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CASE REPORT

Conversion therapy for massive hepatocellular carcinoma: A case report and literature review

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Key Clinical Message

For potentially resectable HCC, a more aggressive conversion therapy strategy (high-intensity combined with multiple treatment modalities) can be used.

Abstract

Hepatocellular carcinoma (HCC) is the sixth most common malignancy worldwide. The best treatment for HCC is radical surgical resection, but 70%–80% of patients are ineligible for surgery. Although conversion therapy is an established treatment strategy for various solid tumors, there is no uniform protocol for treating HCC. In this case, we present a 69-year-old male patient diagnosed with massive HCC with Barcelona clinical liver cancer (BCLC) stage B. Because of the insufficient volume of the future liver remnant, we believed radical surgical resection was temporarily impossible. Therefore, the patient received conversion therapy, including four cycles of transcatheter arterial embolization (TAE) and hepatic arterial infusion chemotherapy (HAIC-Folfox), lenvatinib (8 mg orally once a day), and tislelizumab (an anti-PD-1 antibody, 200 mg intravenously once every 3 weeks). Fortunately, the patient achieved a good treatment response (smaller lesions and improved liver function) and underwent radical surgery finally. There was no clinical evidence of recurrence at 6 months of follow-up. For potentially resectable HCC, this case reveals that a more aggressive conversion therapy strategy (high-intensity combined with multiple treatment modalities) can be used.

KEYWORDS

case report, conversion therapy, hepatocellular carcinoma, liver resection

Zheyu Zhou and Xiaoliang Xu contributed equally to this work.

1 | INTRODUCTION

Primary liver cancer is the sixth most common malignancy and the fourth most lethal tumor globally, of which 75%–90% is hepatocellular carcinoma (HCC).[1,2] Hepatitis B virus (HBV) infection is China's most crucial cause of HCC. Radical surgical resection is the best treatment for HCC, but only 20%–30% of patients are eligible for surgery.[3]

In recent years, targeted agents, immune checkpoint inhibitors (ICIs), and local therapy have effectively treated advanced or unresectable HCC. Lenvatinib is a multi-targeted tyrosine kinase inhibitor (TKI), and the REFLECT study showed significant advantages of lenvatinib over sorafenib.[4] ICIs, including atezolizumab and sintilimab, have been recommended as first-line treatment options for unresectable HCC.[5,6] Furthermore, local therapy, such as transcatheter arterial chemoembolization (TACE), transarterial radioembolization, and hepatic arterial infusion chemotherapy (HAIC), can also provide a survival benefit for HCC patients.[7–9]

Based on the current status of HCC treatment and the remarkable progress in the nonsurgical treatment described above, conversion therapy has also been proposed. Conversion therapy is the conversion of unresectable HCC to resectable HCC.[10] HCC shrinking and downstaging with TACE or external radiation therapy followed by surgical resection have been reported in the 1990s.[11,12] Although conversion therapy is an established treatment strategy for various solid tumors (including gastric, colorectal, and pancreatic cancers),[13,14] there is no uniform protocol for treating HCC. Here, we report a case of massive HCC that underwent successful radical surgery after conversion therapy (combined with lenvatinib, ICIs, and HAIC).

2 | CASE REPORT

A 69-year-old male patient was found to have a liver-occupying lesion on a medical checkup at a local hospital and was diagnosed with highly differentiated HCC by liver aspiration biopsy in December 2021. The patient presented to our hospital on January 6, 2022, seeking further consultation and treatment. He had a previous history of chronic hepatitis B. There is no similar patient in the family. On admission, there were no significant positive signs on physical examination. Laboratory tests are presented in Table 1. His liver function was Child–Pugh class B and albumin–bilirubin (ALBI) grade 2. Contrast-enhanced computed tomography (CT) showed a large occupancy at the junction of the right and left lobes of the liver was thought to be HCC (Figure 1).

TABLE 1 The patient's laboratory tests.

Variables	January 7, 2022	August 16, 2022
WBC (10^9/L)	4.7	3.8
RBC (10^{12}/L)	2.93	4.03
PLT (10^9/L)	192	116
ALT (U/L)	22.7	5.3
AST (U/L)	50.5	15.3
TBIL (umol/L)	38.9	13.8
ALB (g/L)	33.9	43.2
PT (s)	11.4	11.6
AFP (ng/mL)	4563.9	4
DCP (mAu/mL)	30,000	31.61
HBV DNA (IU/mL)	< 20	< 20

Abbreviations: AFP, alpha-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate transaminase; DCP, des-γ-carboxy prothrombin; HBV DNA, hepatitis B virus DNA; PLT, platelet; PT, prothrombin time; RBC, red blood cell; TBIL, total bilirubin; WBC, white blood cell.

After a multidisciplinary treatment (MDT) discussion, the patient was diagnosed with HCC with Barcelona clinical liver cancer (BCLC) stage B. Because of insufficient volume of the future liver remnant (FLR) and poor liver reserve function, we believe radical surgical resection is impossible. The patient underwent the first transcatheter arterial embolization (TAE) and HAIC-Folfox on January 11, 2022. He was discharged on January 15, 2022, and returned to the local hospital for treatment with lenvatinib (8 mg orally once a day) and tislelizumab (200 mg intravenously once every 3 weeks). The patient then received TAE and HAIC-Folfox treatment at our hospital on February 10, March 9, and June 2, respectively. Fortunately, in the hepatic arteriogram performed on June 2, the tumor vessels and staining were significantly reduced, and the tumor-supplying artery became thinner. Except for mild liver dysfunction, no other adverse events were observed during the treatment. The patient had good treatment compliance and tolerance and presented to our hospital again in August 2022. Contrast-enhanced CT showed that the lesions were smaller than before (Figure 2). Based on the modified Response Evaluation Criteria in Solid Tumors (mRECIST), tumor response was the partial response (PR).[15] Laboratory tests are presented in Table 1. Alpha-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP) levels were already within the normal range (Figure 3A). Supportive treatment since admission improved his liver function to Child–Pugh class A and ALBI grade 1. After a second MDT discussion, we concluded that the patient could undergo radical surgery. Ultimately, he underwent hepatic segmental resection (middle liver lobe)

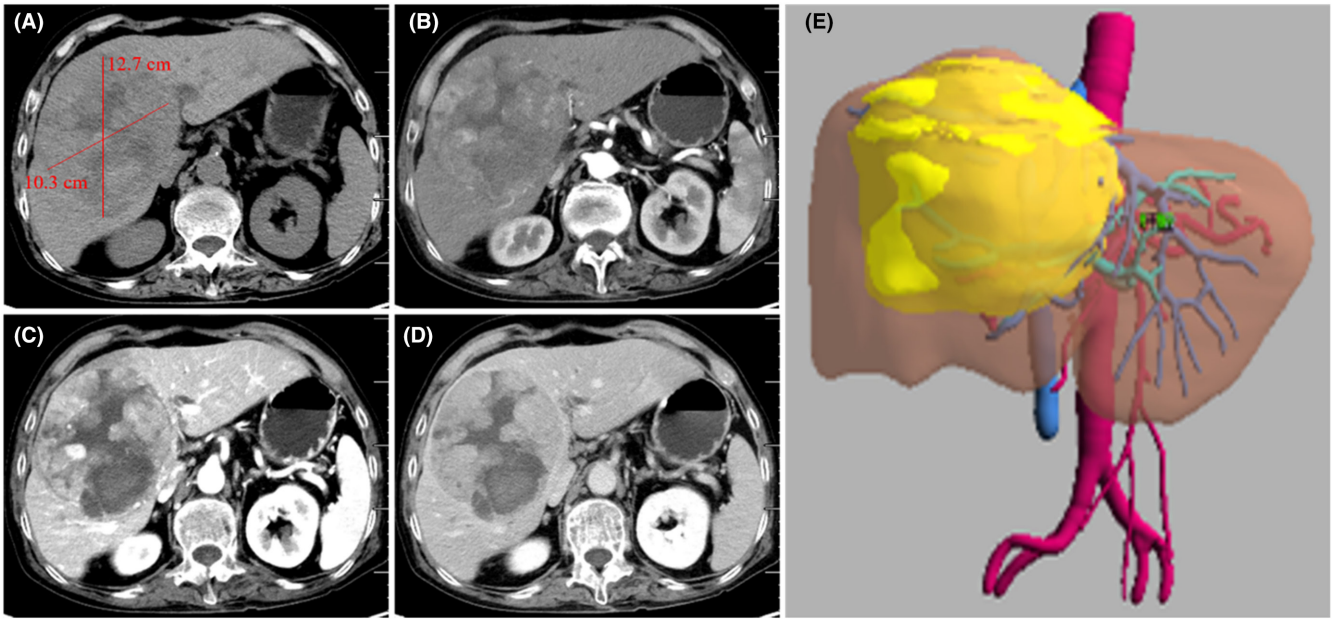

FIGURE 1 Abdominal contrast-enhanced computed tomography before the conversion therapy. (A) Plain scan, the red lines mark the tumor diameter. (B) Early stage of the arterial phase. (C) Late stage of the arterial phase. (D) Equilibrium phase. (E) 3-D image.

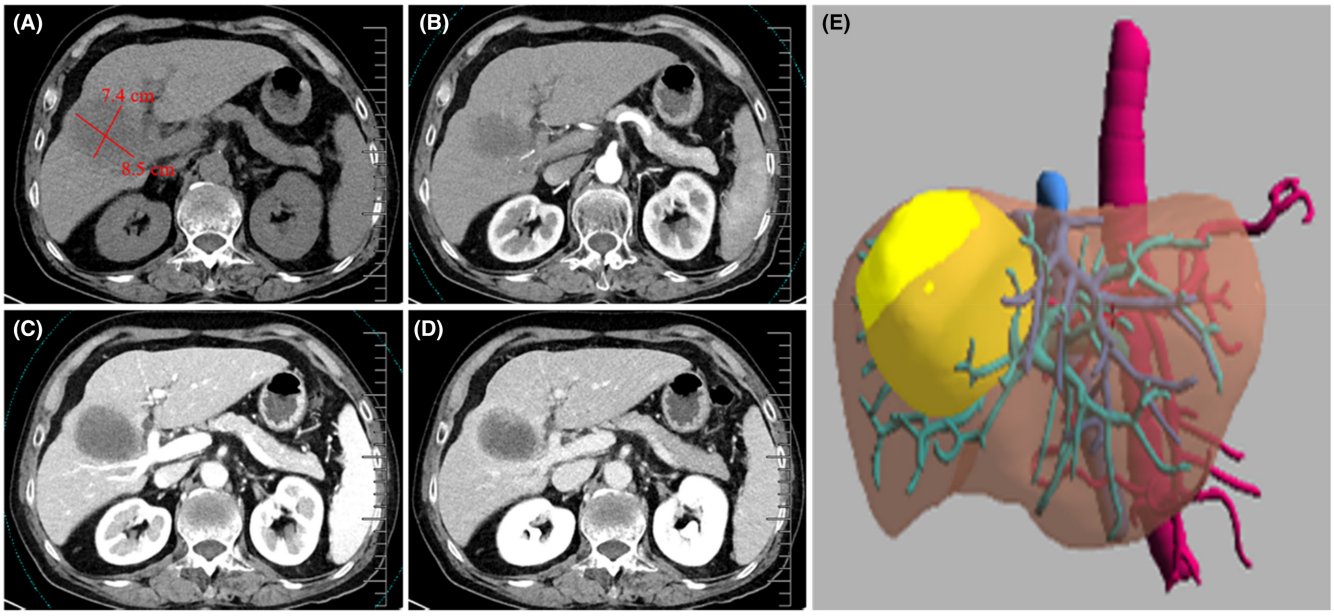

FIGURE 2 Abdominal contrast-enhanced computed tomography after the conversion therapy. (A) Plain scan, the red lines mark the tumor diameter. (B) Early stage of the arterial phase. (C) Late stage of the arterial phase. (D) Equilibrium phase. (E) 3-D image.

and cholecystectomy on August 19, 2022. During the procedure, we performed a precise ligation of the vessels in the hepatic segment where the tumor was located with a hilar approach, followed by a dorsal approach along the ischemic line for hepatic parenchymal dissection (using hepatic inflow occlusion: Pringle-maneuver 15 min-5 min). Finally, we used intraoperative ultrasound to clarify the extent of the tumor and then completely resected the liver tissue where the lesion was located. The pathological examination showed necrosis of HCC with no residual tumor tissue observed on the incisal edge (R0); the Edmondson–Steiner (E-S) classification was Grade II with no microvascular invasion (MVI). The timeline of clinical events is presented in Figure 3B. The patient was discharged on September 8 satisfactorily and received no adjuvant therapy postoperatively. There was no clinical evidence of recurrence at 6 months of follow-up.

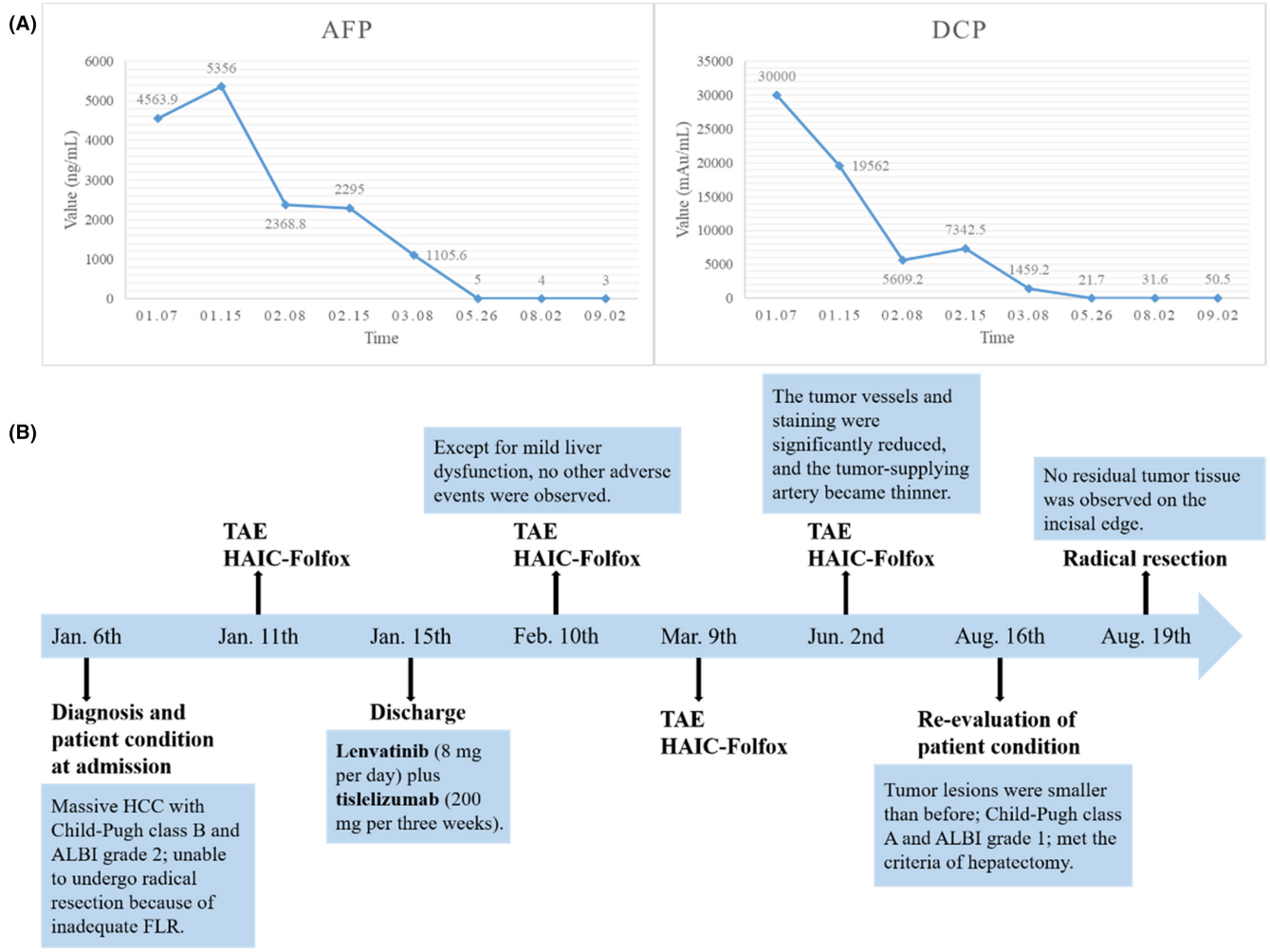

FIGURE 3 Tumor markers change trend and the timeline. (A) Alpha-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP) change trend. (B) The timeline of clinical events. ALBI, albumin-bilirubin; FLR, future liver remnant; HAIC,: hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; TAE, transcatheter arterial embolization.

3 | DISCUSSION

Due to the lack of typical clinical symptoms in the early stage of HCC, 64% of HCC patients in China were already at BCLC stage B or C at the initial diagnosis.[16] The median survival of these patients was about 2 years.[3,17] In recent years, targeted drugs combined with ICIs for advanced or unresectable HCC can achieve an objective response rate (ORR) of about 30%.[5,18,19] Therefore, conversion therapy may be a meaningful way to improve the survival of HCC patients. Notably, patients who underwent successful conversion therapy had a 5-year postoperative survival rate of 50%–60%, comparable to that of early-stage HCC as previously reported.[20]

The reasons for unresectable HCC can be divided into surgical and oncological unresectability. The former includes patients with insufficient volume of FLR, intolerable liver function, and systemic conditions that cannot withstand the trauma of surgery. The latter means that initial resection does not yield better results than nonsurgical treatment.[20] This patient had a massive HCC larger than 10 cm, and initial resection could result in an insufficient volume of FLR and an extremely high risk of liver failure. It is generally accepted that HCC patients with chronic liver disease, parenchymal injury, or cirrhosis need to preserve more than 40% of their liver volume. Patients without liver fibrosis or cirrhosis need to preserve more than 30%. In addition, normal liver function (Child–Pugh class A) and indocyanine green-R15 < 20% are necessary to perform the procedure.[3] A thorough assessment of contraindications to surgery is required, and patients who do not meet these criteria are considered to have inadequate FLR. At the same time, evidence suggests that R0 resection is vital to improving the long-term outcome of the procedure. HCC patients unable to achieve R0 resection did

TABLE 2 The conversion rate of different treatment plans.

Ref.	Number of patients	Treatment plan	Conversion rate (%)
He et al.[22]	35	Sorafenib + HAIC	14.3
He et al.[23]	125	Sorafenib + HAIC	12.8
Zhang et al.[24]	33	Lenvatinib + ICIs	30.3
Zhu et al.[25]	101	TKIs + ICIs	23.8
Peng et al.[7]	170	Lenvatinib + TACE	15.3
Zhang et al.[26]	25	TKIs + ICIs + HAIC	56
Qu et al.[27]	30	Lenvatinib + toripalimab + TACE	50

Abbreviations: HAIC, hepatic arterial infusion chemotherapy; ICIs, immune checkpoint inhibitors; TACE, transcatheter arterial chemoembolization; TKIs, tyrosine kinase inhibitors.

not have significantly better outcomes than those who received nonsurgical treatment. Reducing tumor volume, ensuring negative surgical margins, and ultimately achieving R0 resection are the goals.[10,20]

Lenvatinib is the first type of V TKIs drug with rapid binding and relatively slow dissociation kinetics. Its antivascular endothelial growth factor receptor 2 (VEGFR2) effect is more potent than previously targeted drugs.[21] Systemic antitumor therapy based on lenvatinib and local therapy became an essential modality of conversion therapy. Among patients with initially unresectable HCC, 12.8%–56% successfully underwent radical surgery after conversion therapy (Table 2).[7,22–27] The combination of TKIs, ICIs, and local therapy notably had a higher conversion rate.[26,27] In the immune microenvironment of HCC, lenvatinib can affect the activity of tumor-associated macrophages and cytotoxic T cells and promote the activation and infiltration of natural killer cells.[28] Interestingly, lenvatinib reduces PD-L1 expression in tumor cells and regulatory T cells infiltration by blocking fibroblast growth factor receptor 4.[29] These properties provide an important rationale for combining lenvatinib with immunotherapy. The functional status of the liver in HCC patients is one of the most important factors influencing the long-term efficacy of TACE. Preclinical studies have shown that lenvatinib may inhibit the development of liver fibrosis.[30] Meanwhile, the REFLECT study and a retrospective study in Japan showed that patients treated with lenvatinib had better liver reserve function than those treated with sorafenib.[31,32] Moreover, by inhibiting the expression of VEGF and angiopoietin-2, lenvatinib improved intra-arterial drug transport and distribution by promoting vascular normalization.[33] These provide an essential rationale for the combination of lenvatinib with local therapy.

Tumor differentiation and MVI are vital predictors of poor prognosis in HCC patients. Studies have shown that the absence of MVI, TACE-course >3, and mRECIST with complete response or PR are prognostic protective factors in HCC patients receiving TACE.[34] Furthermore, the propensity score matching study by Wang et al.[35] showed that E-S grade I/II, male sex, age ≥ 50 years old, HBV infection, and other factors could benefit HCC patients from postoperative prophylactic TACE. The heterogeneity of HCC will affect the efficacy of clinical treatment. Clinicopathologic features such as better differentiation and the absence of MVI may be the reasons for the success of conversion therapy in this patient.

4 | CONCLUSION

For potentially resectable HCC, this case reveals that a more aggressive conversion therapy strategy (high-intensity combined with multiple treatment modalities) can be used. Short-term shrinkage and downstaging of HCC, enlargement of FLR, and eventual radical surgical resection are the goals. In the future, we hope to prove further that the combination of TKIs, ICIs, and local therapy is effective by accumulating more successful cases of conversion therapy.

AUTHOR CONTRIBUTIONS

Zheyu Zhou: Visualization; writing – original draft. **Xiaoliang Xu:** Funding acquisition; writing – original draft. **Meiling Sun:** Visualization. **Yang Liu:** Funding acquisition; visualization. **Qiaoyu Liu:** Visualization. **Chaobo Chen:** Conceptualization; project administration; resources. **Yin Yin:** Conceptualization; funding acquisition; project administration; resources.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this case report are included within the article.

ETHICAL STATEMENT

The institutional review board of The Affiliated Drum Tower Hospital of Nanjing University Medical School approved this study.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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