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***Retrospective* *Study***

**Efficacy and safety of targeted therapy plus immunotherapy combined with hepatic artery infusion chemotherapy (FOLFOX) for unresectable hepatocarcinoma**

Lin ZP *et* *al*. Hepatocellular carcinoma

Zhi-Peng Lin, Xiao-Long Hu, Du Chen, Da-Bei Huang, Xu-Gong Zou, Hai Zhong, Sheng-Xiang Xu, Yuan Chen, Xiao-Qun Li, Jian Zhang

**Zhi-Peng Lin, Xiao-Long Hu, Du Chen, Da-Bei Huang, Xu-Gong Zou, Hai Zhong, Sheng-Xiang Xu, Yuan Chen, Xiao-Qun Li, Jian Zhang,** Department of Interventional Medicine, Zhongshan People’s Hospital, Zhongshan 528400, Guangdong Province, China

**Author contributions:** Lin ZP and Zhang J conceived and designed the study; Lin ZP, Hu XL, Chen D, Huang DB, Zou XG, Zhong H, Xu SX, and Chen Y contributed to data collection and analysis; Lin ZP drafted the manuscript; Lin ZP, Li XQ, and Zhang J supervised data analysis and interpretation, revised the manuscript, and gave final approval for the version to be published; and all authors read and approved the final manuscript.

**Corresponding author: Jian Zhang, Doctor, Associate Chief Physician,** Department of Interventional Medicine, Zhongshan People’s Hospital, No. 2 Sun Wen East Road, Zhongshan 528400, Guangdong Province, China. wy18988583838@163.com

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**Abstract**

BACKGROUND

The advent of cutting-edge systemic therapies has driven advances in the treatment of hepatocellular carcinoma (HCC), and therapeutic strategies with multiple modes of delivery have been shown to be more efficacious than monotherapy. However, the mechanisms underlying this innovative treatment modality have not been elucidated.

AIM

To evaluate the clinical efficacy of targeted therapy plus immunotherapy combined with hepatic arterial infusion chemotherapy (HAIC) of FOLFOX in patients with unresectable HCC.

METHODS

We enrolled 53 patients with unresectable HCC who received a combination of targeted therapy, immunotherapy, and HAIC of FOLFOX between December 2020 and June 2021 and assessed the efficacy and safety of the treatment regimen.

RESULTS

The objective response rate was 60.4% (32/53), complete response was 24.5% (13/53), partial response was 35.9% (19/53), and stable disease was 39.6% (21/53). The median duration of response and median progression-free survival were 9.1 and 13.9 months, respectively. The surgical conversion rate was 34.0% (18/53), and 1-year overall survival was 83.0% without critical complicating diseases or adverse events (AEs).

CONCLUSION

The regimen of HAIC of FOLFOX, targeted therapy, and immunotherapy was curative for patients with unresectable HCC, with no serious AEs and a high rate of surgical conversion.

**Key Words:** Hepatocellular carcinoma; Hepatic arterial infusion chemotherapy; Targeted therapy; Immunotherapy; Adverse events

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**Core Tip:** The therapeutic strategy of combining multiple modes of drug delivery for the treatment of hepatocellular carcinoma (HCC) has been shown to be more efficacious than single treatment modality, but the underlying mechanism of action has not been clarified. In this study, we observed the clinical efficacy of targeted therapy plus immunotherapy combined with FOLFOX hepatic artery infusion chemotherapy in the treatment of unresectable HCC, which provides a clinical basis for the clinical application of the combination of therapy in HCC.

**INTRODUCTION**

Globally, the third most prevalent cause of cancer-related mortality and the sixth most frequently occurring cancer type is primary hepatocellular carcinoma (HCC)[1]. The first-line treatment options for early-stage HCC are surgical resection and liver transplantation[2,3]. Most patients with early-stage HCC do not have obvious symptoms, and many of them have already developed middle- or late-stage disease at the time of diagnosis. Additionally, since malignant vascular invasion is considered a contraindication to surgical treatment, only 5%-10% of patients with HCC are suitable candidates[4]. There are a variety of treatment methods for unresectable HCC, including interventional therapy, ablation therapy, antitumor targeted therapy, antitumor immunotherapy, radiation therapy, and radioactive seed implantation therapy. The efficacy of hepatic arterial infusion chemotherapy (HAIC) for advanced HCC with vascular invasion or multiple intrahepatic lesions is highly regarded in clinical practice. The Japan Society of Hepatology recommends HAIC as the first-line option for HCC with portal vein tumor thrombus (PVTT)[5]. HCC tumors receive a dual blood supply from the portal vein and hepatic artery (primarily from the hepatic artery). HAIC involves injecting chemotherapeutic drugs directly into the HCC tumor through the hepatic artery. Although HAIC increases the concentration of anticancer drugs in tumor cells, the incidence of side effects is reduced due to the localized distribution. Therefore, HAIC may have a stronger antitumor effect and a lower incidence of adverse events (AEs) compared with other chemotherapeutic methods. Although sorafenib plus HAIC of FOLFOX was reported to improve the objective response rate (ORR) in patients with HCC rather than sorafenib alone, the survival duration remained inadequate[6].

The advent of cutting-edge systemic therapy has led to rapid advances in HCC treatment. Strategies involving medications with various modes of administration have proved much more effective than monotherapy, even though the causes of the success of such innovative HCC remedies remain poorly clarified. A two-drug approach, including concurrent or successive therapy with personalized treatment and immunotherapy, is among those protocols currently being explored[7-9]. The aim of this study was to retrospectively evaluate the effect of a regimen of targeted therapy, immunotherapy, and HAIC of FOLFOX.

**MATERIALS AND METHODS**

***Patient* *information***

We enrolled patients with HCC who underwent HAIC of FOLFOX combined with antitumor targeted therapy plus immunotherapy at Zhongshan People’s Hospital for HCC from December 2020 to June 2021. The inclusion criteria were as follows: (1) HCC diagnosed by ≥ 2 experienced physicians or pathologically diagnosed and no previous HCC treatment; (2) age 18-75 years old; (3) Child-Pugh class A or B; (4) Eastern Cooperative Oncology Group (ECOG) performance status grade 0 or 1; and (5) Barcelona Clinic Liver Cancer (BCLC) stage B or C. The exclusion criteria were: (1) White blood cell count < 2.0 × 109/L; (2) platelet count < 30 × 109/L; (3) serum total bilirubin > 51 μmol/L; (4) uncontrolled or systemic infection surrounding the lesion (excluding viral hepatitis); (5) severe liver, kidney, heart, or lung function insufficiency; (6) history of other malignant tumors; and (7) known history of human immunodeficiency virus infection.

This retrospective study was approved by the Ethics Committee of Zhongshan People’s Hospital (approval No. 2022-029). All study participants or their legal guardians provided informed written consent prior to study enrollment.

***Surgical* *methods:* *Hepatic* *artery* *catheterization***

The patient was placed supine on the catheter bed, and the bilateral inguinal areas were disinfected. Then, the femoral artery (or radial artery or distal radial artery) was punctured under local anesthesia for the placement of an arterial sheath. The catheter was selectively inserted into the celiac artery and superior mesenteric artery, and angiography was used to observe the blood supply to the intrahepatic tumor. If the intrahepatic tumor was fed by a separate hepatic artery, the microcatheter was placed into the appropriate vascular target. If the intrahepatic tumor was fed by both hepatic arteries, the microcatheter was placed into the appropriate hepatic artery. In cases where the intrahepatic tumor was supplied by the left and right hepatic arteries and the gastroduodenal artery could not be avoided, the gastroduodenal artery underwent coil embolization before placing the microcatheter into the appropriate hepatic artery. Finally, the microcatheter was bandaged and fixed. FOLFOX chemotherapy was initiated upon return to the ward.

***HAIC***

The regimen for HAIC of FOLFOX included oxaliplatin (85 mg/m2 intra-arterial infusion) for 2 h, followed by leucovorin (400 mg/m2 intravenous infusion) combined with 5-fluorouracil (400 mg/m2 intra-arterial infusion) for 1 h and then 2400 mg/m2 for 23 h, repeated every 3 wk. If the tumor shrunk significantly after HAIC treatment, the chemotherapy perfusion dose was appropriately reduced.

***Selection* *of* *antitumor* *targeted* *therapy* *drugs* *and* *immunotherapy* *drugs***

Lenvatinib (Eisai Co., Ltd.), sorafenib (Bayer), sintilimab (Innovent Biologics Suzhou Co., Ltd.), camrelizumab (Suzhou Suncadia Biopharmaceuticals Co., Ltd.), atezolizumab (Roche), and bevacizumab (Roche) were administered within 1 wk after the first HAIC treatment. The dosages were as follows: Lenvatinib, 8 mg [body weight (BW) < 60 kg] or 12 mg (BW ≥ 60 kg), orally, daily; sorafenib, 0.4 g, orally, daily; bevacizumab, 15 mg/kg, intravenous drip, once every 3 wk; sintilimab and camrelizumab, 200 mg, intravenous drip, once every 3 wk; and atezolizumab, 1200 mg, intravenous drip, once every 3 wk. Each drug was suspended, re-used (including dose reduction), or permanently discontinued according to the level of the corresponding drug-related AEs that occurred during treatment.

***Efficacy* *and* *safety* *evaluations***

Each patient underwent enhanced magnetic resonance imaging or enhanced computed tomography of the upper abdomen; routine blood, liver function, and renal function tests; HCC index evaluations; and other examinations prior to HAIC. Curative effects included complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) and were assessed using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and modified RECIST (mRECIST)[10,11]. The ORR was calculated as the PR + CR, and the disease control rate (DCR) was calculated as the PR + CR + SD. The duration of response (DOR), surgical conversion rate, progression-free survival (PFS), 6-month and 12-month PFS, and safety were also determined.

***Statistical* *methods***

Statistical analysis was performed using SPSS 20.0 software. Data were shown as means ± SD or range. Survival data were presented using Kaplan-Meier curves.

**RESULTS**

***Patient* *information***

Of the 61 patients initially recruited, four withdrew after the first or second round of HAIC, and four showed poor compliance and did not come to our hospital for regular treatment on time (HAIC interval > 2 months). The final study cohort (*n* = 53) comprised 45 males and 8 females aged 51.6 (27.0-74.0) years. Of them, 45 (84.9%) had a history of hepatitis B, and 48 (90.1%) had a history of liver cirrhosis. The ECOG performance status was grade 0 in 26 (49.1%) and grade 1 in 27 (50.9%) cases, the BCLC stage was B in 27 (50.9%) and C in 26 (49.1%) cases, and there were 42 (79.2%) cases of Child-Pugh class A and 11 (20.8%) of Child-Pugh class B. Alpha-fetoprotein was elevated in 23 patients (43.4%) and was > 400 ng/mL in 30 (56.6%) patients. The tumor diameter was < 5 cm in 9 (16.9%), 5-10 cm in 18 (34.0%), and > 10 cm in 26 (46.7%) cases. The tumor capsule was complete in 28 (52.8%) and incomplete in 25 (47.2%) cases. Portal and/or hepatic vein tumor thrombus were present in 24 patients, including 5 cases each of PVTT in the second-order branches of the portal vein and the first-order branch of the portal vein, respectively, 11 cases of PVTT in the main trunk and/or a contralateral portal vein, and 6 cases of hepatic vein trunk tumor thrombus. Extrahepatic metastases were present in 12 patients (lung, 7; adrenal gland, 1; bone, 2; bone and lung, 2; and lymph nodes, 6; Table 1). The follow-up end date was June 30, 2022.

***Targeted* *therapy,* *immunotherapy,* *and* *HAIC* *treatment***

Patients received 4-6 rounds of HAIC (average, 4.5 rounds), and the time interval between each round was 28.6 d (median time interval, 27.0 d). The average doses were as follows: Oxaliplatin, 79.9 mg/m2 (arterial infusion); leucovorin, 371.6 mg/m2 (intravenous infusion); 5-fluorouracil, 375.5 mg/m2 (intravenous infusion); and 5-fluorouracil, 2197.3 mg/m2 (arterial infusion).

The choice of targeted therapy drugs and immunotherapy drugs depended on the patient’s wishes and their economic status. There were 18 patients who received sorafenib combined with camrelizumab (sorafenib: 800.0 mg/d, average 666.7 mg/d; camrelizumab: 200 mg every 3 wk, intravenous drip); 10 chose sorafenib combined with sintilimab (sorafenib: 800.0 mg/d, average 640.0 mg/d; sintilimab: 200 mg every 3 wk, intravenous drip); 13 chose lenvatinib combined with camrelizumab (lenvatinib: average 10.8 mg/d; camrelizumab: 200 mg every 3 wk, intravenous drip); 11 chose lenvatinib combined with sintilimab (lenvatinib: < 60 kg BW, 8.0 mg/d and > 60 kg BW, 12.0 mg/d, average 10.5 mg/d; sintilimab: 200 mg every 3 wk, intravenous drip); and 1 chose atezolizumab combined with bevacizumab (atezolizumab: 1200 mg every 3 wk, intravenous drip; bevacizumab, 1100 mg every 3 wk, intravenous drip).

***Tumor* *treatment* *response***

Assessment of the tumor treatment responses using mRECIST revealed that the number of cases of CR, PR, SD, and PD was 13 (24.5%), 19 (35.9%), 21 (39.6%), and 0 (0.0%), respectively, the ORR was 60.4%, and the DCR was 100.0%. Assessment according to RECIST v1.1 revealed that the number of cases of CR, PR, SD, and PD was 2 (3.8%), 23 (43.4%), 28 (52.8%), and 0 (0.0%), respectively, the ORR was 47.2%, and the DCR was 100.0% (Table 2).

***AEs***

AEs of different degrees were observed in all patients after receiving the combination therapy. Abdominal pain, nausea, vomiting, increased levels of transaminases, anorexia, fatigue, and diarrhea mainly occurred in the perioperative period of HAIC, and all patients recovered within a few days. No treatment-related grade 4 or 5 AEs were reported (Table 3).

***Follow-up* *outcomes***

The follow-up period was 14.1 (3.8-23.6) months. PFS at 6- and 12 months was 88.7% and 62.3%, respectively. The median DOR was 9.1 months [95% confidence interval (95%CI): 8.40-not estimable (NE)] and 10.7 months (95%CI: 10.26-NE) according to mRECIST and RECIST v1.1, respectively. The median PFS (mPFS) was 13.9 months (95%CI: 12.63-NE), the 1-year overall survival (OS) rate was 83.0%, and a median OS (mOS) was not reached (95%CI: NE-NE) (Figure 1). Eighteen patients (34.0%) met the criteria for surgical resection, and all underwent surgery (Figure 2).

**DISCUSSION**

HCC is a serious threat to human life and has a high rate of morbidity and mortality. Despite the wide use of a combined therapeutic approach to HCC in recent years, there are no reports of > 2 therapies working together. In this study, we explored the clinical efficacy of targeted therapy plus immunotherapy combined with HAIC in patients with unresectable HCC. We found that HAIC of FOLFOX, targeted therapy, and immunotherapy were effective for patients with unresectable HCC.

In 2018, there were approximately 841000 new cases of HCC worldwide and 781000 associated deaths, of which around 50% of newly reported cases and associated deaths occurred in China[12,13]. The main treatments in early-stage HCC are surgical resection, liver transplantation, and ablation. Transcatheter arterial chemoembolization is effective in middle-stage unresectable HCC with multiple nodules. However, systemic treatments, such as targeted therapy and immunotherapy, are ineffective for some patients with late-stage HCC, and their prognosis is often poor[14]. One of the important means of interventional therapy for HCC is HAIC, and excellent results have been achieved using HAIC of an oxaliplatin-based sequential FOLFOX regimen to treat advanced HCC, making HAIC a more preferred method[15].

HAIC is an interventional treatment method. HCC tumors often have a rich blood supply, with > 95% originating from the hepatic artery, which justifies the treatment of HCC through the hepatic artery[16]. The direct infusion of drugs into the arterial blood supply of the tumor overcomes the physiological barriers through which some intravenous chemotherapeutics are unable to pass, thereby significantly increasing the local drug concentration in the tumor and improving the curative effect. At the same time, the chemotherapeutic drugs circulate in the bloodstream throughout the entire body, playing a role in systemic chemotherapy. Compared with systemic chemotherapy, HAIC improves the local drug perfusion concentration and reduces the systemic toxic and side effects of chemotherapeutics, opening up a wide range of valuable clinical applications[17].

HAIC has been used for HCC treatment for over 60 years, and the earliest date can be traced back to 1961. Some scholars used femoral artery puncture and catheterization or right gastroepiploic artery incision and catheterization to infuse HCC therapeutics[18]. In 1986, there were reports of epirubicin-based HAIC for HCC treatment, but the effect was poor[19]. Around 2000, the cisplatin-based HAIC regimen was used abroad, resulting in the ORR reaching 27.6%-40.5%[20]. Because HAIC has long been used to treat HCC, the arterial perfusion schemes, doses, and number of cycles vary across countries and regions, and their therapeutic effects also differ. However, due to a lack of high-level evidence-based medicine, its clinical application is limited. In 2013, the EACH trial proved the curative effect of FOLFOX chemotherapy for HCC[21]. In 2018, Chinese scholars demonstrated an effective rate of 79.6% for HAIC of FOLFOX[15], and in 2022, an oxaliplatin-based FOLFOX4 regimen of systemic chemotherapy and HAIC therapy became the recommended treatment for advanced HCC[22].

Targeted therapy and immunotherapy have been widely used in clinical practice and are the main treatment methods for advanced tumors. However, their efficacy as a single application is low and does not meet the clinical needs. Thus, a combination of targeted therapy and immunotherapy has been proposed in an effort to develop a more effective treatment method. The current understanding of tumor pathogenesis involves not only the study of tumor cells but also the study of various cells and cytokines within cancer tissues, termed the tumor microenvironment (TME)[23]. For the indefinite proliferation of tumor cells, the TME must be hypoxic, with a low pH and low nutrient levels. This induces the formation of proangiogenic factors and an immunosuppressive microenvironment[24,25]. The TME both increases and decreases immunosuppression, while targeted therapy inhibits the migration and distant metastasis of immune cells. Immunotherapy stimulates the body’s immune system by affecting the target and enhancing the tumor suppression effect of immune cells.

Targeted therapy and immunotherapy have been widely used to treat unresectable HCC. Another option for patients with unresectable HCC is whole-body treatment. The phase III IMbrave150 clinical trial compared a regimen of atezolizumab and bevacizumab (*n* = 336) with that of sorafenib (*n* = 165) in 501 patients with advanced unresectable HCC[9]. The mOS in the combination regimen group was notably increased compared with the sorafenib regimen group (19.2 months *vs* 13.4 months, respectively), while in the 194 Chinese subgroups, the mOS and OS in the combination regimen group were 19.2 and 24 months, respectively, with the risk of death reduced by 47%. Most major guidelines prefer a regimen of atezolizumab and bevacizumab for late-stage HCC. The phase Ib KEYNOTE-524 clinical trial with a regimen of lenvatinib and pembrolizumab[26] reported the mOS and mPFS of 100 patients as 22 months and 9.3 months and the ORR and DCR as 46% and 88%, respectively. However, the OS and PFS of this regimen failed expectations. Study117, a phase Ib clinical study with a regimen of lenvatinib and nivolumab, demonstrated better results than a regimen of lenvatinib and pembrolizumab. For the 30 patients in the study, the CR was 10%, PR was 66.7%, ORR was 76.7%, and DCR was 96.7%[27]. A phase II/III clinical study compared a regimen of sintilimab and bevacizumab with that of sorafenib in 157 patients with unresectable or metastatic HCC[28]. Compared with the sorafenib regimen, the effect of the sintilimab and bevacizumab regimen was markedly better (mOS: NE *vs* 10.4 months), notably reduced the risk of mortality by 44%, and improved ORR by 20%. Targeted therapy and immunotherapy are also effective second-line treatments for unresectable HCC. A phase Ia/IIb clinical study with a regimen of apatinib and camrelizumab in advanced HCC[29] reported an mOS and mPFS of 3.4 and 9.3 months, respectively, an ORR of 46%, and a DCR of 88%.

The continuous exploration and progress of new treatment methods for advanced HCC has revealed that the effect brought about by a single treatment mode is inadequate. The upcoming therapies for progressed, incurable HCC are expected to increasingly integrate local and universal approaches. A prospective randomized controlled study suggested that a regimen of HAIC and sorafenib had better outcomes than that of sorafenib alone[6]. The OS of the combination regimen and sorafenib regimen was 13.37 months and 7.13 months, the PFS was 7.03 months and 2.60 months, and the ORR was 40.80% and 2.46%, respectively. Radical surgical resection was performed for 16 patients with the combined regimen and only 1 patient with the sorafenib regimen, and the success rate of surgical conversion was 12.8% and 0.8%, respectively. A single-center retrospective single-arm study reported the effect of HAIC of FOLFOX combined with targeted therapy and immunotherapy[30], in which the CR was 48.0%, PR was 48.0%, SD was 4.0%, and the ORR was as high as 96.0%. Furthermore, the median time to resolve was 50.5 d (95%CI: 31.02-64.00). Studies have shown that local therapy combined with systemic therapy has a better effect and a higher tumor remission rate.

Multiple treatment combinations can achieve surgical conversion in approximately 15%-20% of cases of unresectable HCC[31]. A potential multidisciplinary strategy for addressing severe HCC involves integrating HAIC-based locoregional treatment with selective treatment and immunotherapy[32]. Furthermore, a retrospective study with a regimen of HAIC and targeted therapy and immunotherapy showed that 15 of 25 (60.0%) patients underwent conversion to operable criteria; 1 refused surgery and the remaining 14 underwent surgical resection. Of them, 7 (28.0%) achieved pathological CR after resection, and the recurrence-free survival was 13.17 months[30]. A prospective, single-arm phase II clinical study on 30 patients with unresectable HCC treated with HAIC combined with sintilimab and bevacizumab biosimilar (IBI305) reported that R0 resections were achieved in all 14 (100.0%) patients who underwent surgical resection (2022 ASCO POSTER Abstract #4073). In this retrospective analysis, the surgical conversion rate did not achieve the above-mentioned results as expected. This might have been because a large proportion of the enrolled patients were BCLC grade C, the tumor burden was high, and there was a large number of patients with PVTT and extrahepatic metastases. Therefore, the surgical conversion rate was not significantly increased.

The common AEs of targeted therapy and immunotherapy combined with HAIC include decreased appetite, fatigue, leukopenia, thrombocytopenia, abdominal pain, nausea and vomiting, hypertension, diarrhea, liver function damage, and hand-foot syndrome, and effective relief occurs after medication. Patients undergoing curative-specific treatment most frequently experienced hypertension as an acute side effect[33,34], occurring in approximately 42% of patients receiving lenvatinib and 36% receiving combination therapy. Furthermore, the first side effect observed in patients with advanced HCC receiving combination therapy was hypertension[26]. Thus, it is recommended that blood pressure is monitored before combined treatment and antihypertensives be timely administered if blood pressure rises. If antihypertensive drugs are ineffective, the dosage of targeted drugs can be reduced or even terminated. In our study, the AEs in both groups were manageable, and no grade 4 or 5 AEs occurred.

The main limitation of our study is its single-center retrospective single-arm design, which leads to selection bias in treatment choice. Thus, higher-quality multicenter prospective studies are necessary to verify our findings. Second, the targeted therapy and immunotherapy drugs used by the patients in this study varied, and there were many different combinations. Third, patients had a large baseline range in terms of tumor stage and liver function, which may have affected clinical treatment effects and outcomes. Fourth, the follow-up period to assess OS was short (1 year), and a longer follow-up of OS is required. Fifth, the intervals between HAIC rounds were relatively long, which may have affected its efficacy.

**CONCLUSION**

Targeted therapy and immunotherapy combined with HAIC of FOLFOX is clinically effective for unresectable HCC, improves the surgical conversion rate, and has controllable AEs.

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**Footnotes**

**Institutional review board statement:** This study was reviewed and approved by the Ethics Committee of Zhongshan People’s Hospital (Approval No. 2022-029).

**Informed consent statement:** Study participants were not required to give informed consent because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

**Conflict of interest statement**: There is no conflict of interest to declare.

**Data-sharing statement:** All data and materials are available from the corresponding author.

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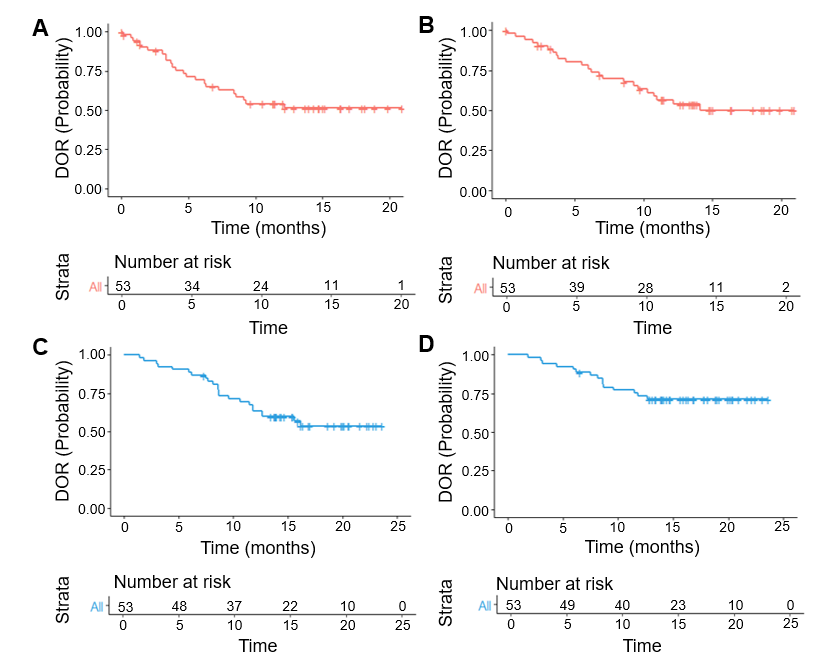
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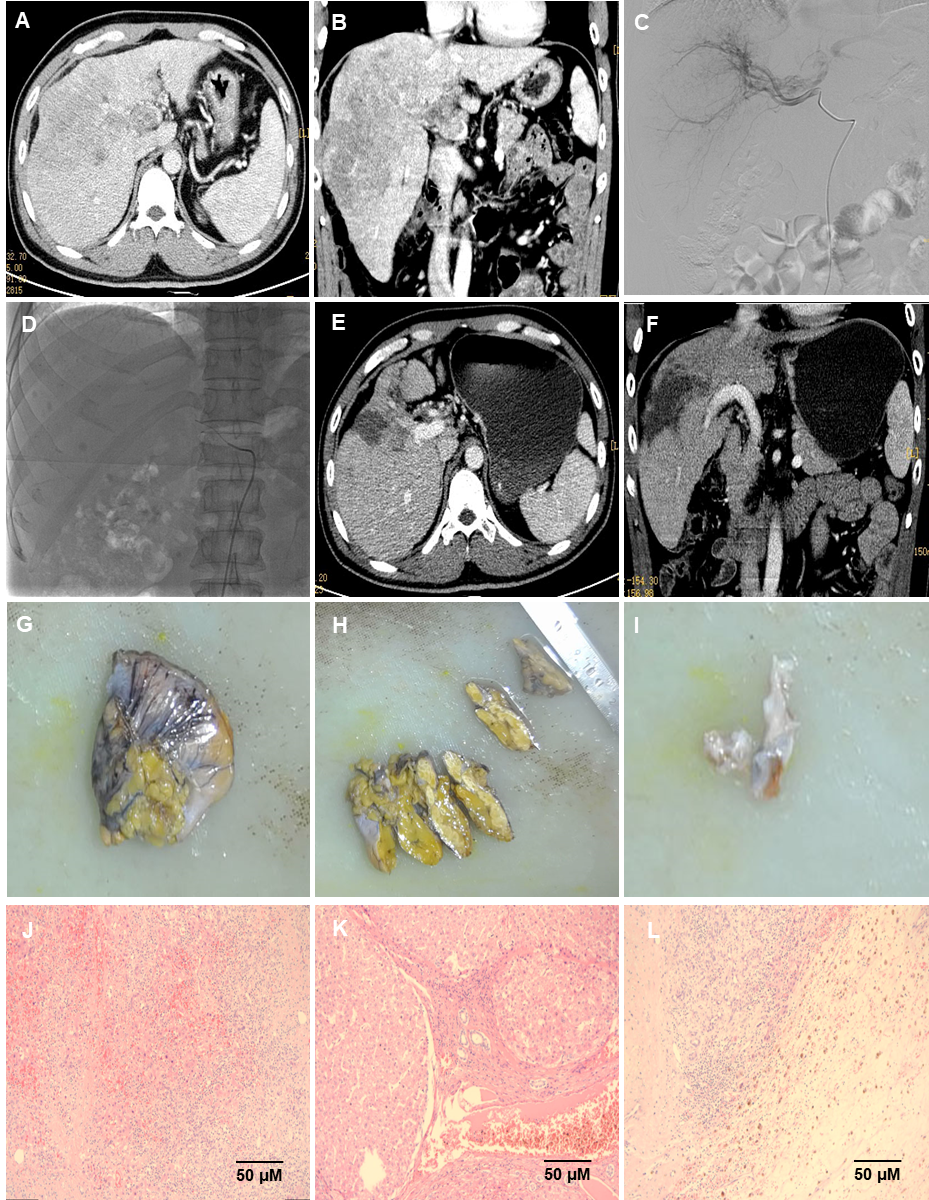
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**Figure Legends**



**Figure 1 Prognostic outcomes of patients with hepatocellular carcinoma followed up within 25 months after treatment.** A: Median duration of response (DOR) using modified Response Evaluation Criteria in Solid Tumors; B: Median DOR using RECIST v1.1; C: Median progression-free survival; D: Median overall survival.



**Figure 2 Imaging and pathological results of patients with hepatocellular carcinoma.** A and B: Massive hepatocellular carcinoma in the right lobe of the liver and tumor thrombus formation in the main portal vein and right branch; C: Digital subtraction angiography showing a mass in the right lobe of the liver; D: Microcatheter insertion into the appropriate hepatic artery for FOLFOX chemotherapy; E and F: After four rounds of hepatic arterial infusion chemotherapy, enhanced computed tomography of the upper abdomen revealed that the intrahepatic lesions were significantly reduced, the portal vein was reopened, and the portal vein tumor thrombus was significantly reduced; G-I: Gross pathological specimens after surgery; J-L: The tumor was completely necrotic with no residual cancer tissue, indicating complete pathological remission.

**Table 1 Basic patient information**

|  |  |  |
| --- | --- | --- |
| **Characteristics** | **Number** | **Proportion (%)** |
| Gender |  |  |
| Male | 45 | 0.849 |
| Female | 8 | 0.151 |
| Age (yr) |  |  |
| < 50 | 22 | 0.415 |
| ≥ 50 | 31 | 0.585 |
| HBsAg |  |  |
| Positive | 45 | 0.849 |
| Negative | 8 | 0.151 |
| Liver cirrhosis |  |  |
| Yes | 48 | 0.901 |
| No | 5 | 0.099 |
| ECOG grade |  |  |
| 0 | 26 | 0.491 |
| 1 | 27 | 0.509 |
| Child-Pugh class |  |  |
| A | 42 | 0.792 |
| B | 11 | 0.208 |
| BCLC stage |  |  |
| B | 27 | 0.509 |
| C | 26 | 0.491 |
| Maximum tumor diameter (cm) |  |  |
| < 5 | 9 | 0.169 |
| 5-10 | 18 | 0.340 |
| > 10 | 26 | 0.491 |
| Tumor capsule |  |  |
| Complete | 28 | 0.528 |
| Incomplete | 25 | 0.472 |
| Alpha-fetoprotein (ng/mL) |  |  |
| < 400 ng/mL | 23 | 0.434 |
| ≥ 400 ng/mL | 30 | 0.566 |
| Number of tumors |  |  |
| ≤ 3 | 30 | 0.566 |
| > 3 | 23 | 0.434 |
| Vascular invasion |  |  |
| Vp2 | 5 | 0.099 |
| Vp3 | 5 | 0.099 |
| Vp4 | 11 | 0.208 |
| Vv2 | 6 | 0.113 |
| Vv3 | 0 | 0.000 |
| Extrahepatic metastases |  |  |
| Yes | 12 | 0.226 |
| No | 41 | 0.774 |
| Lymph node metastases |  |  |
| Yes | 6 | 0.113 |
| No | 47 | 0.887 |

HBsAg: Hepatitis B surface antigen; ECOG: Eastern Cooperative Oncology Group; PVTT: Portal vein tumor thrombus; BCLC: Barcelona Clinic Liver Cancer; Vp2: PVTT in the second-order branches of the portal vein; Vp3: PVTT in the first-order branch of the portal vein; Vp4: PVTT in the main trunk and/or a contralateral portal vein; Vv2: Hepatic vein trunk tumor thrombus.

**Table 2 Tumor treatment response assessment, *n* (%)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Variables** | **CR** | **PR** | **SD** | **PD** | **ORR** | **DCR** |
| mRECIST | 13 (24.5) | 19 (35.9) | 21 (39.6) | 0 (0) | 32 (60.4) | 53 (100.0) |
| RECIST V1.1 | 2 (3.8) | 23 (43.4) | 28 (52.8) | 0 (0) | 25 (47.2) | 53 (100.0) |

CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; ORR: Objective response rate; DCR: Disease control rate; mRECIST: Modified Response Evaluation Criteria in Solid Tumors.

**Table 3 Patient treatment-related adverse events,** ***n* (%)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **AEs** | **Any grade** | **Grade 1** | **Grade 2** | **Grade 3** |
| Leukopenia | 21 (39.62) | 11 (20.75) | 10 (18.87) | 0 |
| Thrombocytopenia | 12 (22.64) | 12 (22.64) | 0 (0.00) | 0 |
| Rash | 7 (13.21) | 3 (5.66) | 4 (7.55) | 0 |
| Itchy skin | 5 (9.43) | 5 (9.43) | 0 (0.00) | 0 |
| Hand-foot syndrome | 17 (32.08) | 10 (18.87) | 7 (13.21) | 0 |
| Increased serum ALT and AST levels | 25 (47.17) | 23 (43.40) | 2 (3.77) | 0 |
| Increased serum bilirubin | 8 (15.09) | 6 (11.32) | 2 (3.77) | 0 |
| Diarrhea | 5 (9.43) | 3 (5.66) | 2 (3.77) | 0 |
| Nausea, vomiting | 24 (45.28) | 13 (24.53) | 11 (20.75) | 0 |
| Proteinuria | 10 (18.87) | 4 (7.55) | 6 (11.32) | 0 |
| Hypothyroidism | 16 (30.19) | 0 (0.00) | 16 (30.19) | 0 |
| Gastrointestinal bleeding | 5 (9.43) | 0 (0.00) | 1 (1.88) | 4 (7.55) |
| Stomachache | 17 (32.08) | 10 (18.87) | 7 (13.21) | 0 |
| Hair loss | 4 (7.55) | 4 (7.55) | 0 (0.00) | 0 |
| Weight loss | 9 (16.98) | 9 (16.98) | 0 (0.00) | 0 |
| Decreased appetite | 25 (47.17) | 23 (43.40) | 2 (3.77) | 0 |
| Fatigue | 19 (35.85) | 19 (35.85) | 0 (0.00) | 0 |
| Hypertension | 24 (45.28) | 2 (3.77) | 22 (41.51) | 0 |