META-ANALYSIS

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# Comparison of Hepatic Arterial Infusion Chemotherapy and Transarterial Chemoembolization for Advanced Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis

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## ABSTRACT

**Aims**: To compare the efficacy, safety, and survival outcomes of hepatic arterial infusion chemotherapy (HAIC) versus transarterial chemoembolization (TACE) for the treatment of advanced hepatocellular carcinoma (HCC), a comprehensive meta-analysis was conducted.

**Methods**: MEDLINE, PubMed, Web of Science, Embase, and the Cochrane Central Register of Controlled Trials were searched from January 1966 to 20 February 2022, and relevant articles were retrieved. The literature search, quality assessment, and data extraction were conducted independently by two reviewers. The primary endpoints were objective response rate (ORR) and overall survival (OS), while the secondary endpoints were disease control rate (DCR), progression-free survival (PFS), and adverse events. The odd ratios (OR) and hazard ratios (HR) with 95% confidence intervals (95%CI) were pooled.

**Results**: Seven studies with a total of 989 patients were included in this meta-analysis. The pooled results showed that HAIC significantly improved ORR (OR=4.94, 95%CI: 3.47-7.05, p<0.001) and DCR (OR=2.97, 95%CI: 2.16-4.08, p<0.001). In addition, HCC patients who received HAIC had significantly longer PFS (HR=0.54, 95%CI: 0.45-0.65, p<0.001) and OS (HR=0.55, 95%CI: 0.46-0.66, p<0.001) than those who underwent TACE. Compared with TACE, HAIC showed a lower incidence for grade 3-4 adverse events (OR=0.52, 95%CI: 0.30-0.88, p<0.001).

**Conclusions**: HAIC may significantly improve survival benefits and exhibit higher local treatment responses with mild side effects in patients with advanced HCC compared to TACE.

**Key words:** hepatocellular carcinoma – hepatic arterial infusion chemotherapy – transarterial chemoembolization – meta-analysis.

**Abbreviations**: ALT: alanine aminotransferase; AST: aspartate aminotransferase; CI: confidence interval; DCR: disease control rate; HAIC: hepatic artery infusion chemotherapy; HCC: hepatocellular carcinoma; OR: odds ratio; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; RCT: randomized controlled trial; TACE: transarterial chemoembolization.

## INTRODUCTION

Hepatocellular carcinoma (HCC) is the seventh most common malignancy and the third most common cause of cancer-related death in the world, and thus, it poses a serious threat to individuals worldwide [1]. The occurrence of HCC is usually insidious. Most patients are diagnosed with intermediate-advanced HCC, and less than 30% of individuals undergo radical resection [2, 3].

Since the first description by Yamada in 1983, transarterial chemoembolization (TACE) has been established as standard therapy for intermediate HCC [4-6]. As a palliative treatment, TACE still has some limitations, including a low tumor complete necrosis rate and a high postoperative tumor recurrence rate [7, 8]. Furthermore, the long-term efficacy is not satisfactory because of tumor heterogeneity [9]. Therefore, novel, and better treatment strategies of HCC are urgently required.

In recent years, hepatic artery infusion chemotherapy (HAIC) has attracted increasing attention in clinical settings. Hepatic artery infusion chemotherapy is a locoregional therapy that directly delivers chemotherapeutic agents into tumor-associated arterial branches and increases local drug concentrations [10]. Several studies indicated that HAIC was

superior to TACE in treating intermediate-advanced HCC patients with an initial indication for TACE [11, 12]. However, HAIC is not yet widely used worldwide since data from large-scale randomized clinical trials are limited and contradictory. Thus, we conducted this meta-analysis to compare the efficacy and toxicity of HAIC versus TACE for the treatment of patients with advanced HCC.

## METHODS

The meta-analysis followed the Preferred Reporting Items for Systematic Review and Meta-Analyses statement [13] and was registered with PROSPERO (CRD42022325155).

### Search Strategy and Study Selection

We searched MEDLINE, PubMed, Web of Science, Embase, and Cochrane Library databases using the following search terms: (hepatocellular carcinoma or liver cell carcinoma or liver cancer or liver cell carcinoma or adult liver cancer or hepatoma or hepatic neoplasm or hepatic cancer) and (HAIC or hepatic arterial infusion chemotherapy or hepatic artery infusion chemotherapy) and (transarterial chemoembolization or TACE). In addition, we supplemented the search by manually reviewing the reference lists of the retrieved articles and relevant reviews. Two investigators (H.L. and M.W.) conducted independently the study selection. Disagreements were resolved by discussion with a third investigator (Z.H.).

### Inclusion and Exclusion Criteria

Studies were considered eligible for meta-analysis if they met the following criteria: (1) diagnosed advanced HCC with clinical and histopathological evidence; (2) randomized controlled trials (RCTs) or observational studies; (3) all patients aged 18 years or older; (4) patients with Eastern Cooperative Oncology Group (ECOG) performance status <2; (5) patients had not been previously treated by surgical resection; and (6) patients who underwent platinum/5-FU-based HAIC regimens.

The major exclusion criteria were as follows: (1) patients with other malignant tumors; (2) risk estimates and associated 95% confidence interval (CI) were not provided; and (3) the publication was in the format of an abstract, comment, or review.

### Data Extraction and Quality Assessment

For data extraction, two authors (X.Q and H.L.) extracted independently the required information using a standardized data-collection form. The following information was recorded, if available: the first author's name, year of publication, sample size, population demographics, study design, and country of origin. The tumor response rate and survival rate were extracted after propensity score matching analysis. Disagreements between data extractors were resolved by consensus and discussion. The types of eligible studies included observational studies and RCTs. The quality of the observational studies was determined according to the Newcastle-Ottawa Scale (NOS). Any study that scored over 7 stars was regarded as a high-quality study, and those with a score between 4 and 6 stars were regarded as moderate-quality studies [14]. The Jadad scale was used to evaluate the quality of the included RCTs [15].

### Statistical Analysis

We compared the efficacy, safety, and survival outcomes between the HAIC group and the TACE group in advanced hepatocellular carcinoma patients. Li and Liu performed all statistical analyses. Pooled odds ratios (ORs) with the corresponding 95% CIs were calculated to assess the efficacy of HAIC versus TACE on the tumor response as well as on the incidence of grade 3-4 adverse events. Hazard ratios (HR) and 95%CIs were used to evaluate the survival advantage of HAIC compared with TACE. Homogeneity of effect size across studies was tested by Q statistics at a $p<0.10$ level of significance. The $I^2$ statistic, which is a quantitative measure of inconsistency across studies, was also calculated. A fixed-effect model was used for $p>0.10$ and $I^2<50\%$; otherwise, a random-effect model was used [16]. We further conducted sensitivity analysis to explore possible explanations for heterogeneity and to examine the influence of various exclusion criteria on the overall risk estimate. Finally, potential publication bias was assessed by Begg's funnel plot and Egger's regression test [17, 18]. All analyses were performed using Stata 15.0 software. The p values <0.05 were considered significant, except where otherwise specified.

## RESULTS

### Study Selection, Study Characteristics, and Quality Assessment

Initially, a total of 364 unique articles were identified. After removal of duplicates, 258 studies remained eligible. By screening the titles and abstracts, reviews, comments, case reports, and meta-analysis were excluded. After reviewing the full texts, 139 articles were excluded with the following reasons: 33 articles were related to other treatments such as sorafenib or transcatheter arterial embolization; 34 articles did not include a control group; 49 articles did not provide sufficient data, and 23 articles did not obtain adequate samples. Finally, seven studies published from 2003 to 2022 were included in the meta-analysis. The search process and strategy are shown in Fig. 1.

The characteristics of the included studies are listed in Table I. The seven studies were all from Asia; one was performed in Japan [19], four in China [20-23], and two in Korea [24, 25]. In this meta-analysis, which contained two prospective studies, one RCT, and four retrospective studies, two studies were analyzed by the propensity score-matched method. Our meta-analysis involved 989 patients with HCC (492 in the HAIC group and 497 in the TACE group). Four studies used fluorouracil, leucovorin, and oxaliplatin as the HAIC regimen, two studies used fluorouracil and cisplatin, and one study used fluorouracil, cisplatin, and carboplatin. According to the NOS scores, four studies that obtained scores of 6-7 were regarded as intermediate-quality, and two studies with a score of 8 were assessed as high-quality. One RCT with a Jadad score of 4 was considered high quality.

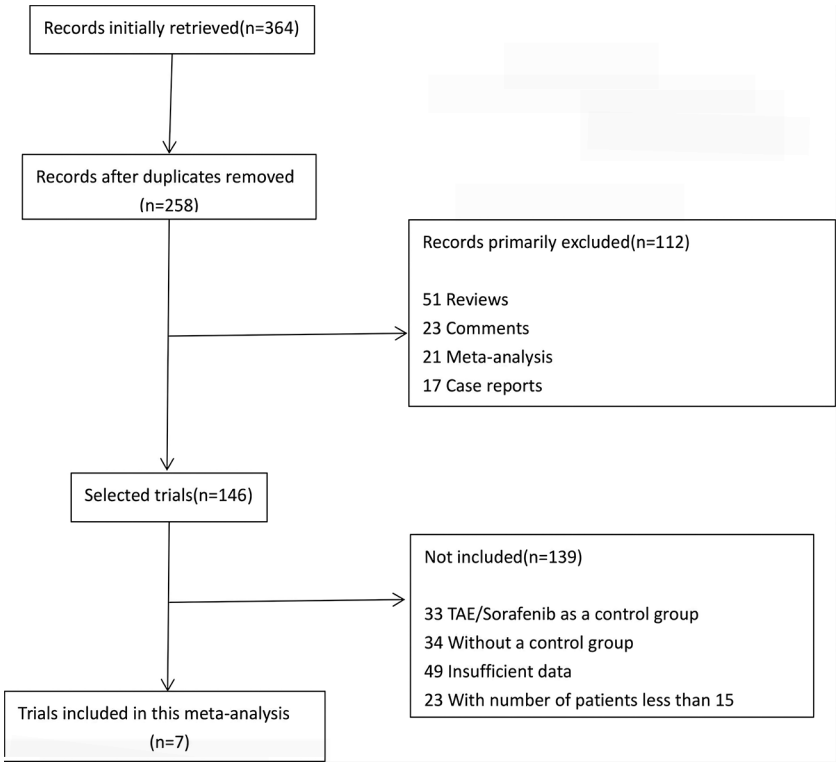


**Fig. 1.** Search flow diagram of the included studies.

**Sensitivity Analysis**

There was large heterogeneity observed among studies reporting grade 3-4 adverse events. Therefore, we conducted sensitivity analyses for the elevated aspartate aminotransferase (AST) to explore the underlying reasons of the heterogeneity. The pooled OR did not change significantly after sensitivity analysis with the removal of one study at a time, which indicated that the results were relatively stable. The causes of heterogeneity might be different follow-up periods, small sample sizes, and different study designs.

**Table I.** Characteristics of selected studies comparing transarterial chemoembolization with hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma

| Study | Year | Country | Research type | Sample size | Propensity score matching | Median OS (HAIC vs TACE), M | Median PFS (HAIC vs TACE), M | HAIC regimen | Score of NOS | Score of Jadad |
|---|---|---|---|---|---|---|---|---|---|---|
| An | 2021 | China | Retrospective study | 160 | Yes | 13.3 vs 10.8 | 7.8 vs 4.0 | Fluorouracil, leucovorin, oxaliplatin | 8 | - |
| Kim | 2014 | Korea | Retrospective study | 99 | No | 8.2 vs 7.5 | 3.4 vs 3.8 | Fluorouracil, cisplatin, carboplatin | 7 | - |
| He | 2017 | China | Prospective study | 79 | No | NA | NA | Fluorouracil, leucovorin, oxaliplatin | 7 | - |
| Li QJ | 2022 | China | Randomized controlled trial | 315 | No | 23.1 vs 16.1 | 9.6 vs 5.4 | Fluorouracil, leucovorin, oxaliplatin | - | 4 |
| Kim | 2010 | Korea | Prospective study | 67 | No | 6.4 vs 4.0 | NA | Fluorouracil, cisplatin | 7 | - |
| Li SL | 2021 | China | Retrospective study | 232 | Yes | 13.9 vs 6.0 | 6.4 vs 2.8 | Fluorouracil, leucovorin, oxaliplatin | 8 | - |
| Sumie | 2003 | Japan | Retrospective study | 37 | No | NA | NA | Fluorouracil, cisplatin | 6 | - |

HAIC: hepatic arterial infusion chemotherapy; M: months; NA: not available; NOS: Newcastle-Ottawa Scale; OS: overall survival; PFS: progression-free survival; TACE: transarterial chemoembolization.

**Primary Endpoints: Objective Response Rate and Overall Survival**

The objective response rate (ORR) was evaluated in six studies, which included 890 patients, and no heterogeneity was found among the included studies (p=0.732, $I^2$=0.0%). The pooled results indicated that HAIC had a significantly improved ORR compared with TACE (OR=4.94, 95% CI: 3.47-7.05) (Fig. 2A).

Four studies with 806 patients with HCC were included in the overall survival (OS) analysis. In HCC patients, HAIC significantly prolonged OS compared with TACE (HR=0.55, 95%CI: 0.46-0.66), and no heterogeneity was found (p=0.490, $I^2$=0%) (Fig. 2B).

**Secondary Endpoints: Disease Control Rate (DCR), Progression-free Survival (PFS), and Adverse Events**

Six studies were included in the meta-analysis that assessed the disease control rate (DCR), and low heterogeneity was found between the two groups (p=0.243, $I^2$=25.4%). Using a fixed effect model, the DCR of the HAIC group was greater than that of the TACE group (OR=2.97, 95% CI: 2.16-4.08) (Fig. 3A).

Three studies were pooled for the analysis of progression-free survival (PFS). Analyses of PFS suggested that patients receiving HAIC showed significantly longer PFS than patients receiving TACE (HR=0.54, 95% CI: 0.45-0.65), and no heterogeneity was noted (p=0.653, $I^2$=0%) (Fig. 3B).

There were six studies that reported grade 3-4 adverse events in two groups. There were no noticeable differences between the two groups in grade 3-4 neutropenia (OR=1.67, 95%CI: 0.36-7.78), anemia (OR=1.30, 95%CI: 0.34-4.95), thrombocytopenia (OR=1.70, 95%CI: 0.76-3.83), and vomiting (OR=1.71, 95%CI: 0.71-4.16). The frequencies of grade 3-4 elevated alanine aminotransferase (ALT) (OR=0.11, 95%CI: 0.03-0.43), elevated aspartate AST (OR=0.20, 95%CI: 0.06-0.63), and hyperbilirubinemia (OR=0.14, 95%CI: 0.04-0.52) were significantly lower in the HAIC group than those in the TACE group. Finally, the overall incidence of grade 3-4 adverse events was lower for patients in the HAIC group than for those in the TACE group (OR=0.52, 95%CI: 0.30-0.88). Heterogeneity was statistically significant (p=0.001, $I^2$=62.7%) (Fig. 3C).

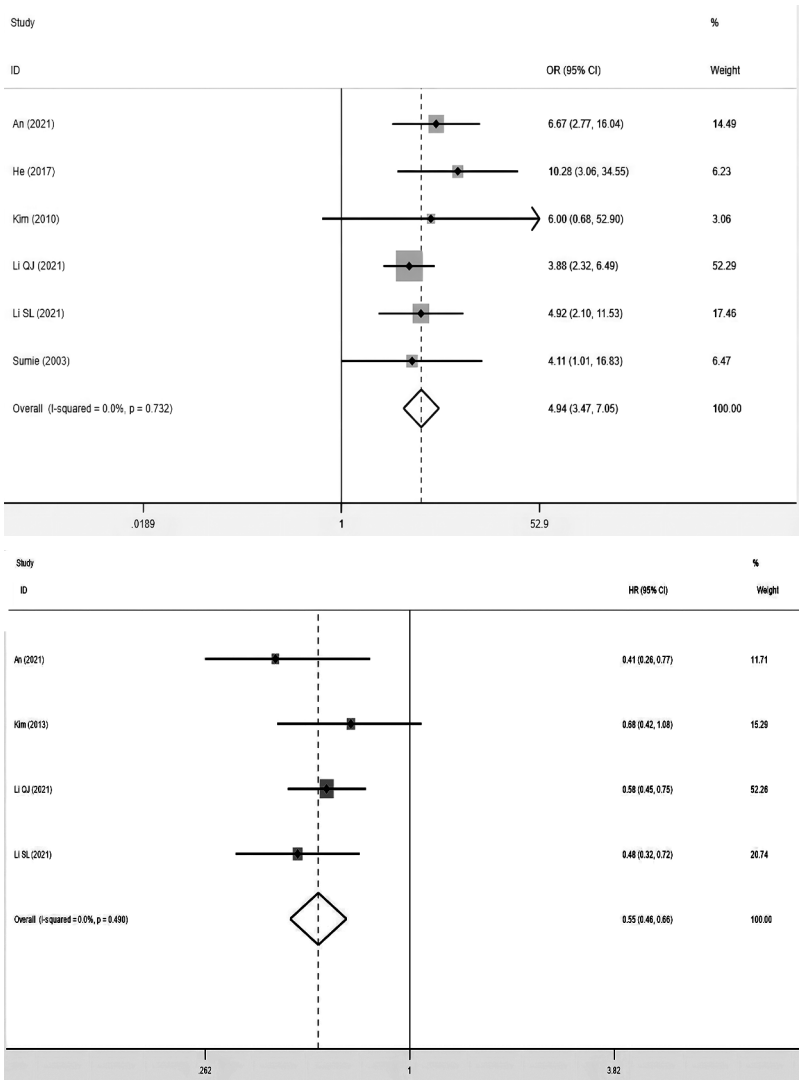


**Fig. 2**. Comparison of hepatic arterial infusion chemotherapy and transarterial chemoembolization for advanced hepatocellular carcinoma in terms of the primary endpoints. 2A: objective response rate; 2B: overall survival.

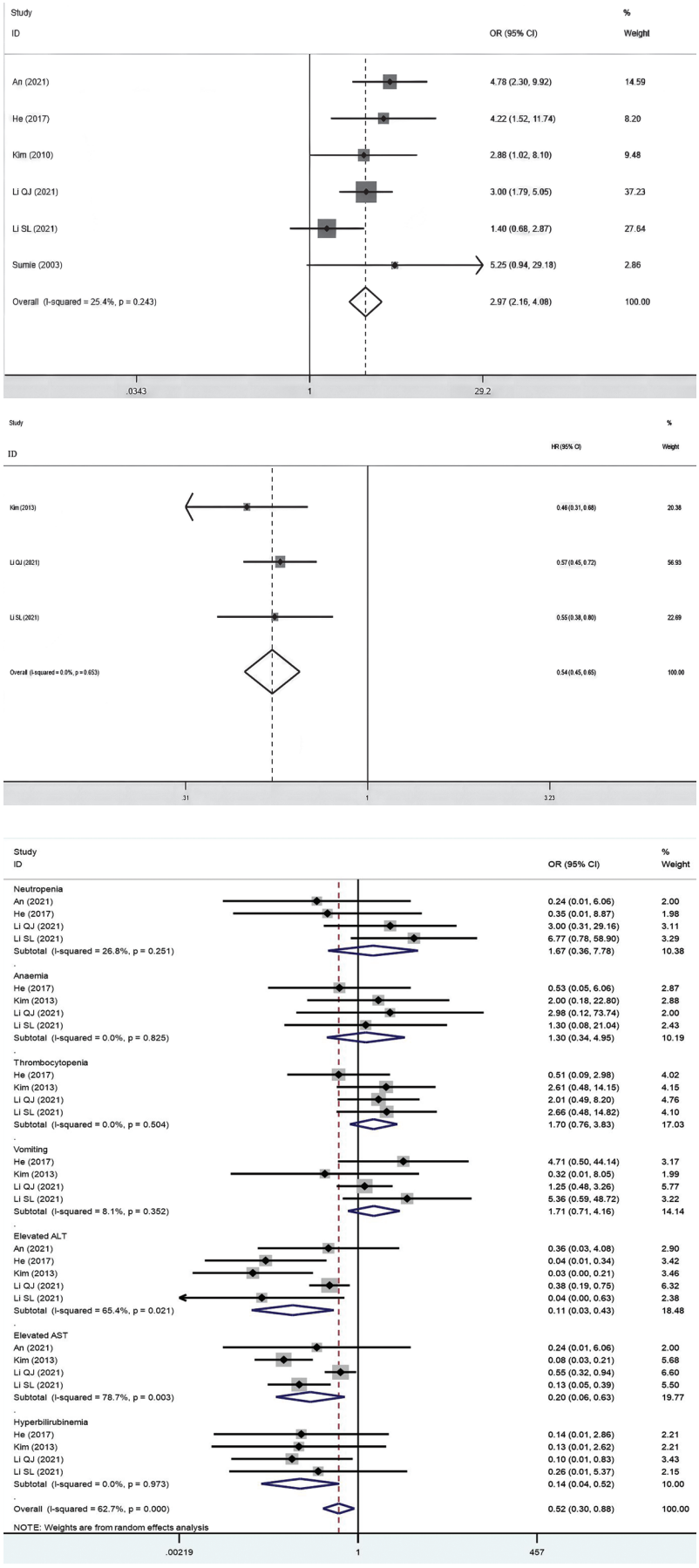


**Fig. 3.** Comparison of hepatic arterial infusion chemotherapy and transarterial chemoembolization for advanced hepatocellular carcinoma in terms of the secondary endpoints. 3A: disease control rate; 3B: progression-free survival; 3C: adverse events.

**Publication Bias**

Visual inspection of the funnel plot did not show substantial asymmetry (Fig. 4). Publication bias was also assessed by Egger's (p=0.231) and Begg's tests (p=0.452). Thus, there was no publication bias.

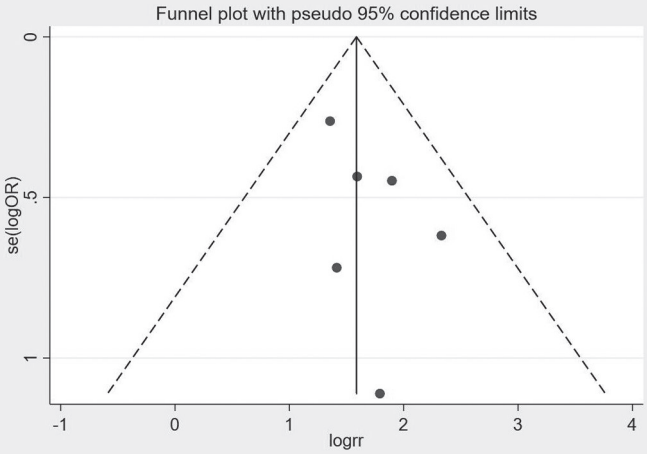


**Fig. 4**. Begg's funnel plot for detecting publication bias.

## DISCUSSION

This meta-analysis compared the tumor response, survival benefit, and tolerability between HAIC and TACE for patients with HCC. The results demonstrated that HAIC had a significant improvement in ORR, OS, PFS, and DCR compared with TACE. In addition, HAIC had fewer grade 3-4 adverse events than TACE.

Most guidelines recommend TACE as a first-line therapy for patients with unresectable intermediate-advanced HCC. However, as a local palliative treatment method, when TACE is conducted repeatedly, its therapeutic effect can gradually wane [26]. Moreover, Shi et al. [27] reported that the survival benefits of TACE are mainly derived from the chemotherapeutic agents; the addition of an embolization component did not prolong the survival but significantly increased the incidence of grade 3-4 adverse events. Hepatic artery infusion chemotherapy was first proposed in Japan, and has been carried out in Japan, South Korea, and other Asian countries for more than 30 years and is recommended by the Japan Society of Hepatology (JSH) Consensus-Based Clinical Practice Guidelines as the standard treatment for liver cancer with portal vein tumor thrombus [28]. At present, there is no universal standard for the treatment of HAIC, and it can be treated with either a single drug or a combination of different drugs. The most widely used regimens include cisplatin monotherapy, the FAIT regimen (interferon and fluorouracil), and the FOLFOX (fluorouracil, leucovorin, and oxaliplatin) regimen. Our meta-analysis used a platinum/5-FU-based regimen.

In this meta-analysis, the ORR and DCR of the HAIC group were both greater than those of the TACE group. The evidence has shown that a high tumor burden is an independent prognostic factor in cancer patients. Thus, a better ORR and DCR can prolong OS and PFS. The favorable results observed in this meta-analysis for HAIC versus those for TACE may be explained by several reasons. First, the liver is a special organ with two blood supplies. The blood supply of liver tumors is almost entirely provided by the hepatic artery, with the portal vein providing very little blood [29]. Because of the large number of blood vessels and their communicating branches in liver tumors, it is difficult to perform complete embolization of tumors due to the limited dose of embolization in TACE. The volume of the chemotherapeutic agent used during TACE does not exceed that of the lipiodol emulsion, and most chemotherapeutic agents will be released into the systemic circulation in less than 1 hour [30]. Compared with TACE, HAIC can be administered by continuous infusion for several days, which can significantly increase the total dose of chemotherapy and prolong the action time of the chemotherapeutic agents in the hepatic lesions and thrombus, thereby maximizing the killing of tumor cells [31]. Second, HAIC is well tolerated by patients. Percutaneous HAIC involves the insertion of a catheter into the hepatic artery for long-term continuous infusion of chemotherapeutic drugs, which improves the local drug concentration and the uptake rate of the drug by the tumor, thereby reducing the frequency of serious adverse events. This resulted in the patients in the HAIC group receiving treatment sessions, but not those in the TACE group. Third, after HAIC, chemotherapy drugs will circulate throughout the body, thus playing a certain role in systemic chemotherapy.

The well-received advantage of HAIC is a lower overall incidence of grade 3-4 adverse events compared with TACE. Next, we conducted subgroup analysis. Due to the first-pass effect of the liver, the dose of most chemotherapy drugs distributed to the whole body is small, and the systemic side effects are manageable [32]. The results had no significant difference in grade 3-4 adverse events related to cytotoxic agents between the two groups, including neutropenia, anemia, thrombocytopenia, and vomiting. Furthermore, HAIC does not use any embolic agent, which reduces grade 3-4 adverse events caused by embolization such as elevated ALT and AST levels and hyperbilirubinemia.

Therapy for advanced HCC has entered an era of comprehensive treatment. With the wide application of targeted drugs and the update of chemotherapy drugs, the significance of HAIC and its combination with other therapies in advanced HCC has received increasing attention. In 2019, Shi et al. [33] recruited 247 patients with advanced HCC with portal vein tumor thrombosis that received HAIC combined with sorafenib therapy and sorafenib monotherapy, respectively. The results showed that the combination therapy group exhibited significantly longer OS and PFS than the monotherapy group (13.37 months vs 7.13 months; 8.07 months vs 3.10 months) [33]. Patients in the combination therapy group achieved a higher ORR than those in the monotherapy group (40.80% vs 2.46%). In addition, the number of patients reporting adverse events was significantly lower in the combination therapy group than that in the monotherapy group [33]. In addition to sorafenib, lenvatinib has also been listed as a first-line therapy for advanced HCC. Torimura et al. [34] reported that lenvatinib and trans-arterial therapy (TACE or HAIC) significantly improved the survival rate compared to lenvatinib monotherapy in patients with intermediate-stage HCC. Thus,

HAIC combined with targeted therapy may be a new option for advanced HCC treatment.

This meta-analysis had several limitations. First, although a similar study was recently published [35], the study included the transarterial infusion chemotherapy (TAI) regimen (zinostatin stimalamer), which is quite different from the platinum/5-FU-based HAIC regimen in our study. Moreover, the study was not registered with PROSPERO. Second, most of the included studies were observational, which indicated that recall bias and selection bias were difficult to avoid. Third, the length of follow-up of the included studies was relatively short. Fourth, the HAIC regimens differed slightly between studies. Compared with cisplatin-based regimens, oxaliplatin has a diamino cyclohexane ligand in its chemical structure, which prevents DNA from binding to repair proteins and has a better inhibitory effect on tumors. Oxaliplatin also has the effect of modulating the immune response, which can cause tumor cells to undergo immunogenic cell death [36]. Fifth, the sample size in this meta-analysis needs to be further expanded. There were only 989 patients in the included trials. Sixth, TACE has known variability (lobar vs. segmental or selective/total embolization vs. slowed flow), which may affect its efficacy. Finally, the patients included in this meta-analysis were all from Asia, where hepatitis B virus (HBV) is the main cause of HCC.

## CONCLUSIONS

Hepatic artery infusion chemotherapy is a promising loco-regional therapy for the initial treatment of patients with locally advanced HCC, with favorable local treatment responses, survival benefits, and safety compared with TACE. Future higher quality RCTs are still required to confirm these results.

**Conflicts of interest**: None to declare.

**Author contributions**: Z.H. and Q.X. conceived and designed the study. H.L. and C.S. analyzed and interpreted the data. H.L. and J.H. prepared the original draft. M.W. and Z.X. critically revised the paper. All authors read and approved the final version of the manuscript submitted for publication.

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## REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-249. doi:10.3322/caac.21660
2. Cabibbo G, Enea M, Attanasio M, Bruix J, Craxì A, Cammà C. A meta-analysis of survival rates of untreated patients in randomized clinical trials of hepatocellular carcinoma. Hepatology 2010;51:1274-1283. doi:10.1002/hep.23485
3. Yoon SM, Ryoo BY, Lee SJ, 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;4:661-669. doi:10.1001/jamaoncol.2017.5847
4. Imai N, Katano Y, Kuzuya T, et al. An increase in lesion density can predict lower local recurrence after transarterial chemoembolization in patients with hepatocellular carcinoma. Hepatogastroenterology 2013;60:965-970. doi:10.5754/hge121229
5. Torimura T, Iwamoto H. Optimizing the management of intermediate-stage hepatocellular carcinoma:Current trends and prospects. Clin Mol Hepatol 2021;27:236-245. doi:10.3350/cmh.2020.0204
6. Yamakado K, Miyayama S, Hirota S, et al. Hepatic arterial embolization for unresectable hepatocellular carcinomas:do technical factors affect prognosis? Jpn J Radiol 2012;30:560-566. doi:10.1007/s11604-012-0088-1
7. Lencioni R, de Baere T, Burrel M, et al. Transcatheter treatment of hepatocellular carcinoma with Doxorubicin-loaded DC Bead (DEBDOX): technical recommendations. Cardiovasc Intervent Radiol 2012;35:980-985. doi:10.1007/s00270-011-0287-7
8. Raoul JL, Sangro B, Forner A, et al. Evolving strategies for the management of intermediate-stage hepatocellular carcinoma:available evidence and expert opinion on the use of transarterial chemoembolization. Cancer Treat Rev 2011;37:212-220. doi:10.1016/j.ctrv.2010.07.006
9. Li H, Wu F, Duan M, Zhang G. Drug-eluting bead transarterial chemoembolization (TACE) vs conventional TACE in treating hepatocellular carcinoma patients with multiple conventional TACE treatments history: A comparison of efficacy and safety. Medicine (Baltimore) 2019;98:e15314. doi:10.1097/MD.0000000000015314
10. Bartkowski R, Berger MR, Aguiar J, et al. Experiments on the efficacy and toxicity of locoregional chemotherapy of liver tumors with 5-fluoro-2-deoxyuridine (FUDR) and 5-fluorouracil (5-FU) in an animal model. J Cancer Res Clin Oncol 1986;111:42-46. doi:10.1007/BF00402774
11. Gourd K, Lai C, Reeves C. ESMO Virtual Congress 2020. Lancet Oncol 2020;21:1403-1404. doi:10.1016/S1470-2045(20)30585-4
12. Hu J, Bao Q, Cao G, et al. Hepatic Arterial Infusion Chemotherapy Using Oxaliplatin Plus 5-Fluorouracil Versus Transarterial Chemoembolization/Embolization for the Treatment of Advanced Hepatocellular Carcinoma with Major Portal Vein Tumor Thrombosis. Cardiovasc Intervent Radiol 2020;43:996-1005. doi:10.1007/s00270-019-02406-3
13. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi:10.1136/bmj.n71
14. Duan H, Deng T, Chen Y, et al. Association between vasectomy and risk of testicular cancer: A systematic review and meta-analysis. PLoS One 2018;13:e0194606. doi:10.1371/journal.pone.0194606
15. Park TH, Oh CK, Park YL, et al. Systematic Review of Randomized Controlled Trials on Acupuncture for Shoulder Pain Based on Jadad Scale and Revised STRICTA Recommendations. Korean J Acupunct 2012;5:324-324. doi:10.1016/j.jams.2012.10.004
16. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods 2010;1:97-111. doi:10.1002/jrsm.12
17. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;1088-1101.
18. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-634. doi:10.1136/bmj.315.7109.629
19. Sumie S, Yamashita F, Ando E, et al. Interventional radiology for advanced hepatocellular carcinoma:comparison of hepatic artery infusion chemotherapy and transcatheter arterial lipiodol

chemoembolization. AJR Am J Roentgenol 2003;181:1327-1334. doi:10.2214/ajr.181.5.1811327

20. An C, Zuo M, Li W, Chen Q, Wu P. Infiltrative Hepatocellular Carcinoma:Transcatheter Arterial Chemoembolization Versus Hepatic Arterial Infusion Chemotherapy. Front Oncol 2021;11:747496. doi:10.3389/fonc.2021.747496
21. He MK, Le Y, Li QJ, et al. Hepatic artery infusion chemotherapy using mFOLFOX versus transarterial chemoembolization for massive unresectable hepatocellular carcinoma: a prospective non-randomized study. Chin J Cancer 2017;36:83. doi:10.1186/s40880-017-0251-2
22. Li QJ, He MK, Chen HW, et al. Hepatic arterial infusion of oxaliplatin, fluorouracil, and leucovorin versus transarterial chemoembolization for large hepatocellular carcinoma:a randomized phase III trial. J Clin Oncol 2022;40:150-160. doi:10.1200/JCO.21.00608
23. Li S, Lyu N, Han X, et al. Hepatic Artery Infusion Chemotherapy Using Fluorouracil, Leucovorin, and Oxaliplatin versus Transarterial Chemoembolization as Initial Treatment for Locally Advanced Hepatocellular Carcinoma:A Propensity Score–Matching Analysis. J Vasc Interv Radiol 2021;32:1267-1276.e1. doi:10.1016/j.jvir.2021.06.008
24. Kim HY, Kim JD, Bae SH, et al. A comparative study of high-dose hepatic arterial infusion chemotherapy and transarterial chemoembolization using doxorubicin for intractable, advanced hepatocellular carcinoma. Korean J Hepatol 2010;16:355-361. doi:10.3350/kjhep.2010.16.4.355
25. Kim KH, Kim MS, Chang JS, et al. Therapeutic benefit of radiotherapy in huge (>/=10 cm) unresectable hepatocellular carcinoma. Liver Int 2014;34:784-794. doi:10.1111/liv.12436
26. Kudo M, Matsui O, Izumi N et al. Transarterial Chemoembolization Failure/Refractoriness: JSH-LCSGJ Criteria 2014 Update. Oncology 2014;87 Suppl 1:22-31. doi:10.1159/000368142
27. Shi M, Lu LG, Fang WQ, et al. Roles played by chemolipiodolization and embolization in chemoembolization for hepatocellular carcinoma:single-blind, randomized trial. J Natl Cancer Inst 2013;105:59-68. doi:10.1093/jnci/djs464
28. Kokudo N, Hasegawa K, Akahane M et al. Evidence-based Clinical Practice Guidelines for Hepatocellular Carcinoma:The Japan Society of Hepatology 2013 update (3rd JSH-HCC Guidelines). Hepatol Res 2015;45(2). doi:10.1111/hepr.12464
29. Breedis C, Young G. The blood supply of neoplasms in the liver. Am J Pathol 1954;30:969-977.
30. He MK, Zou RH, Wei W, et al. Comparison of Stable and Unstable Ethiodized Oil Emulsions for Transarterial Chemoembolization of Hepatocellular Carcinoma: Results of a Single-Center Double-Blind Prospective Randomized Controlled Trial. J Vasc Interv Radiol 2018;29:1068-1077.e2. doi:10.1016/j.jvir.2018.03.027
31. Ueda M, Sai K, Sonoda T, Tanaka M, Shibaoka Y. Complications arising from transfemoral, percutaneous implantation of an indwelling port-catheter system for hepatic infusion chemotherapy:Case series of the management and salvage of the system. Int J Surg Case Rep 2019;65:78-82. doi:10.1016/j.ijscr.2019.10.017
32. Obi S, Sato S, Kawai T. Current Status of Hepatic Arterial Infusion Chemotherapy. Liver Cancer 2015;4:188-199. doi:10.1159/000367746
33. He M, Li Q, Zou R, et al. Sorafenib Plus Hepatic Arterial Infusion of Oxaliplatin, Fluorouracil, and Leucovorin vs Sorafenib Alone for Hepatocellular Carcinoma With Portal Vein Invasion:A Randomized Clinical Trial. JAMA Oncol 2019;5:953-960. doi:10.1001/jamaoncol.2019.0250
34. Shimose S, Iwamoto H, Tanaka M, et al. Alternating Lenvatinib and Trans-Arterial Therapy Prolongs Overall Survival in Patients with Inter-Mediate Stage HepatoCellular Carcinoma: A Propensity Score Matching Study. Cancers (Basel) 2021;13:160. doi:10.3390/cancers13010160
35. Kong SY, Song JJ, Jin YQ, Deng MJ, Yan JX. Hepatic arterial infusion chemotherapy versus transarterial chemoembolization for patients with unresectable hepatocellular carcinoma:a systematic review and meta-analysis. Acta Clin Belg 2022;1-9. doi:10.1080/17843286.2022.2076791
36. Pol J, Vacchelli E, Aranda F, et al. Trial Watch: Immunogenic cell death inducers for anticancer chemotherapy. Oncoimmunology 2015;4:e1008866. doi:10.1080/2162402X.2015.1008866