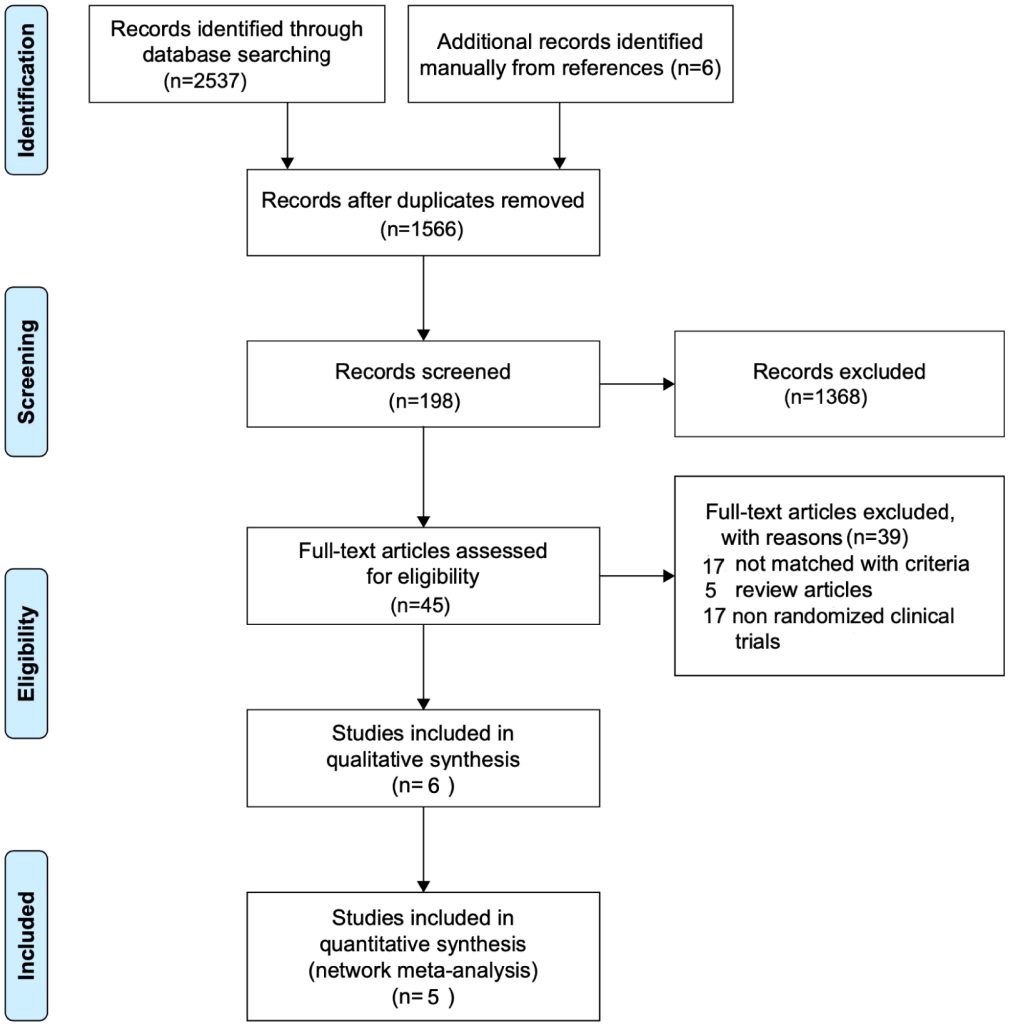

Figure 1. Flowchart of study identification and selection process

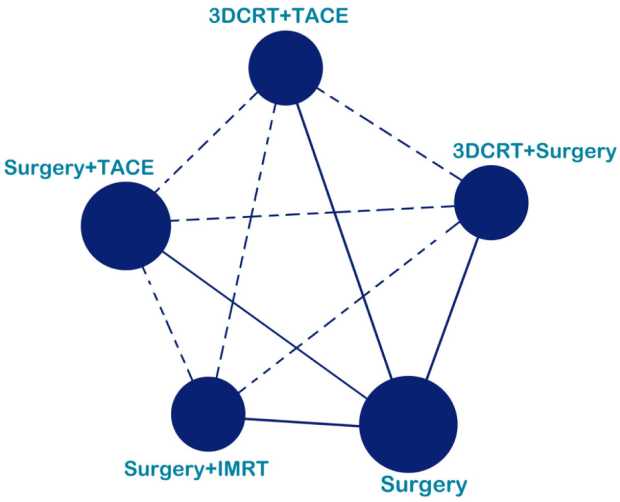

Figure 2. Network maps of comparing interventions. Each circular node represents a type of treatment. The circle size is proportional to the total number of patients (under the drug name). The width of lines is proportional to the number of studies performing head-to-head comparisons in the same study,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

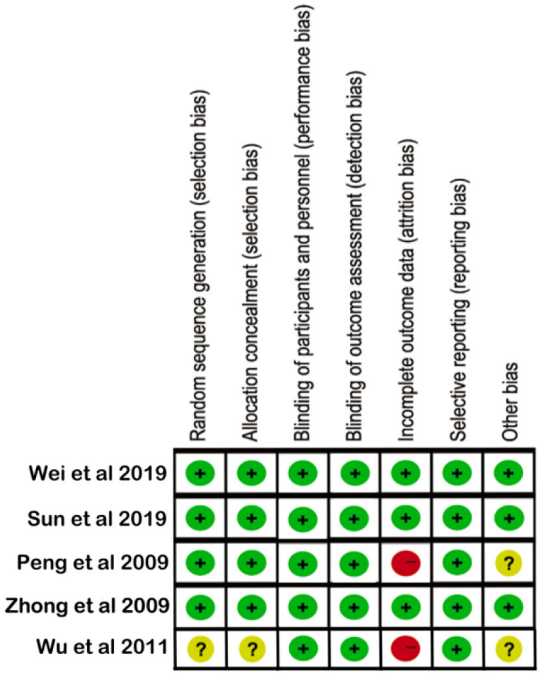

Figure 3. The risk of bias of included studies.

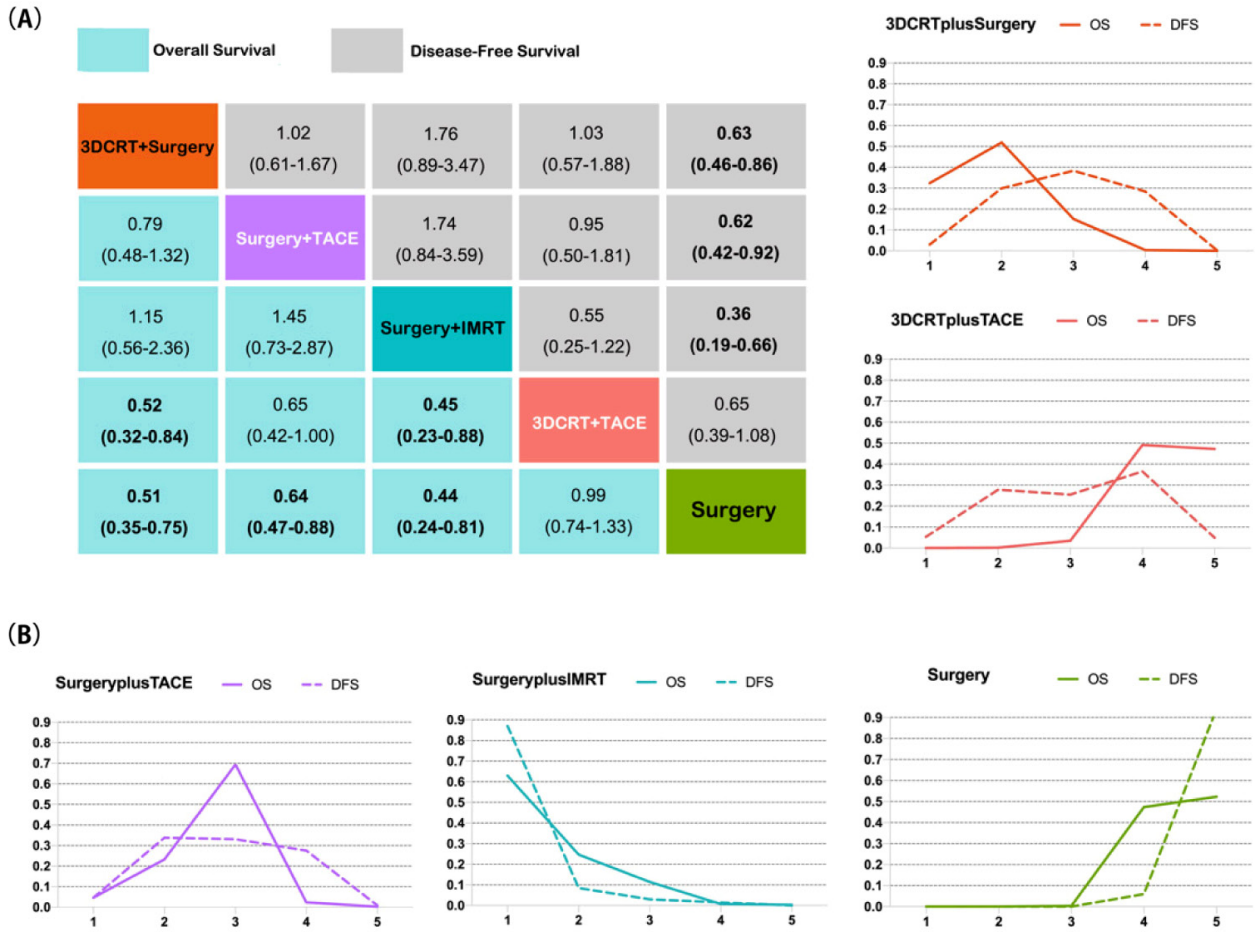

Figure 4. OS and PFS comparisons and ranking curves of efficacy. **A:** Each cell of the block contains the pooled HR and 95% credibility intervals for OS and PFS; significant results are in bold. **B:** Ranking probability of each regimens, higher the area under curve indicates better treatment option.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

NMA results for OS and PFS

When compared with surgery alone, the results suggested that postoperative IMRT significantly prolonged OS (HR 0.44; 95%CI 0.24-0.81), followed with neoadjuvant 3DCRT (HR 0.51; 95%CI 0.35-0.75) and postoperative TACE (HR 0.64; 95%CI 0.47-0.88). Three of the included interventions IMRT (HR 0.36; 95%CI 0.19-0.65), 3DCRT plus surgery (HR 0.63; 95%CI 0.46-0.86) and postoperative TACE (HR 0.62; 95%CI 0.42-0.92) were significantly superior to surgery alone in terms of DFS. Further indirect comparisons of the interventions suggested IMRT (HR 0.45; 95%CI 0.23-0.88) and neoadjuvant 3DCRT (HR 0.52; 95%CI 0.32-0.84) were both superior than 3DCRT plus TACE (Figure 4 A).

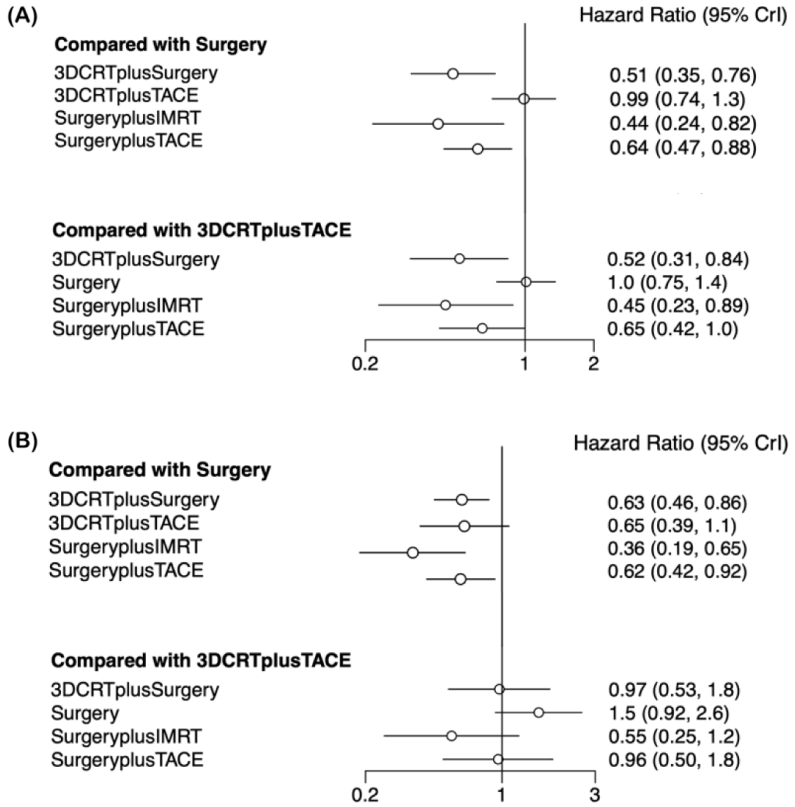

Figure 5. Forest plots depicting the direct and indirect results of head-to-head comparisons. CrI: credible intervals.

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 adverse events*	*3-4 grade adverse events*
Intra-abdominal hemorrhage	NeoRT (2.7), RT & T (2.5)	RT & T (2.5)
Liver failure	NeoRT (2.7)	NeoRT (2.7)
Anemia	NeoRT (3.7)	
Leukocyte count decreased	NeoRT (91), TACE (3.6), RT & T (12.3)	
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 (37.0)	IMRT (7.7)
ALT increase	NeoRT (21.9), TACE (42.6), IMRT (11.5), RT & T (18.5)	NeoRT (2.4), IMRT (11.5), RT & T (8.8)
Bilirubin increase	NeoRT (15), IMRT (7.7), TACE (31.5)	NeoRT (2), IMRT (7.7)
Gastroduodenitis	IMRT (3.8)	IMRT (3.8)
Duodenal ulcer	IMRT (3.8), RT & T (6.2)	IMRT (3.8), RT & T (6.2)

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

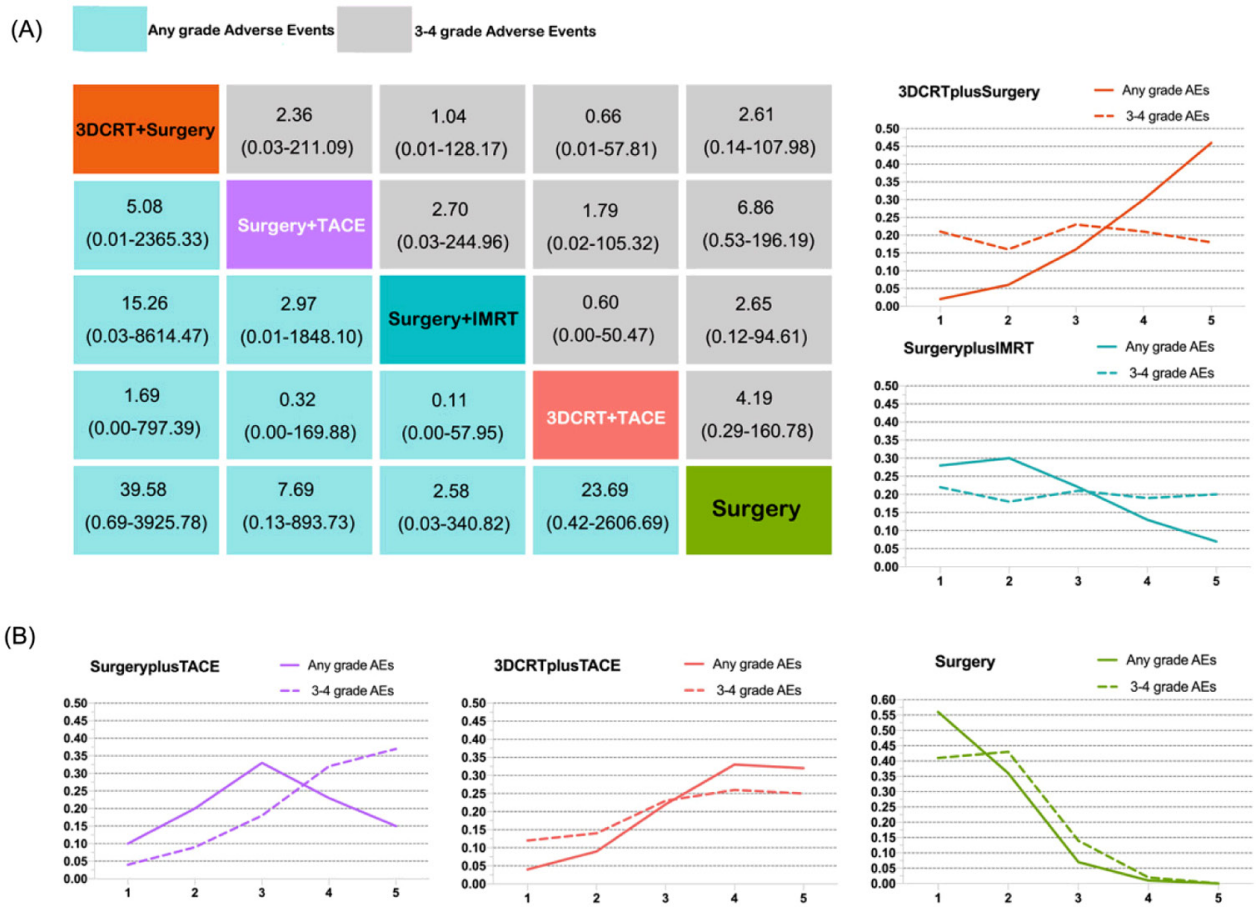

Figure 6. A: Comparisons and **B:** rank probability of any grade and 3-4 grade AEs: adverse events.

The order for these four treatments in terms of OS were ranked from high to low, was as follows: IMRT (87.30%), neoadjuvant 3DCRT (79.09%), postoperative TACE (57.42%) and 3DCRT plus TACE (14.18%). Meanwhile, associated PFS measurements were ranked from high to low were as follows: IMRT (95.22%), postoperative TACE (53.48%), neoadjuvant 3DCRT (51.74%), and 3DCRT plus TACE (48.04%).

Indirect comparisons and descriptive analysis of ORR

Among adverse effects with incidence >10%, ALT increase occurred in all 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 adverse events is provided in Table 2. The results from indirect comparisons suggested no significant difference with regard to grade 3-4 adverse events among the interventions analysed (Figure 6A). Figure 6B also shows that for grade 3-4 adverse events, safety ranking found IMRT to be superior followed by neoadjuvant 3DCRT, 3DCRT plus TACE and postoperative TACE.

Discussion

HCC with portal/hepatic vein invasion has a well-known poor prognosis. Many western experts refuse to operate such patients due to high tumor recurrence or insufficient liver reserves. However, unlike alcohol-related cirrhosis or HCV infection which are the leading causes in liver cancer of western populations, HCC in China is mainly caused by chronic hepatitis B viruses and usually has a good liver reserve function. Surgery or other nonpharmacological methods remain the preferred treatment options among them [3,20]. When combined with some other local control therapies, they have shown promising results in recent years [20]. Downstage of some type III PVTT patients became possible when preoperative small-dose RT was given, it has been reported to 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 advanced stage HCC patients, but researches have indicated that it can only increase the 1-year survival rate [17,21]. The current challenge is to better under-

stand which is the best peri-operative regimen for HCC patient with portal/hepatic veinous invasion which were tolerable for local control treatments, 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 peri-operative regimens in HCC with portal/hepatic vein thrombosis, we collected the direct and indirect comparative data and assessed the survival rate, and severe adverse events in advanced HCC patients undergoing different treatment modalities. The pooled results demonstrated that, Post-operative IMRT, TACE and Neoadjuvant 3DCRT group all have shown significantly better overall survival outcomes rather than Surgery alone group, IMRT and preoperative 3DCRT have shown more favorable result than 3DCRT plus TACE in terms of OS, The SUCRA results indicates that IMRT was a better option for advanced stage HCC patients followed by neoadjuvant 3DCRT and postoperative TACE in regards of OS, while TACE ranked slightly better than 3DCRT but still lower than IMRT in terms of DFS. The reported median Overall Survival for each regimen were as follow: IMRT 18.9 (17.1-20.7) months, postoperative TACE 18.3 (13.9-22.7) months, preoperative 3DCRT 15.2 (14.3-16.1) months, 3DCRT plus TACE 15.2 (14.0-17.6) months. In terms of AEs during the treatment period, the rate of grade 3-4 AEs were not significantly different between the four treatments, although the fewest was associated with IMRT.

Rapid development in radiotherapy technology, including IMRT, breath-holding techniques. Combined with knowledge of liver partial volume, all limit radiation exposure to the liver parenchyma surrounding the tumor which allows massive dosage of radiation deliver directly to HCC tumors precisely and without increasing hepato-toxicity [22]. Hou et al [23] compared 3DCRT and IMRT for advanced HCC patients and found IMRT appears to be an 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 [17,19]. However, researches compared TACE or RT as a more effective adjuvant regimens is 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 [24]. Quantitative comparison of the efficacy and safety of various competing treatments could be made in one single analysis. In clinical practice, some 'head-to-head' comparison can't be made due to some ethical reasons, our study provide 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 the bias. The extend of vascular invasion vary among studies, the population involved in Neoadjuvant 3DCRT group were type II-III PVTT while other studies involve type I-IV PVTT, subgroup analysis could not be achieved due to the lack of information. Second, all five studies were conducted in big medical center in Southeast countries, and the surgery were carried by experienced doctors thus the results might not suitable in a wider range of patient population. Third, due to the ethical reasons, it is impossible for patient to stop receiving other treatment after the regimens mentioned in our study were given, which might differ among each group and could affect the survival data. Fourth, randomized control trials related to perioperative RT among advanced stage HCC patients are still lacking which contributed to the inadequate clinical data and relatively small combined effect size. We still need more RCTs to enrolled in for further in-depth statistical analysis and a more convincible results to get published.

Conclusion

The network meta-analysis provided evidence that the combination of TACE, 3DCRT or IMRT with surgery improved survival and better outcome. IMRT ranks relatively higher in prolonging OS and DFS. Future randomized controlled trials are needed to confirm the advantages of combined therapy of interested modalities over those regimens used alone for HCC patients with hepatic/portal vein thrombosis.

Conflict of interests

The authors declare no conflict of interests.

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