Case Report

Systemic treatment for recurrence of hepatocellular carcinoma after liver transplantation: a case report

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Background: Liver transplantation (LT) is considered the optimal treatment approach for patients with cirrhosis progressing to hepatocellular carcinoma (HCC). LT not only allows for complete removal of tumors from the liver but also potentially eliminates cirrhosis. However, recurrence of HCC after LT remains a significant issue, with recurrence rates ranging from 8% to 20%. The median time to recurrence is 14 months, and the median survival after recurrence is 12.2 months. We present the first case of long-term remission following hepatic arterial infusion chemotherapy (HAIC) combined with targeted therapy in a patient with multifocal recurrence and distant metastasis of HCC after LT.

Case Description: A 62-year-old male experienced recurrence of HCC after LT, with metastases to the sigmoid colon. Following multidisciplinary discussions, he received HAIC combined with small molecule targeted therapy. The liver tumor lesions and hemorrhagic foci remained stable, even tending to shrink, while tumor marker levels steadily declined. The patient did not experience any serious adverse events during treatment. Unfortunately, the patient developed acute enteritis with dysbiosis following a meal in March 2024, which led to rapid onset of septic shock, ultimately resulting in death.

Conclusions: This case suggests that the combination of HAIC and targeted therapy may offer a promising approach for treating recurrent HCC after LT. These findings provide valuable insights for further exploration of treatment strategies for recurrent HCC post-LT and may contribute to advancing clinical research and practice for the benefit of patients.

Keywords: Case report; hepatocellular carcinoma (HCC); liver transplantation (LT); recurrence; hepatic arterial infusion chemotherapy (HAIC)

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Introduction

Liver transplantation (LT) is considered the optimal treatment modality for patients with liver cirrhosis that advances to hepatocellular carcinoma (HCC). LT not only eradicates tumors but also addresses underlying liver cirrhosis, thereby mitigating the risk of HCC progression (1). Nonetheless, despite adherence to stringent LT criteria such as the Milan criteria (2) or the University of California, San Francisco (UCSF) criteria (3), HCC patients undergoing LT still experience recurrence rates ranging from 8–20% (4,5). The median time to recurrence is 14 months, with a median survival post-recurrence of 12.2 months (6,7). Notably, compared to patients without recurrence, those experiencing recurrence exhibit significantly lower survival rates (6). While immunosuppressants serve as the cornerstone of anti-rejection therapy post-transplantation, their direct suppression of the immune system may impede the detection and elimination of circulating cancer cells, thereby posing a heightened risk for HCC recurrence following LT (8,9).

Despite previous reports on various treatment modalities such as local treatment, surgical resection, and combination therapy (10), potential treatment options for recurrent HCC post-LT encompass surgical resection, ablation, intra-arterial therapy (chemotherapy and radiation embolization), and/or systemic chemotherapy (11). Nonetheless, the efficacy of these therapies remains uncertain, and specific treatment modalities for HCC recurrence post-LT are lacking (12). Hence, the exploration of effective treatment modalities holds paramount significance in managing patients with recurrent HCC post-LT.

Previous studies have shown that hepatic artery infusion chemotherapy (HAIC) has a good response rate in the treatment of advanced HCC (13,14). Herein, we present the first case of long-term remission following HAIC combined with targeted therapy in a patient with multifocal recurrence and distant metastasis of HCC after LT. By reporting this case, we aim to provide valuable insights into the treatment of HCC recurrence after LT, particularly highlighting the important clinical significance of HAIC in such patients.

We believe the clinical insights gained from this case can inform both future research and clinical practice in managing this challenging condition. We present this case in accordance with the CARE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-480/rc).

Highlight box

Key findings

- Combined hepatic arterial infusion chemotherapy (HAIC) and targeted therapy have shown promising therapeutic effects on post-liver transplantation recurrent hepatocellular carcinoma (HCC).

What is known and what is new?

- HAIC has a good response rate in the treatment of advanced HCC.
- There have been no reports yet on the application of HAIC in the treatment of recurrent HCC in patients who underwent liver transplantation due to primary HCC.

What is the implication, and what should change now?

- Multicenter, multi-sample clinical trials are still needed to verify the efficacy of HAIC in recurrent HCC after liver transplantation.

Case presentation

A 62-year-old male with a 30-year history of untreated hepatitis B virus (HBV) infection was incidentally found to have a "low-density shadow in the right lobe of the liver" during a routine physical examination in August 2018. Abdominal computed tomography (CT) and B-ultrasound revealed a significant space-occupying lesion in the right lobe, raising suspicion of liver malignancy. Consequently, he sought medical attention at the Affiliated Drum Tower Hospital of Nanjing University Medical School for further evaluation and management. Magnetic resonance imaging (MRI) using gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) detection suggested HCC (S7, solitary, nodular type) (*Figure 1A-1C*). Pathological biopsy confirmed the diagnosis of HCC (Figure S1A). Meld score was calculated at 12.17. According to Milan criteria (15), LT was indicated. Our medical team negotiated treatment strategies with this patient and his family, including surgical resection, or LT. They finally chose LT. Therefore, an orthotopic LT was performed for the patient at the same hospital on December 8, 2018. Tacrolimus (also known as FK506) was used for routine anti-rejection after LT surgery. Postoperative pathology showed HCC, AJCC (American Joint Committee on Cancer) TNM system presented pathologic stage IA (T1a, N0, M0). The postoperative recovery was very well except for hyperglycemia combined with hypertension. In January 2019, he was diagnosed with diabetes and hypertension postoperative LT. Metformin (0.5 g bid, po) was taken orally to lower hyperglycemia and Amlodipine besylate (5 mg qd, po) was also used to deal with hypertension. Hyperglycemia and hypertension have been well controlled till now.

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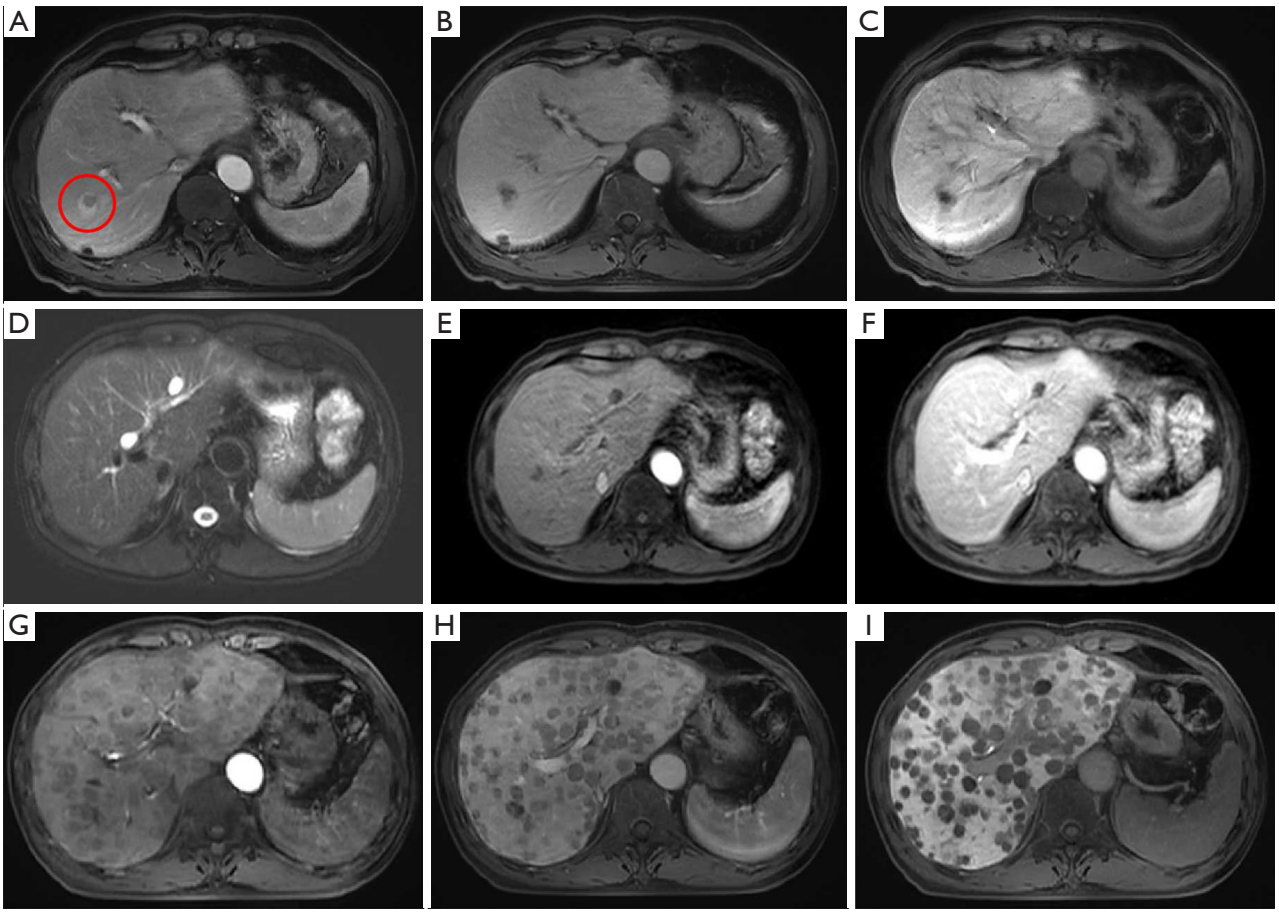

Figure 1 Migration of the Gd-EOB-DTPA-enhanced MRI before and after LT, and the recurrence in 2022. (A) MR enhanced scan arterial phase: there was early enhancement along the edges in S7 segment. The red circle highlights the lesion. (B) portal venous phase: early washout of the lesion. (C) MR enhanced scan of hepatobiliary specific phase: obvious low signal. (D-F) Routine review after LT in June 2022. (G-I) The liver showed diffuse lesions with partial internal bleeding, which were newly developed HCC compared to the previous examination, suggesting multiple intrahepatic metastases. Gd-EOB-DTPA, gadolinium-ethoxybenzyl diethylenetriamine pentaacetic acid; MRI, magnetic resonance imaging; LT, liver transplantation; MR, magnetic resonance; HCC, hepatocellular carcinoma.

After LT, the patient returned for follow-up visits every three to six months and his condition was very stable (*Figure 1D-1F*). Regrettably, he developed sudden chills and high fever on November 20, 2022. Despite receiving symptomatic treatment at a local hospital, his symptoms persisted for one week. Consequently, he was transferred to our hospital for further management. Laboratory investigations revealed a positive COVID-19 test result and severe impairment of liver function (Child-Pugh class B) (Figure S1B). Following antiviral therapy, hepatoprotection, and nutritional support, his condition stabilized. However, during this period, a follow-up MRI (Gd-EOB-DTPA) revealed diffuse liver parenchymal occupation with intraparenchymal hemorrhagic lesions, indicative of recurrent disease with intrahepatic metastases (*Figure 1G-1I*).

Even more disastrous, due to symptoms of tenesmus a painless gastrointestinal examination revealed a mass in the sigmoid colon, which was also thought to be metastatic HCC based on biopsy pathology (Figure S1C). Based on the patient's condition, after multidisciplinary discussions, sirolimus was added to the treatment regimen along with tacrolimus for anti-immune rejection. Sequentially, eight cycles of HAIC treatment (folinic acid, fluorouracil, and oxaliplatin; FOLFOX) were performed since June 4, 2023, combined with oral lenvatinib (2#, bid). The patient's condition was once stable, with the diffuse scope of liver tumor lesions and bleeding lesions shrinking (*Figure 2A-2I*), and tumor indicator levels declining steadily (*Figure 3A-3D*).

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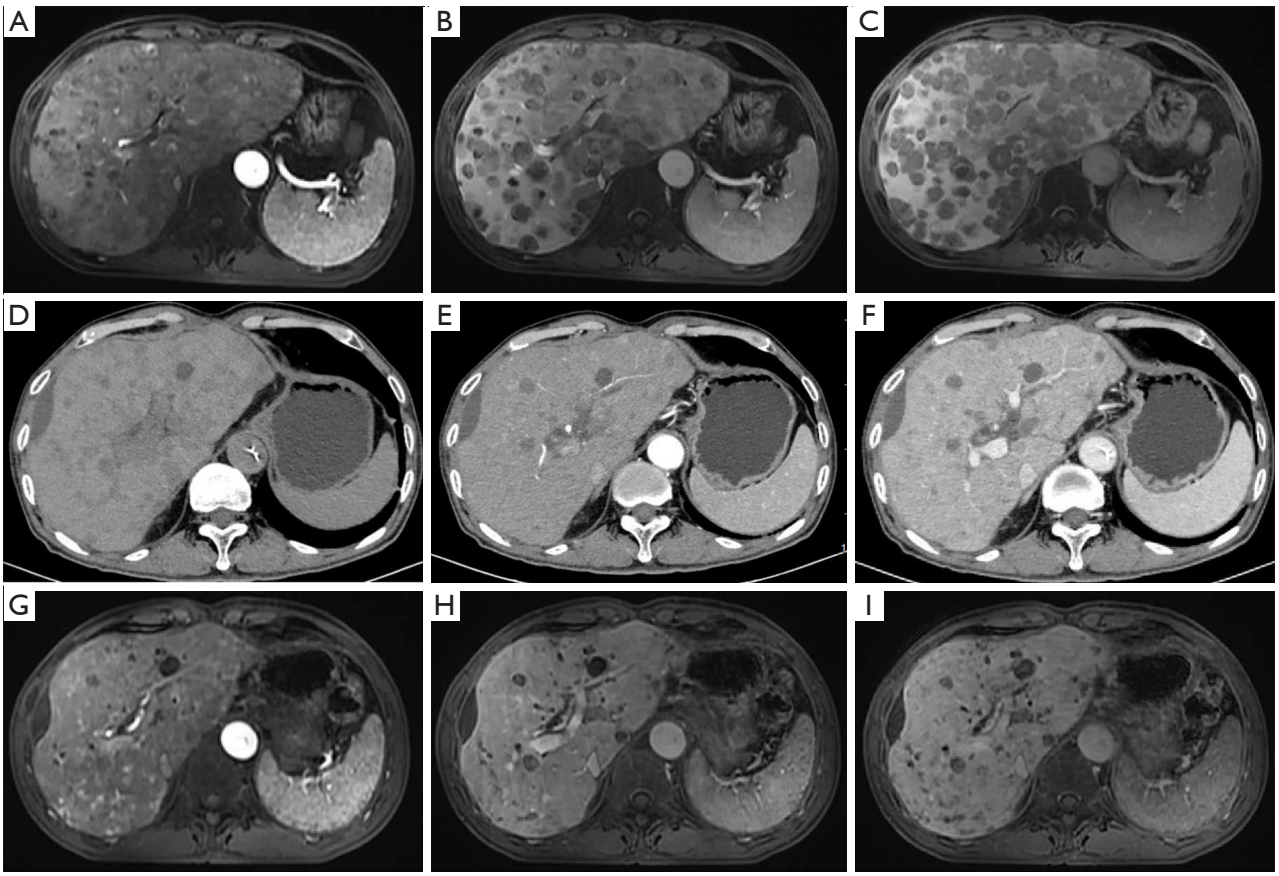

Figure 2 Imaging changes in the treatment of recurrent HCC after liver transplantation. (A-C) Gd-EOB-DTPA-enhanced MRI before treatment (March 15, 2023): Diffuse lesions with partial hemorrhage, with increased size and numbers of nodules. (D-F) Enhanced CT images after the 4-cycle HAIC therapy (August 7, 2023): an irregular margin with decreased and diminished lesions, with diffuse multiple low- and high-density shadows compared to the previous examination (March 15, 2023). (G-I) Gd-EOB-DTPA-enhanced MRI images after 4-cycle HAIC therapy (November 17, 2023): obvious decreased intrahepatic lesions with less partial internal bleeding, compared to the previous examination (August 7, 2023). HCC, hepatocellular carcinoma; Gd-EOB-DTPA, gadolinium-ethoxybenzyl diethylenetriamine pentaacetic acid; MRI, magnetic resonance imaging; CT, computed tomography; HAIC, hepatic arterial infusion chemotherapy.

However, the patient's progressive tenesmus symptoms worsened, suggesting the possible progression of metastatic lesions in the sigmoid colon. Lenvatinib was adjusted to Donafenib (2#, bid, po) on August 10, 2023 since DCP volatility increased.

Although, the recurrence of HCC and implanted metastases in the sigmoid colon after LT, the condition of the liver nodules are stable and even tends to shrink under the treatment of HAIC plus targeted-therapy (Figure S2). The patient did not experience any serious adverse events during treatment. Unfortunately, the patient developed acute enteritis with dysbiosis following a meal in March 2024, which led to rapid onset of septic shock, ultimately resulting in death. All procedures performed in this study were in accordance with the ethical standards of the institution and/or national research committee(s), and with the Helsinki Declaration (as revised in 2013). Written informed consent for publication of this case report and accompanying images was not obtained from the patient or the relatives after all possible attempts were made.

Discussion

Recurrence of HCC after LT has become a current concern, till now the overall survival (OS) and prognosis remain very poor. Treatment strategies for recurrence remain challenging, with existing methods including repeated resection, ablation, embolization, radiation, and systemic

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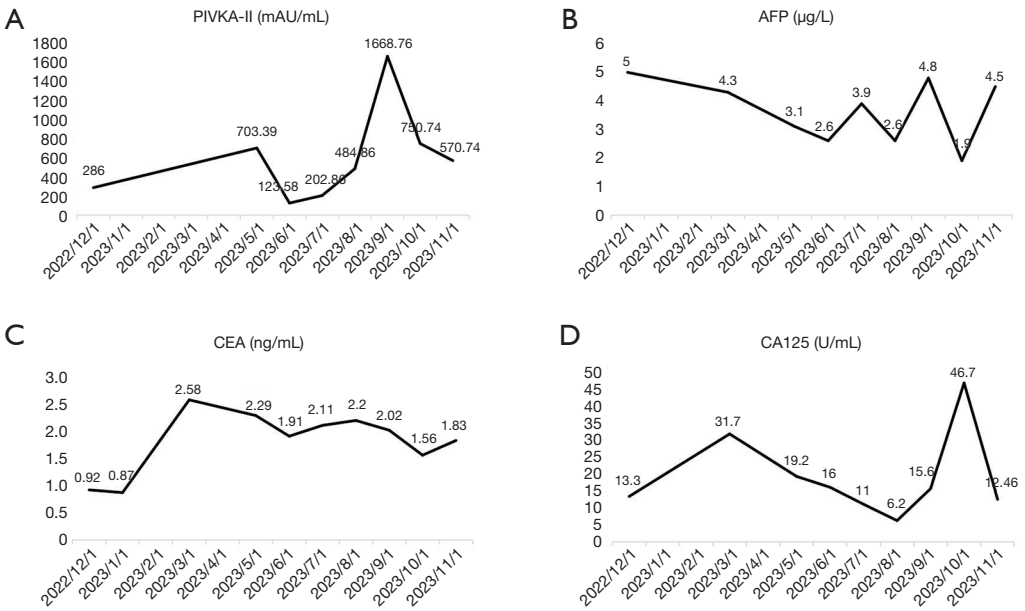

Figure 3 Changes in tumor markers during treatment timeline. (A) The changes in PIVKA-II levels during treatment timeline. (B) The changes in AFP levels during the treatment timeline. (C) The changes in CEA levels during the treatment timeline. (D) The changes in CA125 levels during the treatment timeline. PIVKA-II, protein induced by vitamin K absence or antagonist-II; AFP, alpha-fetoprotein; CEA, carcinoembryonic antigen; CA125, cancer antigen 125.

therapy (16). Additionally, for patients with multifocal liver recurrence who are not suitable for resection or ablation, transcatheter arterial chemoembolization (TACE) or yttrium 90 (Y90) radioembolization for intra-arterial treatment may be a good choice and has also been applied in clinical practice (11). Y90 is an effective treatment for HCC during the bridging/downstaging period before LT. It can enable some patients to achieve extensive or complete necrosis and obtain better recurrence-free survival (RFS), thus it can be recommended as a neoadjuvant treatment before LT (17). However, feedback from clinical studies of many protocols seems to show that the clinical efficacy of treating recurrent HCC after LT is still unsatisfactory.

Importantly, although there are many research reports about using HAIC in the treatment of advanced HCC or postoperative recurrent HCC (18-20), no reports are involved in its application in the treatment of HCC patients with recurrent HCC who have undergone LT due to primary HCC. Currently, our team has tried to use HAIC to treat recurrent HCC after LT, which has effectively controlled the patient's disease progression and improved his quality of life. Therefore, for patients with recurrent HCC after LT in clinical practice, this regimen may provide an effective strategy.

Recurrence of HCC after LT remains a significant concern due to its association with poor prognosis, despite consensus recommendations advocating for close monitoring of HCC recurrence post-LT (21). The routine administration of immunosuppressants for anti-rejection therapy post-LT is considered a potential risk factor for recurrent HCC (9). Immunosuppressive protocols incorporating mammalian target of rapamycin (mTOR) inhibitors, such as sirolimus, exhibit antitumor properties and are speculated to reduce HCC recurrence rates. However, a prospective phase III multicenter randomized trial failed to demonstrate a significant difference in HCC recurrence rates among LT patients, irrespective of the inclusion of sirolimus in the regimen (22). This article reports that after the patient was diagnosed with recurrent HCC, anti-rejection treatment with tacrolimus combined with sirolimus may have a good adjuvant effect in the later treatment of recurrent HCC with HAIC combined with Lenvatinib. At the same time, we conducted transcriptome sequencing on the frozen liver cancer tissue obtained during the patient's transplantation. According to our team's proposed liver cancer fatty acid degradation (FAD) subtypes, it was suggested to be F1 type (Figure S3), indicating that F1 type patients are more sensitive to sorafenib treatment,

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which may partially explain the treatment effect in this patient (23). Research on the correlation between FAD subtypes prediction and response to HAIC treatment is also underway.

As known, alpha-fetoprotein (AFP) is a marker for HCC differentiation and vascular invasion. AFP levels >1,000 ng/mL indicate poor prognosis and have good practicality in predicting HCC recurrence after LT (24). Moreover, the transplant center which proposed the Milan criteria also proposed a new criterion (Metro-ticket 2.0) that considers AFP level as an important factor in selecting LT (25). The protein induced by vitamin K deficiency or antagonist II (PIVKA-II) is an immature form of prothrombin. Alterations in PIVKA-II levels contribute to the diagnosis of primary and recurrent HCC (26). As a growth factor, PIVKA-II can promote cell proliferation and tumor angiogenesis in HCC patients (27). Similar to AFP, PIVKA-II can effectively guide the diagnosis of HCC and recurrent HCC, but its critical value has not yet been unified. PIVKA-II can also serve as a supplement to AFP (28). Relatively, lower AFP and PIVKA-II assessment values were associated with better prognosis. Therefore, continuous detection of these two proteins is often performed clinically, which is of great significance in diagnosing early recurrent HCC. The levels of PIVKA-II before and after treatment can reflect the therapeutic effect of recurrent HCC. For example, a significant increase in PIVKA-II may be closely related to the vascular invasion and intrahepatic metastasis of HCC cells (29). For this patient, his AFP did not significantly increase, but the PIVKA-II levels had significantly increased when diagnosed with recurrent HCC. With the combination of HAIC and Lenvatinib treatment, the PIVKA-II value showed fluctuating changes, which, combined with imaging MRI, indirectly reflected the tumor cell status of the patient.

In fact, it has been reported that most patients with recurrent HCC have extensive metastatic disease and require systemic chemotherapy, while HCC is a tumor that is insensitive to chemotherapy, and the efficacy of drugs including doxorubicin, 5-fluorouracil, and platinum has been poorly reported (11,30). However, studies have confirmed that HAIC has a higher response rate compared to systemic chemotherapy, with longer OS and tolerable toxicity in advanced HCC patients. whilst, only Japan has included HAIC in its guidelines as an optional treatment for advanced HCC (14,19). A retrospective study compared FOLFOX-HAIC with or without sorafenib treatment in advanced HCC patients, results indicated that FOLFOX-HAIC improved survival benefits. However, there is no significant difference in the 1-year, 2-year, and 3-year OS rate and overall regression, while disease-free survival (DFS) of most patients significantly improved in the first two years (13,31). Furthermore, another study confirmed that FOLFOX-HAIC treatment for advanced HCC achieved satisfactory OS which was safe, reliable, and well tolerated. It was speculated that the continuous infusion of FOLFOX drugs may eliminate micro-metastases in the liver parenchyma and blood circulation (18). Therefore, HAIC may treat early recurrence HCC, which is also in line with the treatment principles and the expectations of researchers.

This report is indeed just a case study, lacking multi-sample, multi-center, and long-term follow-up outcomes observation. Therefore, in the later stage, we plan to conduct more similar clinical cases based on clinical practice, to establish a more effective data model and diagnostic and treatment system, and then provide more effective strategies for patients with recurrent HCC after LT.

Conclusions

Collectively, although LT is performed in strict compliance with LT criteria, recurrence of HCC after LT is still a current issue. Existing prevention strategies seem to have little effect, and recurrent HCC can even spread from intrahepatic to extrahepatic and is difficult to control. However, the current strategies seem to be unsatisfactory in diagnosing and treating recurrent HCC after LT. For unresectable patients, multidisciplinary discussions may be beneficial to develop effective strategies based on individual patient specificity, including local combined with systemic therapy. This case suggested that the combination of HAIC and targeted-therapy could be effective in the treatment of recurrent HCC after LT, which provides effective clues for exploring the treatment of recurrent HCC after LT, encouraging the development of clinical research and promoting clinical practice in order to benefit the patients.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-480/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institution and/or national research committee(s), and with the Helsinki Declaration (as revised in 2013). Written informed consent for publication of this case report and accompanying images was not obtained from the patient or the relatives after all possible attempts were made.

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