Journal of Interventional Medicine 6 (2023) 59–63

Contents lists available at ScienceDirect

Journal of Interventional Medicine

journal homepage: www.keaipublishing.com/cn/journals/journal-of-interventional-medicine/

Optimal interventional treatment for liver cancer: HAIC, TACE or iTACE?

Naijian Ge [1], Hongbo Wang [1], Chengjian He, Xiangdong Wang, Jian Huang, Yefa Yang [*]

Mini-Invasive Intervention Center, Third Affiliated Hospital of Naval Medical University/Shanghai Eastern Hepatobiliary Surgery Hospital, Shanghai, 200438, China

ARTICLE INFO

Keywords:
Hepatocellular carcinoma
Hepatic artery infusion chemotherapy
Transcatheter arterial chemoembolization

ABSTRACT

Primary liver cancer is a common and lethal malignancy in China. Transcatheter arterial chemoembolization (TACE) is globally recognized as the preferred treatment modality for the non-surgical resection of hepatocellular carcinoma (HCC), while transcatheter arterial infusion (TAI) is another effective interventional treatment for HCC. In recent years, hepatic arterial infusion chemotherapy (HAIC) has gained increasing attention as an application-regulated modality for TAI. Owing to the current debate in the medical community regarding the use of HAIC and TACE for the treatment of HCC, the application of both approaches should be considered at a higher level, with a broader perspective and a more normative aspect. Accordingly, we aimed to define the rational combination of liver cancer TAI/HAIC with TACE as infusion transcatheter chemoembolization (iTACE), which suggests that the two interventions are not superior but lead to a mutually beneficial situation. In this review, we sought to discuss the development, specification, application, challenge and innovation, debate, and union of TAI/HAIC and TACE, and the clinical application and latest research on iTACE. We aimed to introduce new concepts of iTACE and expect new breakthroughs in the treatment of liver cancer owing to the combined use of the two major interventional tools.

The number of new cases of primary liver cancer in China accounts for approximately half of the world's total new cases every year. Primary liver cancer is the fourth most common malignant tumor and the second leading cause of tumor-related death. According to the "Guidelines for the diagnosis and treatment of primary hepatocellular carcinoma (HCC) (2019 edition),"[1] several treatment methods can be adopted for unresectable liver cancer in the middle or advanced stages, including interventional therapy, ablation therapy, radiation therapy, and systemic therapy. Transcatheter arterial chemoembolization (TACE) is globally recognized as the preferred treatment for nonsurgical resection of HCC. In fact, comprehensive treatment based on TACE has gradually become a first-line therapy for advanced liver cancer. However, owing to the high heterogeneity of liver tumors, it is difficult to effectively guarantee the efficacy of TACE in the treatment process. Chinese scholars have standardized the application of the FOLFOX (oxaliplatin-based) regimen to hepatic arterial infusion chemotherapy (HAIC), which has significantly improved the response rate and patient survival rate of liver cancer, and formulated "Chinese Expert Consensus on Hepatic Arterial Infusion Chemotherapy for Hepatocellular Carcinoma (2021 Edition)."[2] Treatment with TACE and HAIC has led to extensive debate in the medical community. However, as these therapies are two effective interventional treatments for liver cancer, their application should be considered from a higher level and wider perspective. Accordingly, we defined the rational combination of HAIC and TACE for liver cancer as infusion Transcatheter Chemoembolization (iTACE) and carried out a review of the literature on the development and application, including current research on HAIC, TACE, and iTACE.

1. Origin and standardized application of HAIC

1.1. Development of TAI

Transcatheter arterial infusion (TAI) is an important means of tumor interventional therapy. The maximum anti-cancer efficacy of chemotherapy in addition to debates regarding its efficacy compared to that of hepatic artery embolization (HAE). In 1983, Charnsangavej et al.[3] compared the curative effects of TAI and HAE. In their study, one of the 24 patients with liver cancer received both treatments at the same time; 10 of the 14 patients who received TAI achieved (71.4%) partial response (PR) with a median survival time of 12.3 months; and 6 of the 9 patients (66.7%) who received HAE achieved PR with a median survival time of 17.4 months. Since then, TAI has attracted the attention of the medical

* Corresponding author.
E-mail address: yangyefa66@163.com (Y. Yang).
[1] Naijian Ge and Hongbo Wang contributed equally to this work and are the co-first authors.

https://doi.org/10.1016/j.jimed.2023.03.001
Received 29 June 2022; Received in revised form 18 February 2023; Accepted 1 March 2023
Available online 2 May 2023

community. Further, many variants and different drug regimens have been developed that have had a profound impact on interventional therapy for liver cancer and other diseases.

1.2. Origin of HAIC

HAIC evolves from TAI, which prolongs and sustains the perfusion of chemotherapy drugs via percutaneous catheterization of the target hepatic artery, thereby improving the local drug concentration and tumor uptake rate of the drugs and minimizing systemic toxicity. As early as 1961, the use of HAIC was proposed by Japanese professors of surgery who used femoral artery puncture and catheterization or the gastroepiploic right artery during laparotomy and catheterization to administer chemotherapy drugs for primary liver cancer treatment.[4]

HAIC has attracted the attention of experts worldwide in recent years. Medical experts have made various attempts to improve HAIC. In 1985, Hochster et al.[5] compared the response rates of epirubicin and doxorubicin for HCC for the first time. Based on their results, epirubicin could be applied in the clinic as a relatively less toxic chemotherapeutic agent for HCC under the premise of similar response rates. Since then, more HAIC studies have been performed on this basis; however, most of these studies have revealed less than optimal clinical effects. In the 1990s, cisplatin-based chemotherapy regimens were replaced by traditional regimens. Cisplatin combined with 5-fluorouracil (PF regimen) is the most commonly used HAIC regimen in Japan.[6,7] Thus, the combined regimen gradually becomes the main approach involving HAIC.

At present, most regimens prescribed for HAIC in China employ the FOLFOX regimen containing oxaliplatin, leucovorin, and 5-fluorouracil, and are mainly used to treat advanced HCC. In 2018, Zhao Ming from Sun Yat-sen University Cancer Center reported that the FOLFOX regimen was used as HAIC treatment, with an overall response rate of 79.6%, which was significantly better than that of sorafenib.[8]

1.3. Clinical application of HAIC

In recent years, clinical research and the application of HAIC have been extensively conducted for advanced liver cancer. The standard treatment for patients with Barcelona Clinic Liver Cancer (BCLC) stage C liver cancer is sorafenib.[9] Some scholars have conducted comparative studies using HAIC and sorafenib for the treatment of patients with stage C liver cancer. A meta-analysis by Shi[10] revealed that HAIC is superior to sorafenib at improving overall survival (OS), progression-free survival (PFS), and disease control rate (DCR) in patients with HCC and portal vein tumor thrombus (PVTT). Zaizen et al.[11] compared HAIC and sorafenib and assessed the OS of patients with advanced HCC. Based on their results, HAIC was identified to be more effective than sorafenib. In a retrospective study, Lyu et al.[12] compared the efficacy of FOLFOX-HAIC and sorafenib in patients with advanced HCC. FOLFOX-HAIC was found to be more beneficial in improving PFS and OS.

Many scholars conducted research on the effects of HAIC combined with sorafenib for advanced liver cancer. By using HAIC combined with sorafenib for the treatment of advanced HCC, Liu[13] found that the total clinical effective rate of the study group after treatment was higher than that of the control group (69.84% vs. 50.79%, $P < 0.05$). After treatment, the levels of alanine aminotransferase (ALT), total bilirubin (TBIL), and total bilirubin (AST) in the two groups were lower than those recorded before treatment. Further, the levels in the study group were lower than that of the control group. The combination was identified to be more effective at reducing the levels of apoptotic factors in HCC tissues, improving the quality of life, exhibiting mild adverse effects, and having a high clinical value. Zheng et al.[14] divided 64 patients with HCC and PVTT equally to receive sorafenib plus HAIC or sorafenib alone. The combination group was found to have a median OS of 16.3 months, while the single-agent group had a median OS of 6.5 months. The combination group also had a longer median PFS than the single-agent group (9.0 months vs 2.5 months; $P < 0.001$). Shi[15] conducted a clinical trial on HCC with PVTT and compared the clinical effects of sorafenib alone and sorafenib with FOLFOX-HAIC. The median OS was 13.37 months (95% CI, 10.27–16.46) in the Sora-HAIC group and 7.13 months (95% CI, 6.28–7.98) in the sorafenib group (hazard ratio [HR], 0.35; 95% CI, 0.26–0.48; $P < 0.001$). The Sora-HAIC group had a higher response rate than the sorafenib group (51 [40.8%] vs. 3 [2.46%]; $P < 0.001$) and a longer median progression-free survival (7.03 [95% CI, 6.05–8.02] vs. 2.6 [95% CI, 2.15–3.05] months; $P < 0.001$). Overall, sorafenib combined with HAIC improved OS relative to sorafenib alone and was tolerable in patients with toxic effects. HAIC was associated with a greater probability of myelosuppression, whereas sorafenib was associated with more diarrhea and hand-foot syndrome.

Many relevant studies have been conducted on HAIC combined with other modalities for the treatment of advanced liver cancer. Kosaka[16] revealed that HAIC combined with radiotherapy (RT) led to good results in patients with VP4 type (main portal vein or bilobar tumor thrombus formation) HCC. Further, none of the patients developed liver failure. As a result, this researcher suggested that HAIC combined with RT might be a good therapy for VP4 advanced HCC. In a study on HCC with vascular invasion (MVI) (MVI-HCC), Niizeki et al.[17] compared the efficacy of New FP (a fine powder of cisplatin suspended with lipiodol plus 5-fluorouracil) and low-dose FP (LFP/cisplatin plus 5-fluorouracil) for the treatment of patients with Child-Pugh A grade MVI-HCC. New FP led to a significantly higher complete response rate (CR = 29%) and objective response rate (ORR = 76%) than LFP ($P < 0.001$). Further, New FP had better efficacy than LFP-HAIC. Currently, interventional therapy combined with targeted immunotherapy for HCC is still in its infancy. Clinical studies on HAIC in combination with targeted immunization are underway, and the results are expected to be published soon.

2. Development and challenge innovation of TACE

2.1. Development of TACE

TACE was originally developed for HAE. Conventional TACE (cTACE) is defined as a treatment plan based on lipiodol emulsion with chemotherapeutic drugs supplemented with granular embolic agents. Granular embolic agents include gelatin sponge particles, blank microspheres, and polyvinyl alcohol (PVA) particles. With the development of material technology, drug-eluting microspheres, which can be preloaded with chemotherapeutic drugs to slowly and continuously release the drug, have been developed. In drug-eluting bead TACE (DEB-TACE) therapy, drug-eluting beads can embolize tumor-feeding arteries and enable the slow and continuous release of the loaded chemotherapeutic drugs in local tumors, maintaining a relatively high blood drug concentration in the local tumor and exerting a better anti-cancer effect. A randomized trial compared the outcome of embolization using microspheres alone with chemoembolization using doxorubicin-eluting microspheres. The median PFS was 6.2 versus 2.8 months (hazard ratio, 1.36; 95% CI, 0.91 to 2.05; $P = 0.11$), while OS was 19.6 versus 20.8 months (hazard ratio, 1.11; 95% CI, 0.71 to 1.76; $P = 0.64$) for bead block and LC beads, respectively.[18] This trial questioned the usefulness of drug-eluting microspheres in clinical treatment. However, their application in actual treatment needs further exploration. In addition, based on the TACE technology, new technologies, such as balloon-occluded transarterial chemoembolization (B-TACE) and transarterial radioembolization (TARE), have been developed.

2.2. Challenge and innovation research of TACE

As the first-line treatment for middle and advanced unresectable HCC, TACE has always been the first choice of many experts in the intervention, oncology, hepatobiliary, and other relevant fields. TACE is constantly challenged by various treatment options and has been continuously improved and innovated through a series of clinical exploratory studies.

Exploratory studies on the technical operation aspects of TACE. The concept of refined TACE was proposed by Prof. Z. Yan's team at the Shanghai Zhongshan Hospital. A proper amount of lipiodol emulsion was administered for supraterminal embolization of liver cancer. Thereafter, small-sized microspheres were used as the main embolization material to perform the distal terminal arterial embolization. Finally, larger-sized particles were supplemented to embolize the proximal tumor feeding artery for the different grades (tumor tissue, portal vein branches, arteriolar collaterals, and tumor feeding arteries) and multilevel full-scale embolization of the tumor feeding arteries was performed with different calibers.[19]

Exploratory studies to mitigate the adverse effects of TACE. Wang et al.[20] conducted a prospective randomized controlled clinical trial in which 70 consecutive patients who underwent TACE were recruited and randomly divided into two groups: group A received intra-arterial lidocaine injection immediately before TACE, and group B received lidocaine-epirubicin-iodized oil emulsion during TACE. Analgesia in group B was better than that in group A. The efficacy and safety of intra-arterial injection of lidocaine using the emulsification technique (W/O emulsion) have been demonstrated for the relief of intraoperative and postoperative pain caused by TACE. Ogasawara et al.[21] revealed that a regimen of dexamethasone administered intraoperatively could effectively prevent most adverse effects caused by TACE in patients with HCC, such as fever, anorexia, and nausea/vomiting.

Exploratory studies on the TACE chemotherapy drug regimen. Aramaki et al.[22] conducted a multicenter, randomized, phase II-III trial in 21 hospitals in Japan to compare the curative effect of cisplatin with epirubicin in TACE for unresectable HCC. Cisplatin and epirubicin were found to have similar effects in the TACE treatment regimens. Naganuma et al.[23] compared the superiority of miriplatin TACE to epirubicin TACE regimen in terms of OS for HCC patients. Their findings revealed that the postoperative OS of miriplatin TACE was similar to that of epirubicin TACE. Moreover, the incidence of hepatic adverse effects was lower with miriplatin TACE. Overall, these studies demonstrated that platinum-based TACE regimens are safe and feasible. In a randomized, multicenter, open-label study in Asian patients with advanced HCC, Qin et al.[24] found that FOLFOX4 provided a better survival benefit as a palliative chemotherapy regimen in patients with advanced HCC than doxorubicin. Although the study did not meet its primary endpoint, the OS, PFS, and RR showed that FOLFOX4 may offer some benefits in Asian patients.

Exploratory studies on different types of TACE. A multicenter propensity score-matched analysis of DEB-TACE and cTACE revealed that both DEB-TACE and cTACE were safe and feasible for the treatment of unresectable HCC and DEB-TACE was more effective than cTACE at improving progression-free survival; however, the results were similar in terms of short-term efficacy.[25] Experts have pointed out that the future direction of drug-eluting bead embolization technology is to improve the OS of HCC patients via imaging capability and DEB size for tumor anatomy and drug combinations.[26]

Exploratory study of TACE combined with other treatment modalities. Yoon et al.[27] confirmed TACE plus radiation therapy as a first-line regimen for patients with advanced HCC with vascular invasion. This regimen was well tolerated and led to a significant improvement in PFS. At present, numerous clinical studies, such as studies with TACE combined with molecular targeted agents or immunotherapy for HCC, are being conducted, especially the series of CHANCE001-005 national multicenter controlled studies led by G. Teng academicians. The findings of such studies have been presented in a preliminary summary.

3. Birth of iTACE

3.1. HAIC vs TACE debate

The choice between HAIC and TACE has been a focus of debate in the field of liver cancer treatment. TACE, as a classic interventional therapy, induces an obvious response in patients with HCC and has been accepted by many guidelines as a standard treatment for mid-stage HCC. China liver cancer staging (CNLC) has adopted TACE as the main treatment for stage I, b, and III liver cancer patients. Some studies have revealed the high efficacy of HAIC, which challenged the status of classic TACE. In a study comparing the efficacy and safety of HAIC versus TACE for the treatment of advanced HCC with PVTT, Hu et al.[28] found that the HAIC group had a higher ORR than the TACE group (59.1% vs 22.7%; $P = 0.014$) and longer median PFS (9.6 vs 1.5 months; $P < 0.001$). Cai[29] also revealed that HAIC was superior to TACE for the treatment of unresectable ICC. Although HAIC is proven to be effective, some scholars believe that it can only be used in a limited population; thus, HAIC cannot be compared with TACE.[30] Kudo[31] found that HAIC did not improve the OS of patients with advanced unresectable HCC. According to the European Association for the Study of the Liver (EASL), the FOLFOX-HAIC regimen does not demonstrate an advantage in survival improvement. The better results obtained with HAIC should be adapted to a special population.

A randomized, multicenter, open-label phase III trial by Shi Ming at Sun Yat Sen University[32] was conducted to compare the curative effects of FOLFOX-HAIC with TACE as a first-line regimen for patients with HCC ≥7 cm without macrovascular invasion or extrahepatic spread. A total of 315 patients were randomly assigned to the FOLFOX-HAIC group (n = 159, treatment cycle of 3 weeks) or TACE group (epirubicin and lobaplatin with lipiodol for chemoembolization; n = 156, treatment cycle of 6 weeks). The median OS, PFS, and ORR of patients in the FOLFOX-HAIC group were significantly higher than those in the TACE group (23.1 vs 16.1 months, 9.6 vs 5.4 months, and 48.4% vs. 32.7%, respectively; all $P < 0.05$). Further, serious adverse events were more frequent in the TACE group than the FOLFOX-HAIC group (30% vs. 19%, respectively; $P = 0.03$). Conclusions: FOLFOX-HAIC significantly improved the OS of patients with unresectable large liver cancer compared to TACE. This study led to more debates in the interventional community following its publication owing to (1) the inclusion of only four centers in this phase III clinical trial, and the difficulty of avoiding selection bias based on patient enrollment and subsequent treatment; (2) significantly more treatments in the HAIC group than the TACE group, and a lack of uniform usage of the evaluation criteria of mRECIST in the two groups to judge the efficacy; (3) the evidently lower ORR (32.7%) and OS (16.1 months) for patients in the TACE group relative to the average ORR (52.5%) and OS (19.4 months) for patients receiving TACE treatment for advanced liver cancer in the past 30 years; and (4) a lack of interventional physicians with comprehensive interventional qualifications and experience in TACE treatment.

Undeniably, the results of multiple studies and clinical practice highlight the therapeutic value of HAIC. HAIC and TACE should be considered objectively: (1) various guidelines have not recommended HAIC as a standard treatment for HCC, including the BCLC staging, American Association for the Study of Liver Disease (AASLD), EASL, European Society for Medical Oncology (ESMO), and Asia Pacific Association for the Study of the Liver (APASL). TACE is the most widely used therapy for middle- and advanced-stage liver cancer. HCC interventionalists should recommend that TACE operations be standardized as much as possible to minimize the differences in the efficacy of TACE. HAIC is effective in limited populations,[17,29,33,34] such as downstaging during perioperative management of HCC, postoperative adjuvant therapy, and palliative treatment for patients with advanced HCC. According to the "Guidelines for the diagnosis and treatment of primary HCC (2019 edition)" issued in China, the FOLFOX4 regimen is suitable for advanced or metastatic liver cancer that cannot be surgically or locally treated, or disease with poor outcomes after multiple sessions of TACE, or HCC accompanied by portal invasion.

3.2. iTACE: the union of HAIC and TACE

Based on the above academic debate, we believe two technical approaches are effective for liver cancer intervention therapy: TACE, which locally and directly embolizes the blood supply-rich tumor with

obvious advantages; and HAIC, which can act sustainably on scattered lesions, metastatic tumors, or tumor thrombus. To increase the applicability of interventional techniques to treat HCC and lead to more benefits in patients, and effectively combine the two therapies to obtain a long and short supply, and attain a win-win outcome, we defined the rational combination of TAI/HAIC with TACE as iTACE (infusion TACE). Before the concept of iTACE was proposed, numerous scholars performed exploratory studies on the combination of the two interventional techniques. In 2012, Prof. Renjie Yang's team at Peking University Cancer Hospital launched a phase II single-arm, open-label clinical study and reported on TACE combined with HAIC for the treatment of HCC. Based on their results, 50 patients with intermediate and advanced HCC had an ORR of 62%, DCR of 74%, median PFS of 9.3 months, median OS of 21.4 months, and 1-year and 2-year survival rates of 76% and 44%, respectively.[35] Shao Song et al. assessed the value of HAIC combined with TACE in the treatment of primary liver cancer. The ORR of the combined therapy group was 93.3% higher than that of the TACE group alone, indicating that the combined therapy has a high application value.[36] S. Chen et al.[37] compared the effects of TAE combined with FOLFOX-HAIC and TACE alone in HCC patients with PVTT. The survival rate of the study group was found to be higher than that of the control group within 12 months ($P < 0.05$, log-rank test). At 3, 6, and 12 months, the survival rate of patients in the study group was higher than that of patients in the control group (100%, 73.3%, and 46.7% vs. 73.3%, 33.3%, and 13.3%; $P < 0.05$). Further, the ORR and DCR of PVTT in the study group were significantly higher than those in the control group (46.7% and 80.0% vs. 13.3% and 40%, respectively; $P < 0.05$). The ORR and DCR in the study group were slightly higher than those in the control group (26.7% and 60.0% vs. 13.3% and 40%, respectively; $P > 0.05$). These findings indicate that FOLFOX4-TAE is safe and feasible for the treatment of HCC complicated by PVTT, and its short-term clinical efficacy is better than that of TACE, which provides a new safe and effective treatment approach for HCC complicated by PVTT. Du[38] performed cisplatin thermos chemoperfusion combined with TACE in patients with HCC with an exact curative effect. The tumor recurrence rate in the observation group was found to be lower than that in the control group (15.00% vs. 45.00%, $\chi2 = 12.375$, $P < 0.05$). Further, a higher survival rate was found in the observation group than in the control group (82.50% vs.65.00%, $\chi2 = 5.952$, $P < 0.05$). There was no significant difference in the survival rate between the two groups (70.00% vs. 65.00%, $\chi2 = 0.228$, $P > 0.05$). The findings prove that cisplatin-HAIC combined with TACE could significantly improve cytokine levels, reduce the tumor recurrence rate, and improve survival rate in patients with HCC. Some scholars have attempted to combine D-TACE and FOLFOX regimen-based hepatic arterial perfusion chemotherapy (D-TACE-HAIC) to treat unresectable giant HCC. Relative to patients who received D-TACE, patients who received D-TACE-HAIC had a higher ORR (71.0% vs 53.1%; $P = 0.033$), longer median PFS (9.3 months vs 6.3 months; $P = 0.005$), and better median OS (19.0 months vs 14.0 months; $P = 0.008$). Therefore, D-TACE combined with HAIC was confirmed to be superior to D-TACE alone for the treatment of unresectable large liver cancer.[39]

Our team established a set of criteria for iTACE therapy based on the results of previous studies: (1) several tumors located in different lobes of the liver or distant metastasis; (2) tumor blood supply that is complex in origin and difficult to completely super-select and thorough embolization; (3) most of the tumor is necrotic after several HAICs, with residual portions of active tumor; and (4) tumor blood supply that is rich, and can be partially embolized (incomplete devascularization) and then combined with HAIC. In the initial observation of iTACE treatment in 55 patients with intermediate or advanced HCC, AFP reduction reached 54.5% and was stable in 25.5%. Protein II induced by vitamin K absence (PIVKA-II) reduction was achieved in 54.5% and stable in 20%. Further, the short-term safety profile was excellent: 11 for CR, 22 for PR, 8 for SD, and 14 for PD. The long-term efficacy remains under investigation.

4. Summary and outlook

Liver resection has long been considered the standard radical treatment for resectable HCC, with a 5-year survival rate between 50 and 70%. Less than 40% of HCC patients meet the criteria for radical resection. Interventional therapy remains the most widely used therapy for liver cancer. Canonical HAIC and classic TACE serve as two niches for liver cancer intervention, each with an applicable dominant population. Based on the current academic debate to determine which therapy is better or worse, we explored the rational combination of the two to observe the exact clinical efficacy. Nonetheless, we must consider: (1) the sensitivity, toxicity, and drug resistance of HAIC treatment; (2) iTACE as a reasonable combination of TAI/HAIC and TACE that should be improved, and the potential optimization of TACE; (3) although the efficiency of iTACE is proven to be higher than that of HAIC/TACE, whether the survival period is prolonged must be further examined. TACE or HAIC combined with targeted immunotherapy may be a new strategy to improve the interventional efficacy of liver cancer. At present, iTACE has been explored and clinically used in various large hospitals throughout the country and is expected to lead to new approaches for the treatment of liver cancer, ultimately enabling greater therapeutic gains for patients.

Declaration of competing interest

Yefa Yang is an editorial board member for Journal of Interventional Medicine and was not involved in the editorial review or the decision to publish this article. All authors declare that there are no competing interests.

References

1. Guidelines for the diagnosis and treatment of primary liver cancer (2019 edition). *Infectious Disease Information*. 2020;33:481–500.
2. Association Lcpcoca-C. Chinese expert Consensus on hepatic arterial infusion chemotherapy for hepatocellular carcinoma (2021 edition). *Chinese Journal of Digestive Surgery*. 2021;20:754–759.
3. Charnsangavej C, Chuang VP, Wallace S, et al. Work in progress: transcatheter management of primary carcinoma of the liver. *Radiology*. 1983;147:51–55.
4. Ito I, Hattori T, Koyama Y, et al. [Chemotherapy of primary and metastatic hepatic cancer by hepatic artery infusion]. *Gan No Rinsho*. 1964;10:423–424. Japanese.
5. Hochster HS, Green MD, Speyer J, et al. 4'Epidoxorubicin (epirubicin): activity in hepatocellular carcinoma. *J Clin Oncol*. 1985;3:1535–1540.
6. Takao T, Nisida M, Maeda Y, et al. [Significance of reduction surgery for giant hepatocellular carcinoma with diffuse lung metastases and multiple intrahepatic metastases]. *Gan To Kagaku Ryoho*. 2000;27:1947–1950. Japanese.
7. Itamoto T, Nakahara H, Tashiro H, et al. Hepatic arterial infusion of 5-fluorouracil and cisplatin for unresectable or recurrent hepatocellular carcinoma with tumor thrombus of the portal vein. *J Surg Oncol*. 2002;80:143–148.
8. Lyu N, Lin Y, Kong Y, et al. FOXAI: a phase II trial evaluating the efficacy and safety of hepatic arterial infusion of oxaliplatin plus fluorouracil/leucovorin for advanced hepatocellular carcinoma. *Gut*. 2018;67:395–396.
9. Bruix J, Gores GJ, Mazzaferro V. Hepatocellular carcinoma: clinical frontiers and perspectives. *Gut*. 2014;63:844–855.
10. Yi SJ. *A Systematic Review of Hepatic Arterial Infusion Chemotherapy versus Sorafenib in the Treatment of Hepatocellular Carcinoma with Portal Vein Tumor Thrombus [D]*. Chongqing Medical University; 2020.
11. Zaizen Y, Nakano M, Fukumori K, et al. Hepatic arterial infusion chemotherapy with cisplatin versus sorafenib for intrahepatic advanced hepatocellular carcinoma: a propensity score-matched analysis. *Cancers (Basel)*. 2021;13:5282.
12. Lyu N, Kong Y, Mu L, et al. Hepatic arterial infusion of oxaliplatin plus fluorouracil/leucovorin vs. sorafenib for advanced hepatocellular carcinoma. *J Hepatol*. 2018;69:60–69.
13. Fei LJ, Feng L, Fang WN, et al. Effects of hepatic arterial infusion chemoembolization combined with radiofrequency ablation on survival rate, liver function and T lymphocyte subsets in patients with advanced hepatocellular carcinoma. *Progress in Modern Biomedicine*. 2021;21:1669–1672, 1701.
14. Zheng K, Zhu X, Fu S, et al. Sorafenib plus hepatic arterial infusion chemotherapy versus sorafenib for hepatocellular carcinoma with major portal vein tumor thrombosis: a randomized trial. *Radiology*. 2022;303:455–464.
15. 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.
16. Kosaka Y, Kimura T, Kawaoka T, et al. Hepatic arterial infusion chemotherapy combined with radiation therapy for advanced hepatocellular carcinoma with tumor

thrombosis of the main trunk or bilobar of the portal vein. *Liver Cancer*. 2021;10:151–160.
17. Niizeki T, Iwamoto H, Shirono T, et al. Clinical importance of regimens in hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with macrovascular invasion. *Cancers (Basel)*. 2021;13:4450.
18. Brown KT, Do RK, Gonen M, et al. Randomized trial of hepatic artery embolization for hepatocellular carcinoma using doxorubicin-eluting microspheres compared with embolization with microspheres alone. *J Clin Oncol*. 2016;34:2046–2053.
19. Wen Z, Jie ZY, Ping YZ. Further discussion on the precision TACE therapy. *J Interv Radiol*. 2021;30:971–975.
20. Wang LZ, Hu XX, Shen XC, et al. Intraarterial lidocaine administration for pain control by water-in-oil technique in transarterial chemoembolization: in vivo and randomized clinical trial. *J Hepatocell Carcinoma*. 2021;8:1221–1232.
21. Ogasawara S, Chiba T, Ooka Y, et al. A randomized placebo-controlled trial of prophylactic dexamethasone for transcatheter arterial chemoembolization. *Hepatology*. 2018;67:575–585.
22. Aramaki O, Takayama T, Moriguchi M, et al. Arterial chemoembolisation with cisplatin versus epirubicin for hepatocellular carcinoma (ACE 500 study): a multicentre, randomised controlled phase 2/3 trial. *Eur J Cancer*. 2021;157:373–382.
23. Naganuma A, Hoshino T, Takagi H, et al. Randomized controlled trial of epirubicin and miriplatin using together with TACE for hepatocellular carcinoma. *Ann Oncol*. 2015;26:vii94.
24. Qin S, Bai Y, Lim HY, et al. Randomized, multicenter, open-label study of oxaliplatin plus fluorouracil/leucovorin versus doxorubicin as palliative chemotherapy in patients with advanced hepatocellular carcinoma from Asia. *J Clin Oncol*. 2013;31:3501–3508.
25. Fei KX. *Efficacy Analysis of DEB-TACE and cTACE in the Treatment of Unresectable Liver Cancer [D]*. Nanchang University; 2018.
26. Lewis AL, Dreher MR. Locoregional drug delivery using image-guided intra-arterial drug eluting bead therapy. *J Control Release*. 2012;161:338–350.
27. 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.
28. 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. *CVIR (Cardiovasc Interventional Radiol)*. 2020;43:996–1005.
29. Cai Z, He C, Zhao C, et al. Survival comparisons of hepatic arterial infusion chemotherapy with mFOLFOX and transarterial chemoembolization in patients with unresectable intrahepatic cholangiocarcinoma. *Front Oncol*. 2021;11:611118.
30. Xu ZD, Lei Z, Qing JX, et al. Is HAIC an obsolete technology or a novel therapeutic method? HAIC should be treated rationally. *J Interv Radiol*. 2022;31:2–8.
31. Kudo M, Ueshima K, Yokosuka O, et al. Sorafenib plus low-dose cisplatin and fluorouracil hepatic arterial infusion chemotherapy versus sorafenib alone in patients with advanced hepatocellular carcinoma (SILIUS): a randomised, open label, phase 3 trial. *Lancet Gastroenterol Hepatol*. 2018;3:424–432.
32. 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.
33. Li S, Xu J, Zhang H, et al. The role of hepatic arterial infusion chemotherapy in the treatment of hepatocellular carcinoma: a systematic review and meta-analysis. *Chemotherapy*. 2021;66:124–133.
34. Hendi M, Mou Y, Lv J, et al. Hepatic arterial infusion chemotherapy is a feasible treatment option for hepatocellular carcinoma: a new update. *Gastrointest Tumors*. 2021;8:145–152.
35. Song G, Xu Z, Jie YR, et al. TACE combined with oxaliplatin, fluorouracil, and calcium folinate hepatic arterial chemotherapy in the treatment of advanced primary liver cancer. *J Interv Radiol*. 2012;21:377–383.
36. Song S. The value of hepatic arterial infusion chemotherapy combined with interventional embolization in the treatment of primary liver cancer. *China Practical Medicine*. 2021;16:149–151.
37. Song C, Qiang WZ, Quan ZW, et al. Short-term clinical efficacy evaluation of transhepatic arterial embolization combined with FOLFOX4 regimen continuous arterial infusion chemotherapy in the treatment of 15 patients with hepatocellular carcinoma complicated with portal vein tumor thrombus. *J Interv Radiol*. 2019;28:328–333.
38. Feng D, Wei YW, Yao L. Effect of cisplatin thermochemotherapy infusion combined with TACE on curative effect and tumor cytokine levels in patients with liver cancer. *Guizhou Medical Journal*. 2021;45:27–28.
39. Huang J, Huang W, Zhan M, et al. Drug-eluting bead transarterial chemoembolization combined with FOLFOX-based hepatic arterial infusion chemotherapy for large or huge hepatocellular carcinoma. *J Hepatocell Carcinoma*. 2021;8:1445–1458.