Japanese Journal of Gastroenterology and Hepatology

Review Article

ISSN: 2435-1210 | Volume 8

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 Control Trials

Qi-Qiao Wu[1], Yi-Xing Chen[2], Ting-Ting Zheng[1], Yong Hu[2], Shi-Suo-Du[2] and Zhao-Chong Zeng[2]

[1]Department of Radiation Oncology, Fudan University Zhongshan Hospital, Xiamen Branch, Jinhu Road 668, Xiamen, China

[2]Department of Radiation Oncology, Fudan University Zhongshan Hospital, Fenglin Road 188, Shanghai, China

***Corresponding author:**

Zhao-Chong Zeng,
Department of Radiation Oncology, Fudan University Zhongshan Hospital, Fenglin Road 180,
Shanghai, China,
E-mail: zeng.zhaochong@zs-hospital.sh.cn

Received: 18 Nov 2021
Accepted: 16 Dec 2021
Published: 21 Dec 2021
J Short Name: JJGH

Citation:

Zhao-Chong Zeng, 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 Control Trials. Japanese J Gstro Hepato. 2021; V8(1): 1-9

Keywords:

IMRT; 3D-CRT; TACE; Advanced hetpatocellular carcinoma; Network meta-analysis

1. Abstract

1.1. Purpose: We assessed the efficacy and safety of different local-regional regimens using the network metaanalysis

for hepatocellular carcinoma (HCC) with portal/hepatic vein tumor thrombosis. The interested modalities included neoadjuvant three-dimensional radiotherapy(3D-CRT), postoperative intensity-modulated radiation therapy(IMRT), Postoperative transarterial chemoembolization (TACE), 3DCRT plus TACE, and Surgery alone.

1.2. 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), disease-free

survival(DFS) were extracted and compared using a Bayesian approach. Adverse Events(AEs) were assessed

and compared.

1.3. Results: Five studies published between 2009 and 2020 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 significantly differ.

1.4. Conclusions: Adjuvant IMRT showed more favorable treatment responses compared with other regimens in

HCC patients with portal/hepatic vein tumor.

2. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second most frequent cause of cancerrelated

death globally [1]. 70-80% of HCC patients are diagnosed at an advanced stage and their prognosis are

extremely poor, with limited survival 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 systemic therapy rather than local-regional regimens as treatments [2]. While experts from Southeast Asian countries hold different opinions [3]. Kokudo [4]et al have compared surgical and non-surgical treatments in HCC with portal vein thromnbosis patients and found surgery yields better survival outcomes. Two meta-analysises con-

ducted by Liang[5]et al and Zhang [6] at al also suggest similar trending. Some opine a multidisciplinary therapy including transcatheter arterial chemoembolization (TACE), radiotherapy (RT) should also be 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 researches 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 and determine which is the best local-regional regimen in HCC patients with portal/hepatic vein thrombosis.

3. Methods

3.1. 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 the PubMed and Cochrane Library from 4 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]) 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.

3.2. 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) regimens were mainly focus on local-regional treatments, surgery alone were used as control group. 3) detailed data on method, characteristics of patient population, the rate of all grade and grade 3–4 adverse events, and overall survival; 4) compared at least two arms that consisted of the abovementioned interested regimens. 5)Design---Only RCTs.

3.3. Data Extraction and Quality Assessment

Two authors (QW and YC) 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 patients, interventions, sample size, numbers randomized to each arm (Table 1). The assessment primary outcome in this study was Overall Survival and Disease-Free Survival. Adverse Events rates was the secondary outcome we measured and compared.

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
Wu	Unknown;TypeI-III PVTT	Stage C/IIIb	145	3DCRT+TACE/Surgery
Zhong	Resectable; TypeI-IV PVTT	Stage B-C/IIIa-IIIb	115	Surgery+TACE/Surgery

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),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),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.

3.4. 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 judgment 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. 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 v0.8-7 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 DIC(8.03),I^2=0.6% and versus random effects model. OS and PFS data are expressed as HR, with corresponding 95% CIs . We utilized the addis version 1.16.5 to analyzed the AE rates using relative risk (RR), with corresponding 95% CIs. Non-informative prior distributions were used 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 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 choosed to analyse each study separately. Indirect comparisons were performed for different treatment regimens, such as Neoadjuvant 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 – 6 HR)]/ (1.96×2); HR <1 or RR <1 was used to identify treatment superiority, we use surface under the cumulative ranking curve(SUCRA) for ranking.

4. Results

4.1. Study Selection and Patient Characteristics

A total of five trials involving 567 patients were included [13,15-19]. The trial selection process is provided as shown in Figure.1. Five trials provided complete OS data, four trials provided complete PFS, and AE data. Detailed study and participant characteristics are also provided. Please see Table 1 for details.

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

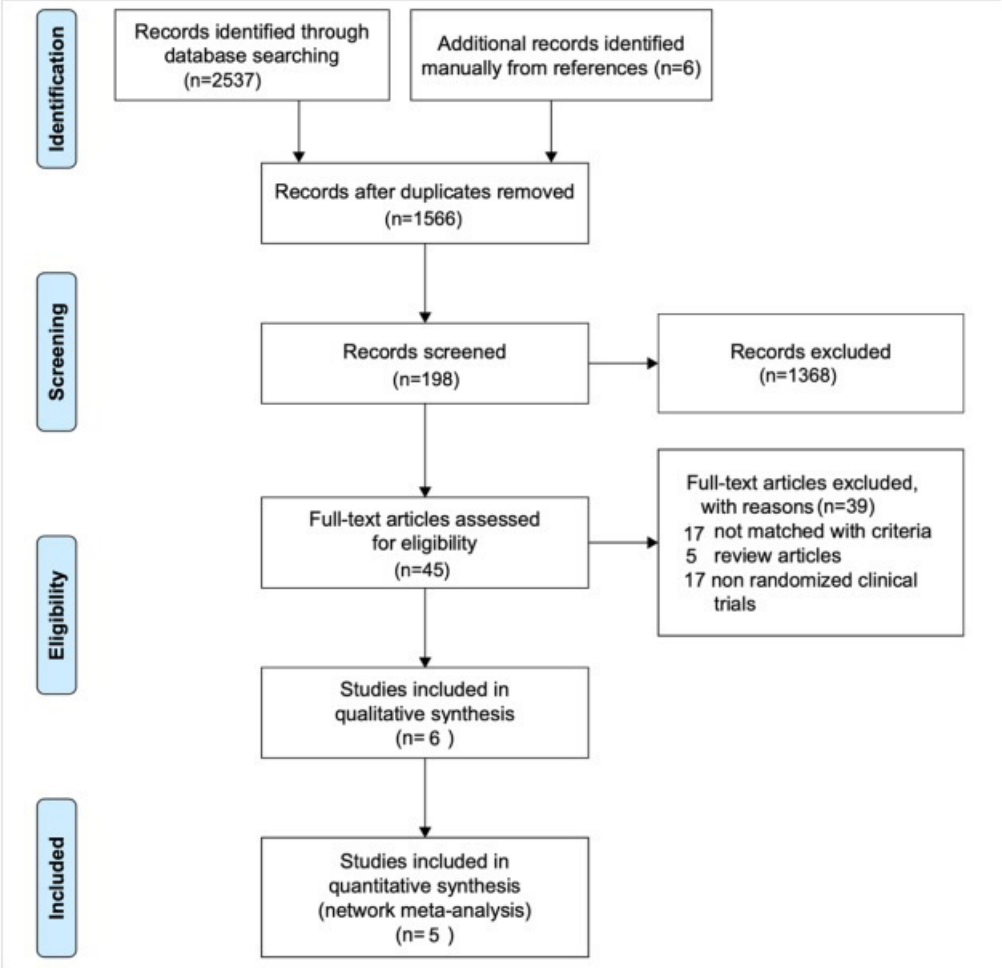


Figure 1: Flowchart of study identification and selection process.

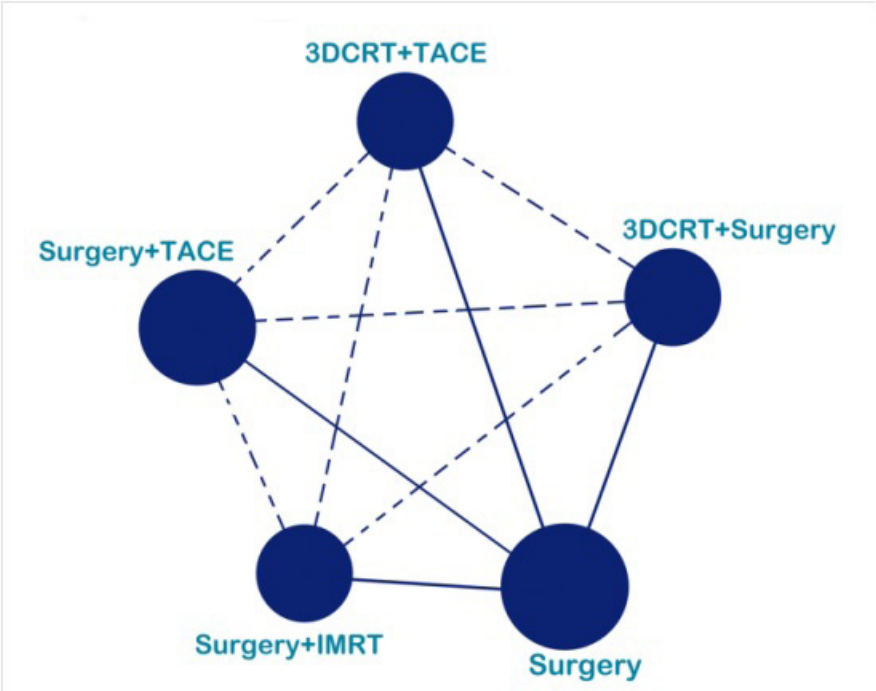


Figure 2: Network maps of comparing interventions. Each circular node represents a type of treatment. The circle size is proportional to the total number of patients (under the drug name). The width of lines is proportional to the number of studies performing head-to-head comparisons in the same study,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

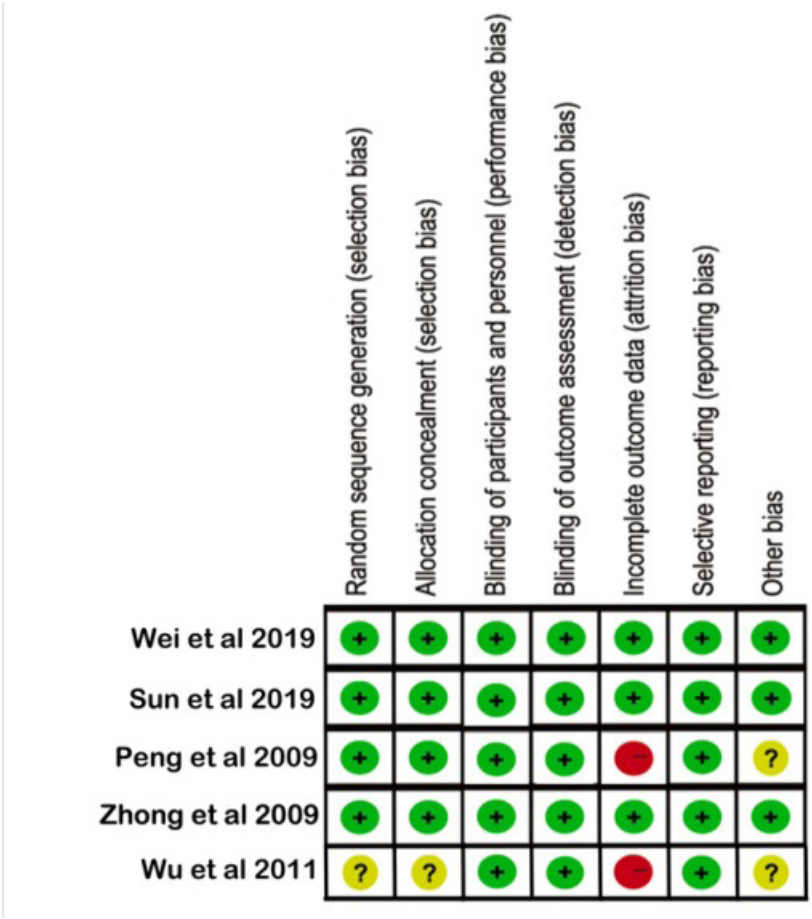


Figure 3: The risk of bias of included studies.

4.3. NMA Results for OS, PFS

When compared with surgery alone, the results suggest that Postoperative IMRT significantly prolong OS (HR

0.44; CI 0.24–0.81), followed with Neoadjuvant 3DCRT (HR 0.51; 0.35-0.75) and postoperative TACE (HR 0.64;

CI 0.47-0.88). Three of the included interventions IMRT (HR 0.36; 0.19-0.65), 3DCRT plus Surgery (HR 0.63;

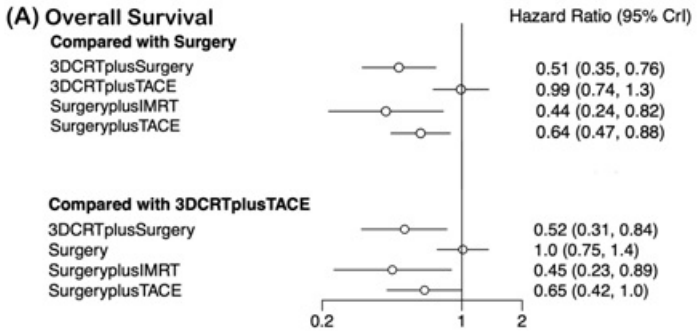
0.46-0.86) and postoperative TACE (HR 0.62; 0.42-0.92) was significantly superior to surgery alone in terms of

DFS. Further indirect comparisons of the interventions suggest IMRT (HR 0.45; 0.23-0.88) and neoadjuvant 3DCRT (HR 0.52; 0.32-0.84) were both superior than 3DCRT plus TACE (Figure 4.A and Figure 5). The order for these four treatments in terms of OS using percentage which were ranked from high to low, as follows: IMRT (87.30%), neoadjuvant 3D-RT (79.09%), postoperative TACE (57.42%) and 3DCRT plus TACE (14.18%). Meanwhile, associated PFS measures were ranked from high to low were as follows: IMRT (95.22%), postoperative TACE (53.48%), neoadjuvant 3DCRT (51.74%), 3DCRT plus TACE (48.04%). (Figure4. B) 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 decreased was the most common side effect of Neoadjuvant 3DCRT. Whereas TACE commonly manifests with nausea and vomiting. A detailed overview of treatment-related AEs is provided in Table 2. The results from indirect comparisons suggest there is no significant difference with regard to 3–4 grade AEs among the interventions analysed (see Figure 6.A). For 3–4 grade AEs, safety ranking found IMRT to be superior followed by neoadjuvant 3DCRT, 3DCRT plus TACE and postoperative TACE. (Figure6.B).

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.



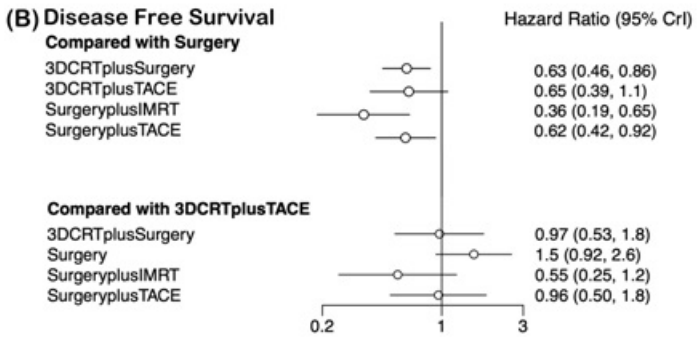


Figure 5: Forest plots depicting the direct and indirect results of head-to-head comparisons. CrI, credible intervals.

Figure 6(A): Comparisons and (B) rank probability of any grade and 3–4 grade AEs. AE, adverse event.

5. Discussion

HCC with portal/hepatic vein invasion has a well-known poor prognosis. Many western experts refused to give them surgery due to high tumor recurrence or insufficient liver capacity. However, unlike alcohol-related cirrhosis or HCV infection which account the leading causes in western liver cancer. HCC in China were mainly caused by chronic hepatitis B viruses infection and usually have a good liver reserve function. Surgery or other nonphramacological methods remain the preferred treatment options among them [3,20]. When combined with some other local control regimens, they have shown promising results in recent years [20]. Downstage of some type III PVTT patients became possible when preoperative small-dose RT were 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 understand 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 local-regional 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 hepato9 Toxicity [22]. Hou [23]at al 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 China, 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.

6. 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.

Reference

1. Llovet JM, Zucman-Rossi J, Pikarsky E, Sangro B, Schwartz M, Sherman M, et al. Hepatocellular carcinoma. Nat Rev Dis Prim 2016; 2.
2. Bangaru S, Marrero JA, Singal AG. Review article: new therapeutic interventions for advanced hepatocellular carcinoma. Aliment Pharmacol Ther. 2020; 51: 78-89.
3. Cheng S, Chen M, Cai J, Sun J, Guo R, Bi X, et al. Chinese Expert Consensus on Multidisciplinary Diagnosis and Treatment of Hepatocellular Carcinoma with Portal Vein Tumor Thrombus (2018 Edition). Liver Cancer 2020; 9: 28-40.
4. Kokudo T, Hasegawa K, Matsuyama Y, Takayama T, Izumi N, Kadoya M, et al. Survival benefit of liver resection for hepatocellular carcinoma associated with portal vein invasion. vol. 65. European Association for the Study of the Liver. 2016.
5. Liang L, Chen TH, Li C, Xing H, Han J, Wang M Da. A systematic review comparing outcomes of surgical resection and non-surgical treatments for patients with hepatocellular carcinoma and portal vein tumor thrombus. Hpb 2018; 20: 1119-29.
6. Zhang ZY, Dong KS, Zhang EL, Zhang LW, Chen XP, Dong HH. Resection might be a meaningful choice for hepatocellular carcinoma with portal vein thrombosis: A systematic review and meta-analysis. Med (United States) 2019; 98.
7. Zheng N, Wei X, Zhang D, Chai W, Che M, Wang J, et al. Hepatic resection or transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombus. Med (United States) 2016; 95: 1-6.
8. Yoon SM, Ryoo BY, Lee SJ, Kim JH, Shin JH, An JH, et al. Efficacy and safety of transarterial chemoembolization plus external beam radiotherapy vs sorafenib in hepatocellular carcinoma with macroscopic vascular invasion : A randomized clinical trial. JAMA Oncol 2018; 4: 661-9.
9. Su F, Chen KH, Liang ZG, Wu CH, Li L, Qu S, et al. Comparison of three-dimensional conformal radiotherapy and hepatic resection in hepatocellular carcinoma with portal vein tumor thrombus. Cancer Med 2018; 7: 4387-95.
10. Li N, Feng S, Xue J, Wei XB, Shi J, Guo WX, et al. Hepatocellular carcinoma with main portal vein tumor thrombus: A comparative study comparing hepatectomy with or without neoadjuvant radiotherapy. Hpb 2016; 18: 549-56.
11. Lee D, Lee HC, An J, Shim JH, Kim KM, Lim YS, et al. Comparison of surgical resection versus ransarterial chemoembolization with additional radiation therapy in patients with hepatocellular carcinoma with portal vein invasion. Clin Mol Hepatol. 2018; 24: 144-50.
12. Zhang YF, Guo RP, Zou RH, Shen JX, Wei W, Li SH, et al. Efficacy and safety of preoperative chemoembolization for resectable hepatocellular carcinoma with portal vein invasion: a prospective comparative study. Eur Radiol. 2016; 26: 2078-88.
13. Sun J, Yang L, shi J, Liu C, Zhang X, Chai Z, et al. Postoperative adjuvant IMRT for patients with HCC and portal vein tumor thrombus: An open-label randomized controlled trial. Radiother Oncol. 2019; 140: 20-5.
14. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011; 343.
15. Wu ZJ, Cai J, Xu AB, Su XQ, Wang XQ, Zhang YX, et al. Combined three-dimensional conformal radiotherapy plus transcatheter arterial chemoembolization and surgical intervention for portal vein tumor thrombus in patients with hepatocelular carcinoma. Natl Med J China. 2011; 91: 2841-4.
16. Li Q, Wang J, Sun Y, Cui YL, Juzi JT, Li HX, et al. Efficacy of postoperative transarterial chemoembolization and portal vein chemotherapy for patients with hepatocellular carcinoma complicated by portal vein tumor thrombosis - A randomized study. World J Surg. 2006; 30: 2004-11.
17. Peng BG, He Q, Li JP, Zhou F. Adjuvant transcatheter arterial chemoembolization improves efficacy of hepatectomy for patients with hepatocellular carcinoma and portal vein tumor thrombus. Am J Surg 2009; 198: 313-8.

18. Wei X, Jiang Y, Zhang X, Feng S, Zhou B, Ye X, et al. Neoadjuvant three-dimensional conformal radiotherapy for resectable hepatocellular carcinoma with portal vein tumor thrombus: A randomized, open-label, multicenter controlled study. J Clin Oncol. 2019; 37: 2141-51.

19. Zhong C, Guo RP, Li JQ, Shi M, Wei W, Chen MS, et al. A randomized controlled trial of hepatectomy with adjuvant transcatheter arterial chemoembolization versus hepatectomy alone for Stage III A hepatocellular carcinoma. J Cancer Res Clin Oncol. 2009; 135: 1437-45.

20. Liu PH, Huo TI, Miksad RA. Hepatocellular Carcinoma with Portal Vein Tumor Involvement: Best Management Strategies. Semin Liver Dis. 2018; 38: 242-51.

21. Zhang ZM, Lai ECH, Zhang C, Yu HW, Liu Z, Wan BJ, et al. The strategies for treating primary hepatocellular carcinoma with portal vein tumor thrombus. Int J Surg. 2015; 20: 8-16.

22. Jiang W, Zeng ZC. Is it time to adopt external beam radiotherapy in the NCCN guidelines as a therapeutic strategy for intermediate/advanced hepatocellular carcinoma? Oncol., vol. 84, S. Karger AG. 2013; p. 69–74.

23. Hou JZ, Zeng ZC, Wang BL, Yang P, Zhang JY, Mo HF. High dose radiotherapy with image-guided hypo-IMRT for hepatocellular carcinoma with portal vein and/or inferior vena cava tumor thrombi is more feasible and efficacious than conventional 3D-CRT. Jpn J Clin Oncol. 2016; 46: 357-62.

24. Li T, Puhan MA, Vedula SS, Singh S, Dickersin K. Network meta-analysis-highly attractive but more methodological research is needed. BMC Med 2011; 9.