Efficacy of Different Treatments for Patients with Advanced Hepatocellular Carcinoma: A System Review and Network Meta-Analysis

REVIEW ARTICLE

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ABSTRACT

Background: Over the past decade, the treatment landscape for advanced hepatocellular carcinoma (HCC) has expanded considerably. Therefore, this network meta-analysis aimed to compare the efficacy of combination treatment versus sorafenib.

Materials and Methods: A systematic literature review was conducted to select eligible studies. A network meta-analysis was performed to compare the overall survival (OS) and objective response rate (ORR) among anti- programmed death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) plus anti-vascular endothelial growth factor (VEGF), hepatic arterial infusion chemotherapy (HAIC) plus sorafenib and sorafenib in patients with advanced HCC. Furthermore, for patients without extrahepatic spread, the comparison of the OS among transarterial chemoembolization (TACE) plus radiotherapy (RT), anti-PD-1/PD-L1 plus anti-VEGF, HAIC plus sorafenib and sorafenib was conducted.

Results: A total of 1182 articles were screened through database searching, among which 7 studies involving 1639 patients were included in the analysis. By comparison of 6-month OS, 12-month OS and ORR, anti-PD-1/PD-L1+anti-VEGF was considered the best intervention in advanced HCC anti-PD-1/PD-L1 plus anti-VEGF versus sorafenib: 12-month OS: HR, 0.64; 95% CI, 0.47–0.88; ORR: odd ratio, 0.53; 95% CI, 0.38–0.74). While for patients without extrahepatic spread, the above four interventions showed similar OS; however, TACE plus RT rank the best with a P-score of 57.07%.

Conclusions: In patients with advanced HCC, anti-PD-1/PD-L1+anti-VEGF was associated with highest ranking of OS compared with HAIC plus sorafenib and sorafenib. TACE plus RT might be a more favorable choice than other treatments in advanced HCC without extrahepatic spread.

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Highlights:

- The treatment landscape for advanced hepatocellular carcinoma (HCC) has expanded considerably over the last decade. This network meta-analysis was conducted to compare the efficacy of combination treatment versus sorafenib.
- Based on the findings, anti-PD-1/PD-L1+anti-VEGF was considered the best intervention in advanced HCC via comparison of 6-month OS and 12-month OS.
- In patients without extrahepatic metastases, TACE plus RT and anti-PD-1/PD-L1 plus anti-VEGF yielded similar outcomes for advanced HCC without extrahepatic spread in OS.
- The analysis presented that anti-PD-1/PD-L1 plus anti-VEGF ranked the highest on P-score in terms of ORR.
- TACE plus RT rank the best with a P-score of 57.07% in overall survival compared with anti-PD-1/PD-L1 plus anti-VEGF and HAIC plus sorafenib.
- Future studies could focus on the role of radiation and other potential combinations.

1. INTRODUCTION

Liver cancer is the sixth common cancer and the third leading cause of cancer-related death globally in 2020, of which hepatocellular carcinoma (HCC) accounts for 75%–85% [1]. More than half of HCC patients were diagnosed at an advanced stage with an unfavorable prognosis due to the palliative nature of available systemic and local therapies [2, 3].

Sorafenib, an oral multi-kinase inhibition, was considered as the first-line systemic treatment with significantly improved overall survival (OS) for unresected HCC [4–6]. However, only 30% of patients could benefit from sorafenib, and a relatively high risk of specific adverse events with Tyrosine kinase inhibitors (TKI) treatment also influenced life quality of patients [4, 7]. Several studies on other treatment options, including hepatic arterial infusion chemotherapy (HAIC), transarterial chemoembolization (TACE), radiotherapy (RT) and immunotherapy have demonstrated favorable survival outcomes, contributing to expansion of first-line and second-line treatment options for advanced HCC.

Immunotherapies have demonstrated efficacy in variable malignancies [8, 9]. Recently, some trials reported promising results of immune checkpoint inhibitors (ICI) in advanced HCC. In phase 2 KETNOTE-224 trial, Pembrolizumab, as a programmed death 1 (PD1) inhibitor, was effective for patients who had contraindications to or could not tolerate sorafenib, which was identified as a second-line treatment of advanced HCC [9]. The phase 3 IMbrave 150 trial showed a significant benefit in OS and progression-free survival with atezolizumab plus bevacizumab compared with sorafenib in patients with locally advanced metastatic or unresectable HCC [10]. Radiotherapy, as one of the potent local modalities [11], has been used for locally advanced HCC which could be safely and effectively leading to sustained local control and survival rates higher than in historical controls with the development of radiation technology [12]. A meta-analysis involving 25 trials revealed that patients with unresectable HCC could benefit from TACE plus RT [13]. HAIC, a widely employed palliative treatment modality, was used to treat patients with advanced HCC, which increased local drug concentration and reduced systemic distribution of the drugs. In addition, HAIC plus sorafenib yield a better OS for patients with advanced HCC than sorafenib alone as reported in a multicenter phase 2 trial [14–17]. When compared with the standard of care sorafenib, HAIC plus sorafenib, TACE plus RT and anti-PD-1/ programmed cell death ligand 1 (PD-L1) plus anti-vascular endothelial growth factor (VEGF) showed a favorable benefit in patients with advanced HCC. However, little is known on the efficacy of the above three options for patients with advanced HCC. Therefore, this network meta-analysis aimed to compare the survival outcomes and the response rates of HAIC plus sorafenib, TACE plus RT, and anti-PD-1/PD-L1 plus anti-VEGF in advanced HCC.

2. MATERIAL AND METHODS

This systematic review of the literature about the efficacy of combination treatment on advanced HCC was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 statement. The work has been reported in line with the PRISMA criteria [18].

2.1. REGISTRATION

This network meta-analysis was registered with the Research Registry for Systemic Reviews with unique

identifying number of reviewregistry1434. (https://www.researchregistry.com/browse-theregistry#registryofsystematicreviewsmeta-analyses/registryofsystematicreviewsmeta-analysesdetails/630348d4b710df0022f656fb/ accessed on 22 August 2022).

2.2. ASSESSMENT OF METHODOLOGICAL QUALITY OF THE SYSTEMATIC REVIEW (AMSTAR 2)

The AMSTAR 2 (Assessing the methodological quality of systematic reviews) Guidelines was completed to evaluate the quality of our methodology [19].

2.3. DATA SOURCES AND SEARCHES

For this systematic and network, we searched PubMed, Cochrane Library, and Web of Science databases to identify relevant articles up to May 2021. The detailed search strategy is provided in the Supplementary Table A. Additionally, we manually checked the reference titles of the relevant articles. Finally, the titles and abstracts were assessed by two independent reviewers. No language restrictions were adopted for our search.

2.4. STUDY SELECTION CRITERIA

The selected studies had to meet the following criteria:

a. Studies that enrolled patients with locally advanced metastatic or unresectable HCC;
b. Studies that compared any two or more different arms that consisted of the above-mentioned treatments;
c. Studies that contained at least one of the following outcome measures:
   - OS, measured from the time of randomization or initial treatment to the time of death from any cause.
   - The objective response rate (ORR), defined as the proportion of patients with a confirmed complete or partial response according to HCC-specific modified RECIST [20].

2.5. DATA EXTRACTION AND QUALITY ASSESSMENT

The following data were independently extracted by two reviewers and cross-checked: general information (i.e., document title, publication time, journal name, author, country), patient characteristics (i.e., age, gender, Eastern Co-operative Oncology Group performance status, Barcelona clinic liver cancer classification, Child-Pugh A classification, percent hepatitis B/C), details of interventions, and efficacy endpoints (i.e., OS as a primary and tumor response in terms of ORR as a secondary endpoint. Survival data that was not directly provided in the studies would be extracted from Kaplan-Meier curves using Engauge Digitizer software (version 11.1) [21, 22]. Two reviewers used the Cochrane Risk of Bias Tool to assess the quality of the randomized studies and the Newcastle Ottawa Scale to assess the non-randomized studies and evaluated explicitly with the following judgement system independently: low risk of bias, high risk of bias, or unclear (either lack of information or uncertainty for bias). And disagreements between two reviewers were resolved by referring to a third reviewer. The quality of evidence (i.e., certainty in the estimates) was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation approach [23].

2.6. STATISTICAL ANALYSIS

All direct and indirect evidence from the included studies were synthesized to compare the efficacy of the different treatments. For OS, estimated hazard ratios (HR) were calculated to compare treatments. For discrete variable such as ORR, the odds ratios with 95% confidence intervals (CI) were estimated to compare treatments.

The interventions based on a network meta-analysis of advanced HCC were performed in Bayesian framework using Markov chain Monte Carlo methods in JAGS 4.3.0. This network used a random-effects consistency model which was a multivariate meta-regression way to pool evidence from direct and indirect comparisons. Intend to fit the model, we used non-informative prior distribution and four chains of initial value, which lead to yield 100 000 iterations and a thinning interval of 1. The possibility of each treatment being the most effective was ranked according to the HR, odds ratios and posterior probabilities. The I^2 statistics were used to assess statistical heterogeneity. I^2 values, under 25%, between 25% and 50%, and over 50% were regarded as indications of low, moderate, and high heterogeneity. P-score, as frequentist analogues to surface under the cumulative ranking curve, were computed to rank treatments. We used ranking grams based on P-score to visualize treatment ranking. A higher P-score was associated with a better efficacy. All analysis were performed in R software (version 4.0.5).

3. RESULTS

3.1. STUDY SELECTION AND PATIENT CHARACTERISTICS

Overall, 1182 potentially relevant studies were identified: PubMed, n = 850; Web of science, n = 288; Cochrane Library: n = 104. The PRISMA flow diagram was presented in Figure A. After removing duplicate, screening the initial title and abstract, retrieving and reviewing the full text, seven references were identified reporting 6 articles in the advanced HCC setting [10, 14, 24–27] and 5 studies reporting data on HCC without extrahepatic spread were selected [10, 14, 25, 26, 28]. A total of 1639 advanced HCC patients with predominantly Child-Pugh A were included in the analysis. Four trials compared sorafenib with HAIC plus sorafenib [14, 24–26] and two comparing anti-PD-1/PD-L1 plus anti-VEGF with sorafenib. More

than 75% subjects were men with a mean or median age of 53.0 to 72.4 years. The characteristics of the included patients were summarized in the Supplementary Table B.

3.2. QUALITY ASSESSMENT

The qualitative assessment was performed by assessing various indicators for each individual study using the Cochrane tool for risk of bias. All the trials selected exposed cohorts from the same population. Overall, 2 trials were at low risk of bias in all domains, 4 showed some concern, and none was at high risk of bias. The other study was non-randomized study. In general, the quality of the included studies was deemed to be relatively high (Figure B).

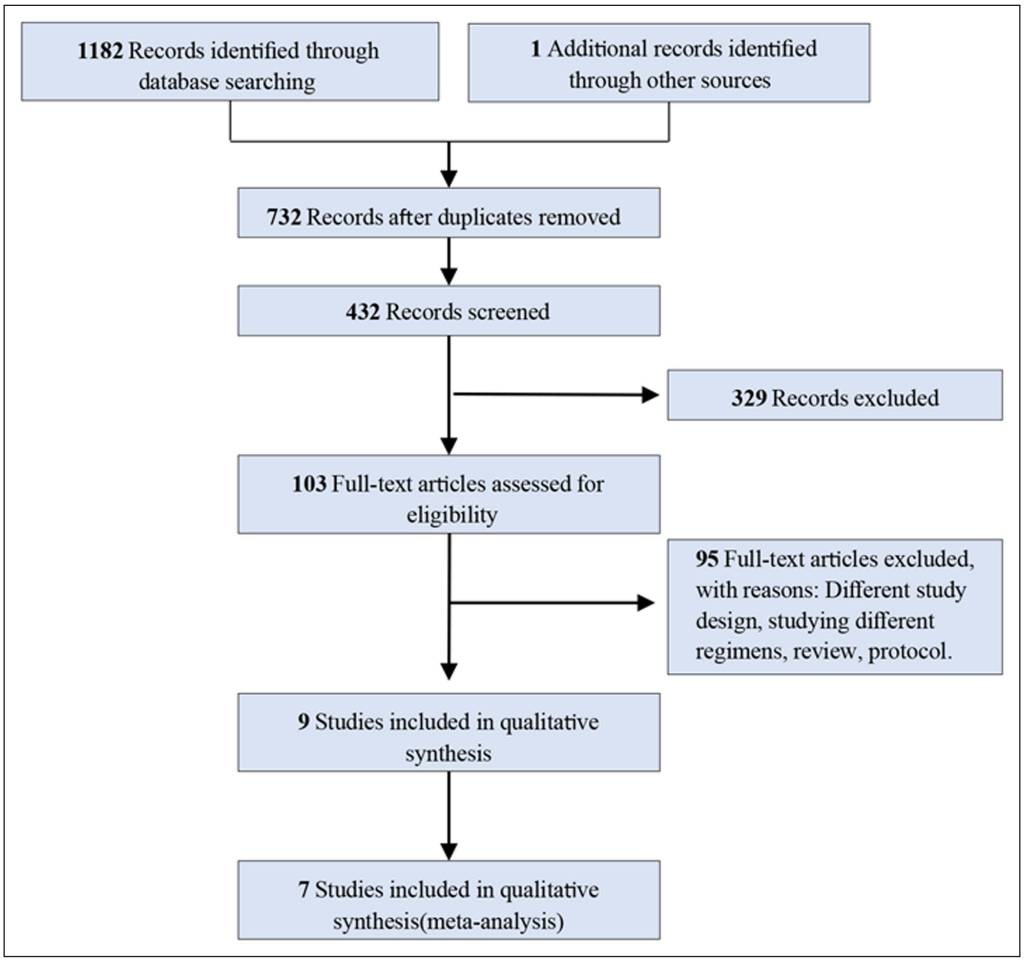
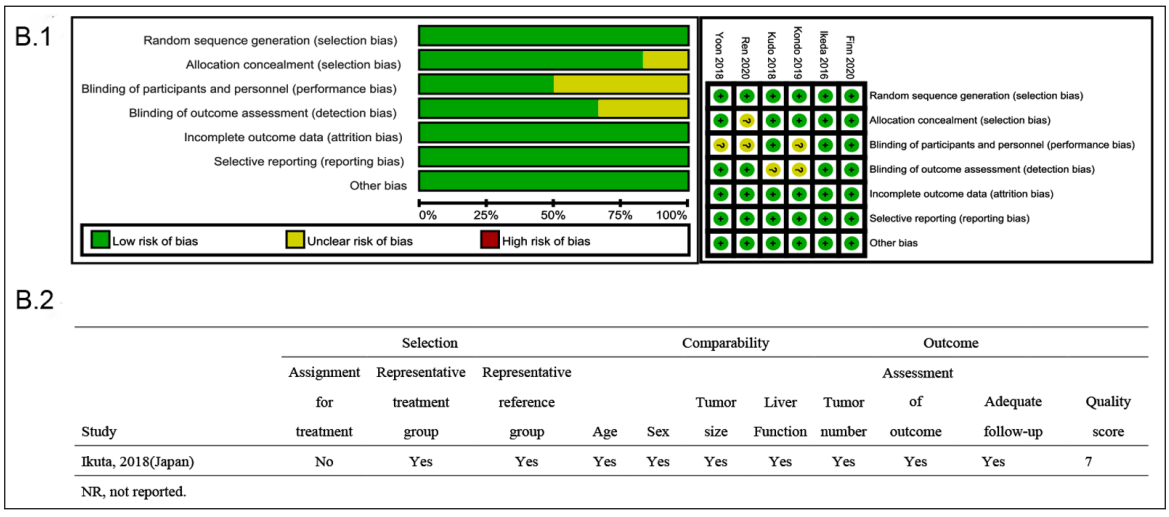


Figure A PRISMA Flow Diagram Showing Screening and Selection Process.



Study	Selection: Assignment for treatment	Selection: Representative treatment group	Selection: Representative reference group	Comparability: Age	Comparability: Sex	Comparability: Tumor size	Comparability: Liver Function	Comparability: Tumor number	Outcome: Assessment of outcome	Outcome: Adequate follow-up	Quality score
Ikuta, 2018(Japan)	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7

NR, not reported.

Figure B Risk of bias graph for studies. **Figure B.1.** Risk of bias graph for randomized study; **Figure B.2.** Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all retrospective studies using modified.

3.3. OVERALL SURVIVAL

A total of 6 studies reported 6-month and 12-month OS with 3 interventions (Supplementary Figure A). The heterogeneity between the studies whose treatments were HAIC plus sorafenib and sorafenib was considered moderate (6-month OS, I^2 = 48.3%; 12-month OS, I^2 = 39.4%). No significant difference was found regarding 6-month OS among sorafenib and the other two combined regiments (HAIC plus sorafenib: HR, 0.96; 95% CI, 0.45–1.70; anti-PD-1/PD-L1 plus anti-VEGF: HR, 0.56; 95% CI, 0.27–1.20) (Table A). The P-score indicated that anti-PD-1/PD-L1 plus anti-VEGF was the highest ranked treatments (P-score = 89.81%), and HAIC plus sorafenib ranked the second with a P-score of 8.66% (Supplementary Figure B). In addition, anti-PD-1/PD-L1 plus anti-VEGF and HAIC plus sorafenib showed a significant improvement in 12-month OS relative to sorafenib (anti-PD-1/PD-L1 plus anti-VEGF: HR, 0.64; 95% CI, 0.47–0.88; HAIC plus sorafenib: HR 0.95; 95% CI 0.70–1.30) (Table A & Supplementary Figure C). As shown in Table A & Supplementary Figure B, anti-PD-1/PD-L1 plus anti-VEGF ranked the highest on P-score in 12-month OS (96.16% for anti-PD-1/PD-L1 plus anti-VEGF group and 3.52% for HAIC plus sorafenib group).

3.4. OBJECTIVE RESPONSE RATE

Six studies involving 1535 patients and 3 interventions reported ORR (Supplementary Figure A). The heterogeneity was absent (I^2 = 0%). The network analysis demonstrated that patients gained a significant benefit from anti-PD-1/PD-L1+anti-VEGF (Table B & Supplementary Figure C). In addition, the analysis presented that anti-PD-1/PD-L1 plus anti-VEGF ranked the highest on P-score in terms of ORR (Supplementary Figure B).

3.5. OUTCOMES IN PATIENTS WITHOUT EXTRAHEPATIC SPREAD

Five above studies contributed to survival outcomes of the advanced HCC patients without extrahepatic spread (Supplementary Figure D). And research conducted by Yoon et al [28] comparing TACE plus RT with sorafenib in advanced HCC without extrahepatic spread were also included. The subgroup analysis of advanced HCC without extrahepatic metastasis involved five studies and 425 patients, for comparing the survival outcomes of four inventions including sorafenib, HAIC plus sorafenib, TACE plus RT and anti-PD-1/PD-L1 plus anti-VEGF. The heterogeneity among the studies was absent (I^2 = 0%). As shown in Supplementary Figure E, the ranking for OS from high to low was TACE plus RT(P-score = 57.07%), anti-PD-1/PD-L1 plus anti-VEGF (P-score = 35.35%) and HAIC plus sorafenib (P-score = 7%). In terms of OS, TACE plus RT and anti-PD-1/PD-L1 plus anti-VEGF yielded similar outcomes for advanced HCC without extrahepatic spread (anti-PD-1/PD-L1 plus anti-VEGF versus TACE plus RT: HR, 1.16; 95% CI, 0.40–3.37) (Table C & Supplementary Figure F).

4. DISCUSSION

A systematic review and network meta-analysis of patients with advanced HCC was conducted to assess the efficacy of treatments focusing on sorafenib, and several combination therapy. We found that the combination of anti-PD-1/PD-L1 and anti-VEGF treatment showed better 12-month OS and ORR outcomes than HAIC plus sorafenib treatment and sorafenib monotherapy in advanced HCC.

TREATMENT	12-MONTH OS		
6-month OS	**anti-PD-1/PD-L1+anti-VEGF**	0.68 (0.44, 1.05)	0.64 (0.47, 0.88)
	0.59 (0.24, 1.81)	**HAIC + sorafenib**	0.95 (0.70, 1.30)
	0.56 (0.27, 1.20)	0.96 (0.45, 1.70)	**Sorafenib**

Table A League table showing indirect comparisons among the three treatments for OS.

CI, confidence interval; HR, Hazard ratio; OS, overall survival.

Hazard ratios and 95% CIs for the pairwise comparisons of the network meta-analysis. Indirect comparisons should be read from left to right. Data of each cell are hazard for the comparison of row-defining treatment versus column-defining treatment. For 6-month OS, a HR of less than 1 favors column-defining treatment. For 12-month OS, a hazard ratio of less than 1 favors row-defining treatment.

TREATMENT	ANTI-PD-1/PD-L1+ANTI-VEGF		
ORR	0.84 (0.53, 1.32)	**HAIC + sorafenib**	
	0.53 (0.38, 0.74)	0.63 (0.47, 0.87)	**Sorafenib**

Table B League table showing indirect comparisons among the three treatments for ORR.

ORR, Objective response rate.

HRs and 95% CIs for the pairwise comparisons of the network meta-analysis. Indirect comparisons should be read from left to right. Data of each cell are hazard for the comparison of row-defining treatment versus column-defining treatment. For ORR, an odd ratio of less than 1 favors row-defining treatment.

TREATMENT	ANTI-PD-1/PD-L1+ANTI-VEGF			
OS	1.16 (0.40, 3.37)	**TACE+RT**		
	0.80 (0.33, 2.02)	0.68 (0.31, 1.55)	**HAIC + sorafenib**	
	0.71 (0.32, 1.61)	0.61 (0.31, 1.20)	0.89 (0.58, 1.31)	**Sorafenib**

Table C League table showing indirect comparisons for OS in advanced HCC without extrahepatic spread.

HRs and 95% CIs for the pairwise comparisons of the network meta-analysis. Indirect comparisons should be read from left to right. Data of each cell are hazard for the comparison of row-defining treatment versus column-defining treatment. For OS, a HR of less than 1 favors row-defining treatment.

However, in patients without extrahepatic spread, the combination of TACE and RT had a greater survival benefit compared with anti-PD-1/PD-L1 plus anti-VEGF therapy.

Over the past decade, various treatment options have been tried in advanced HCC; however, controversial exists over the optimal treatment regime. Sorafenib, a multikinase inhibitor that increases the rate of apoptosis and inhibits tumor-cell proliferation and tumor angiogenesis, has been recommended as the first-line systemic therapy in advanced HCC for a decade [4]. However, side effects were frequent in sorafenib treatment, such as hand foot skin reaction (HFSR) and diarrhea. HFSR which was associated with tyrosine kinase inhibitors was characterized by keratinocytic necrosis, dermal edema, parakeratosis, and hyperkeratosis [29]. The phase III trials of sorafenib in patients with HCC reported that up to 10% experienced grade 3/4 HFSR, which was the most common adverse events resulting in dose reductions [30]. Therefore, the superiority of sorafenib was reduced by its toxicities, including HFSR, even if it prolonged survival in patients with HCC [4, 29, 31–33]. Thus, new systemic treatments of HCC for improved clinical outcomes and safety remained an urgent need.

Recently, several clinical trials have been recently completed or are currently underway evaluating vascular endothelial growth factor receptor tyrosine kinase inhibitors and immune checkpoint inhibitors in the monotherapy of combination therapy for advanced HCC. Atezolizumab, which targeted the PD-L1/PD-1 pathway, could prevent connection between receptors PD-1 and B7-1 which spare T-cell from suppression. Bevacizumab, as a monoclonal antibody targeting VEGF, controlled tumor growth and angiogenesis. The phase 3 trial showed that compared with sorafenib, the combination of atezolizumab with bevacizumab had a superiority advantage which was considered as the first-line treatment of most patients with advanced HCC according to current guidelines [2, 34]. Furthermore, in the phase 3 ORIENT-32 trail, sintilimab in combination with bevacizumab biosimilar improved both OS and progression-free survival of HCC when compared with sorafenib. Sintilimab was a newly approved PD-1 antibody for cancer immunotherapy with unknown binding epitope on PD-1 which was similar to atezolizumab. Therefore, the combination of ICIs and VEGF inhibitors played an important role in advanced HCC. Similar to the present findings, two previous network-analysis showed that atezolizumab with bevacizumab ranked first for OS in patients with advanced [35, 36].

HAIC or HAIC plus sorafenib is frequently used to treat patients with advanced HCC with increasing evidence supporting, especially for those with portal vein tumor thrombus in Asian countries [15–17]. Sorafenib plus HAIC therapy demonstrated a favorable improvement in the response rate to chemotherapy and therefore prolong the OS of patients with advanced HCC in the previous multicenter randomized trial and meta-analysis study [24, 26]. Although HAIC plus sorafenib was ranked second in the network meta-analysis (NMA) comparison, it did not demonstrate a significant advantage of HAIC plus sorafenib compared sorafenib monotherapy. Similar to other studies, our findings demonstrated favorable overall survival in the sorafenib plus HAIC compared with sorafenib. However, there were no studies for comparing anti-PD-1/PD-L1 plus anti-VEGF with HAIC plus sorafenib. In our study, sorafenib has no advantage over other combination treatments. Hence, a promising activity could be found in multiple other combinations of PD-1/PD-L1 inhibitors with VEGF inhibitors or with Cytotoxic T lymphocyte associate protein-4 inhibitors. Moreover, various trials are evaluating the combination of VEGF TKIs and checkpoint inhibitors.

In clinical trials IMbrave 150, and ORIENT-32, the percentage of extrahepatic metastases reached 60% and 81% [10, 27]. However, at the first diagnosis in advanced HCC, patients with mega liver masses and macrovascular invasion were commonly, while with extrahepatic metastases were less (77.5% vs. 37,9%) [37]. TACE was recommended for patients with a large or multinodular HCC extrahepatic metastasis. RT could be considered an alternative optional treatment for advanced HCC which was beneficial to use higher radiation doses at the tumor directly that also presented the organ at risk from substantial radiation [38]. Moreover, recent developments in RT technique made three-dimensional conformal liver irradiation to be a feasible and safe treatment for advanced HCC, contributing to improved outcomes for

patients receiving TACE in combination with RT. In the NMA, our findings revealed that TACE plus RT ranked the highest with significance advantage compare with all other combination agents including ICIs and HAIC plus sorafenib in the advanced HCC without extrahepatic spread. A meta-analysis including 25 trial conducted by Huo and colleagues demonstrated that TACE plus RT had more therapeutical benefit comparing with TACE alone which was suitable patients with unresectable HCC [13]. Furthermore, subsequent curative surgical could apply to some patients due to downstaging by TACE plus RT as reported in a randomized trial [28]. This was further confirmed in our NMA analysis showing TACE plus RT ranking the highest with significant advantage compared with other treatments. In advanced HCC without extrahepatic metastases, the control of local lesions may be important to facilitate subsequent treatment of the primary tumor. Tumor thrombus of the portal vein often decreased blood supply to the normal liver, led to extensive intrahepatic dissemination of the tumor through the portal tract and caused portal hypertension resulting in the rupture of collateral vessels, ascites, hepatic encephalopathy, and deteriorating liver function which could limit further treatment options in patients with HCC [39]. Thus, the locoregional treatment was considered a favorable therapy compared with systemic therapy for advanced HCC patients with disease limited to the liver.

This study has potential limitations which are related to the analysis of the network and the individual trials. For example, in this observational network meta-analysis which based on data entirely from clinical trials was remained unavoidable confounding factors. In addition, this analysis was performed with study-level data rather than individual patient data that limited the power of our analysis.

5. CONCLUSION

This network-analysis revealed that the combination of anti-PD-1/PD-L1 and anti-VEGF was associated with the best OS and ORR in patients with advanced HCC. However, in patients without extrahepatic metastases, TACE plus RT demonstrated a highest rank in OS compared with anti-PD-1/PD-L1 plus anti-VEGF and HAIC plus sorafenib. Future studies could focus on the role of radiation and other potential combinations.

ABBREVIATIONS

HCC, hepatocellular carcinoma; PD-1, programmed death 1; PD-L1, programmed cell death ligand 1; VEGF, vascular endothelial growth factor; TACE, transarterial chemoembolization; RT, radiotherapy; OS, overall survival; HR, hazard ratio; ORR, objective response rate.

DATA ACCESSIBILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

ADDITIONAL FILES

The additional files for this article can be found as follows:

- **Supplemental Material 1.** Tables A, B and Figures A to F. DOI: https://doi.org/10.29337/ijsonco.140.s1
- **Supplemental Material 2.** AMSTAR 2 checklist. DOI: https://doi.org/10.29337/ijsonco.140.s2
- **Supplemental Material 3.** PRISMA 2020 checklist. DOI: https://doi.org/10.29337/ijsonco.140.s3

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COMPETING INTERESTS

The authors have no competing interests to declare.

AUTHOR CONTRIBUTIONS

Dr Peng had full access to all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

- Study concept and design: ZW Peng.
- Acquisition, analysis, or interpretation of data: YY Ling, M Jin, MY Zhu, Y Wang, Y Chen, ZW Peng.
- Drafting of the manuscript: YY Ling, M Jin.
- Critical revision of the manuscript for important intellectual content: ZW Peng.
- Final approval of the version to be published: YY Ling, M Jin, MY Zhu, Y Wang, Y Chen, ZW Peng.

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