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CASE REPORT

Massive Hepatocellular Carcinoma with Insufficient Future Liver Remnant Achieved Complete Response After Two-Stage Hepatectomy Combined with Hepatic Arterial Infusion Chemotherapy and Lenvatinib-sintilimab: A Case Report

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Abstract: Massive hepatocellular carcinoma (HCC) is not suitable for radical surgery due to the factors of high tumor burden and poor postoperative liver function tolerance. There are few reports on the conversion therapy for HCC with insufficient future liver remnant (FLR) volume using a combination of two - stage hepatectomy (TSH), hepatic arterial infusion chemotherapy (HAIC), and lenvatinib - sintilimab. We report a case of a 62-year-old male with massive HCC (81mm×11.5mm×95mm). At the initial diagnosis, the ratio of his FLR to standard liver volume (SLV) was 34%. After multidisciplinary team (MDT) discussion, the patient decided to undergo conversion therapy. After three formal cycles (9 weeks) of conversion therapy, the FLR/SLV ratio increased to 65%, and then right hepatectomy was performed. The lesion achieved a partial response (PR) according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria. The second hepatectomy was successfully performed, and there was no recurrence during the 36-month postoperative follow-up. In this case, portal vein ligation (PVL) surgery, HAIC, and targeted immunotherapy contributed to the conversion therapy of HCC through different dimensions, including mechanical blood flow blockage, local chemotherapy, and immune regulation, laying the foundation for the safety of radical surgery and long-term postoperative survival.

Keywords: conversion therapy, massive hepatocellular carcinoma, insufficient future liver remnant, portal vein ligation, hepatic arterial infusion chemotherapy

Introduction

Primary liver cancer (PLC) is the sixth most common malignant tumor worldwide and the third leading cause of cancer-related deaths globally.[1] The number of newly diagnosed liver cancer cases globally is projected to increase from approximately 870,000 in 2022 to about 1.52 million by 2050, while liver cancer-related deaths are expected to rise from 760,000 in 2022 to 1.37 million in 2050,[2] exacerbating the global public health burden. The most prevalent type of primary liver cancer is hepatocellular carcinoma (HCC), a highly heterogeneous malignant tumor. According to HCC

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treatment guidelines worldwide, radical surgery is still the most common and effective way to treat HCC.[3–5] However, in patients with massive or multiple HCC, insufficient future liver remnant (FLR) and the increased risk of postoperative liver failure (PHLF) still affect the application of radical resection surgery. Residual liver dysfunction caused by insufficient remnant liver volume is the main factor that hinders the use of radical resection.[3,4]

In 1920, Rous and Larimore first reported the outcomes of portal vein ligation (PVL). They discovered that excessive blood flowed to the contralateral hepatic lobe, leading to hypertrophy of the contralateral lobe and atrophy of the ipsilateral lobe after PVL.[6] Honjo et al[7] were the first to apply PVL to two-stage hepatectomy in humans Both PVL and portal vein embolization (PVE) can block the portal venous blood supply to the liver lobe containing the tumor and induce compensatory hypertrophy of the remaining liver (the success rate of PVE/PVL ranges from 60% to 80%, with a complication rate of approximately 10%-20%[8]). However, while PVL/PVE offer relative advantages of being minimally invasive and simple to perform, they also have certain limitations. The time required for hypertrophy of the remaining liver after PVE/PVL is relatively long (usually 4–6 weeks), and more than 20% of patients lose the opportunity for surgery due to tumor progression or insufficient hypertrophy of the remaining liver.[8–10]

With the emergence of various targeted and immunotherapeutic drugs, the treatment landscape for HCC has been completely transformed. Numerous clinical trials have demonstrated that the combination therapy of TKI and ICI has achieved remarkable clinical efficacy, showing a higher objective response rate (ORR) and better survival outcomes compared to monotherapy, bringing new hope to patients with advanced HCC. The combination therapy represented by regimens such as apatinib-camrelizumab,[11] lenvatinib-pembrolizumab,[12] bevacizumab-atezolizumab,[13] and bevacizumab-sintilimab[14] has demonstrated an ORR greater than 20% in the treatment of unresectable HCC, exhibiting significantly greater conversion potential compared to monotherapy.

Additionally, hepatic arterial infusion chemotherapy (HAIC) base on the fact that 90% of the blood supply to HCC is provided by the hepatic artery, approximately, which significantly increases drug concentration in tumor while reducing the distribution of chemotherapy drugs in peripheral blood, thereby minimizing systemic adverse reactions. Increasing cases have been reported regarding its use in combination with ICI-TKI for the conversion therapy of HCC. A study investigating the efficacy and safety of FOLFOX-HAIC combined with atezolizumab-bevacizumab in the treatment of advanced HCC demonstrated an ORR of 67.3% based on the mRECIST criteria and 44.2% based on the RECIST1.1 criteria. The median progression-free survival (PFS) of patients was 10.6 months (95% CI, 8.37–13.8).[15] Our center has also reported on the treatment outcomes of 20 patients with solitary CNLC stage Ib hepatocellular carcinoma who received FOLFOX-HAIC combined with ICI-TKI as neoadjuvant therapy. The ORR reached 70%, and the disease control rate was 100%. After treatment, 12 patients (60%) underwent hepatic tumor resection.[16]

Herein we present a case of a patient with massive HCC who underwent conversion therapy consists of PVL and systemic therapy with HAIC and lenvatinib-sintilimab. The patient was ultimately able to undergo a radical resection and has not shown any signs of recurrence during the post-operative follow-up period.

Case Presentation

The study was approved by the Ethics Committee of Guangxi Medical University, First Affiliated Hospital (approval number: 2025-E0754), and has been approved by the First Affiliated Hospital of Guangxi Medical University for the publication of relevant details. Written informed consent both for the procedures and for publication of the case details was obtained from the patient in this study. The patient is a 62-year-old male of Han ethnicity, with a height of 162 cm and a weight of 64 kg, and a BMI of 24.4 kg/m^2. He presented to our hospital in 22 March, 2022 with the complaints of "persistent upper abdominal distending pain for one week and a liver space-occupying lesion detected for four days". The patient developed persistent upper abdominal distending pain one week ago, without nausea, vomiting, abdominal distension, radiating pain, or jaundice of the skin and sclera. Blood tests conducted at a local hospital revealed an alpha-fetoprotein (AFP) level of 2718 ng/mL. An abdominal computed tomography (CT) scan indicated a large space-occupying lesion in the right lobe of the liver, suggesting the possibility of massive hepatocellular carcinoma. Four days ago, the patient was found to have "hepatitis B small triple positive" (a specific pattern of hepatitis B serology indicating chronic infection) during examination and had a history of clonorchiasis for many years, with history of

surgery or other treatment. Specialist physical examination revealed a soft abdomen without tenderness, and the liver and spleen were not palpable below the rib cage. After admission, upper-abdominal enhanced CT scan revealed a -8.1×11.5×8.7 cm mass-like hypodense lesion in the right lobe of the liver (Figure 1A–D), and enhanced magnetic resonance imaging(MRI) demonstrated an inhomogeneously enhancing signal lesion measuring 8.1×11.5×9.5cm in segments V, VI, and VIII of the liver during the arterial phase of the contrast-enhanced scan (Figure 1E and F). Esophageal varices were not detected during upper gastrointestinal endoscopy, and no invasion of the hepatic vessels or portal vein, nor the formation of tumor thrombi was observed. Laboratory tests showed an AFP level of 122,902.21 ng/mL, a des-gamma-carboxy prothrombin (DCP) level of 100.49 mAU/mL, a CEA level of 7.15 ng/mL, and a Child-Pugh grade of A (with a score of 5). The result of hepatitis B surface antigen (HBsAg), Hepatitis B e antibody (HBeAb), and hepatitis B core antibody (HBcAb) were 3392.51 IU/mL, >4.40 PEIU/mL, 9.20 PEIU/mL, and hepatitis C core antibody (HCV-Ab) was negative. The indocyanine green retention rate at 15 minutes (ICG-R15) was 2%. After 3D reconstruction modeling of the liver and calculation using the Chinese adult standard liver volume assessment formula (SLV = 11.508 × body weight + 334.024[17]), the FLR/SLV ratio was determined to be 34%. Due to the large tumor size, radical resection was not feasible, as hepatectomy with a substantial tumor burden could lead to PHLF and related complications. To determine the optimal treatment strategy, a multidisciplinary discussion (MDT) involving experts from hepatobiliary surgery, oncology, ultrasound, radiology, radiation oncology, and infectious diseases was organized. The patient was initially diagnosed with HCC (S5/6/8, Child-Pugh grade A, Chinese Liver Cancer (CNLC) stage Ib,

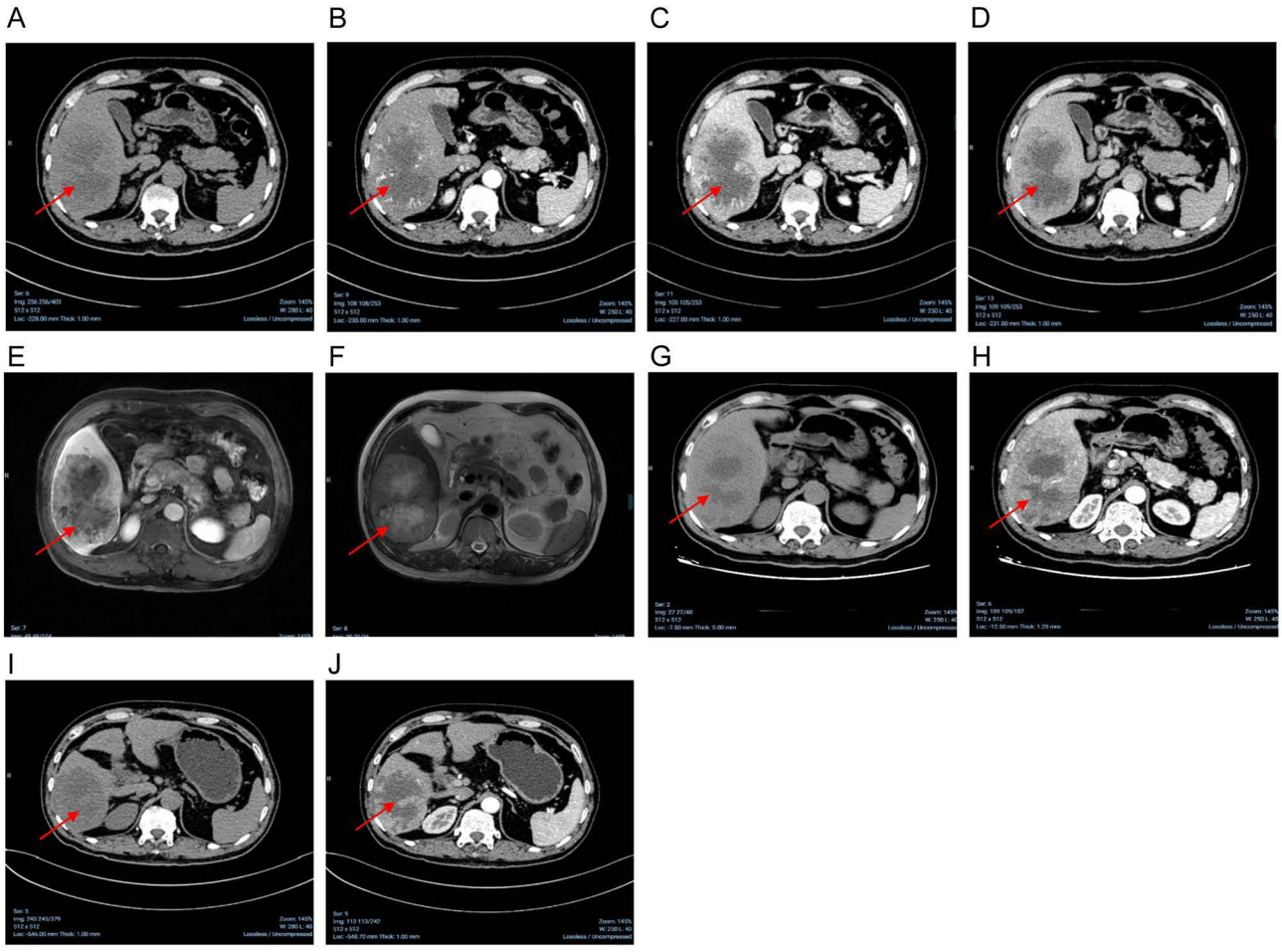

Figure 1 Imaging findings before stage I surgery. (**A**–**D**).Computed tomography (CT) scan revealed a 8.1×11.5×8.7 cm giant mass (red arrow) in right lobe of the liver. (**A**). Plain scan (**B**). Arterial phase (**C**). Portal venous phase; (**D**). Venous phase; (**E** and **F**).Magnetic resonance imaging(MRI) demonstrated an inhomogeneously enhancing signal lesion measuring 8.1×11.5×9.5cm in segments V, VI, and VIII of the liver (red arrow).(**E**).T1-weighted image (**F**).T2-weight image (G–N).Imaging findings of every cycle of treatment (**G** and **H**).CT after the first HAIC therapy (**I-J**).CT after the first formal cycle of conversion therapy. The red arrow points to the target lesion. The red arrow points to the target lesion.

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Barcelona Clinic Liver Cancer (BCLC) stage A). Doctors from all the departments above pointed that the large size of tumor (diameter > 5 cm), heavy tumor burden, unclear margins, and high DNA levels were all high-risk factors for postoperative recurrence of liver cancer. Besides, the inadequate volume of the left hepatic lobe posed a high risk for direct partial hepatectomy. Therefore, conversion therapy was considered, and it was recommended to undergo right portal vein ligation combined with local treatment (hepatic arterial infusion chemotherapy, HAIC) and targeted immunotherapy, aiming to control tumor progression while increasing the volume of the left hepatic lobe. Hepatectomy reevaluation will be conducted when the FLR/SLV exceeds 50%.

Stage I Surgery

The patient and their family decided to proceed with one cycle of the FOLFOX-HAIC regimen initially and make further decisions based on the observed changes in the patient's condition. Fully respecting the patient's wishes, the FOLFOX-HAIC treatment was administered on 29 March, 2022. After returning to the ward, the patient received continuous infusion chemotherapy with fluorouracil/oxaliplatin/leucovorin, and no specific discomfort was reported postoperatively.

On 15 May, 2022, the patient was admitted for the second time. After communicating with the patient's family and obtaining their signed informed consent, the MDT-recommended treatment strategy was approved. On 17 May, 2022, the patient underwent right PVL combined with cholecystectomy, followed by the first formal cycle of FOLFOX-HAIC treatment on the third postoperative day with sintilimab injection (200mg Q3W) and lenvatinib mesylate (12mg QD). Imaging re-examination after twice HAIC treatments showed a reduction in tumor size and an increase in the volume of the left liver lobe (Figure 1G–J). During the third hospitalization on 21 June, 2022, the patient received the second cycle of HAIC therapy combined with sintilimab-lenvatinib therapy. The patient also received anti-HBV therapy (oral entecavir 0.5 mg once daily) and liver-protective treatment throughout this period. On 25 July, after two cycles of conversion therapy, the patient's AFP and DCP levels significantly decreased compared to previous measurements (AFP: 6,226.97 ng/mL; DCP: 36.18 mAU/mL)(Figure 2). Enhanced MRI revealed that the original lesion had shrunk to 7.1×4.2×5.9 cm, with reduced tumor activity (Figure 3A and B). The FLR/SLV was 52.6%, which mets the criteria for right hepatectomy. Following the second MDT discussion, it was decided to administer one more cycle of FOLFOX-HAIC combined with ICI-TKI therapy to achieve a deeper conversion response before proceeding with radical resection.

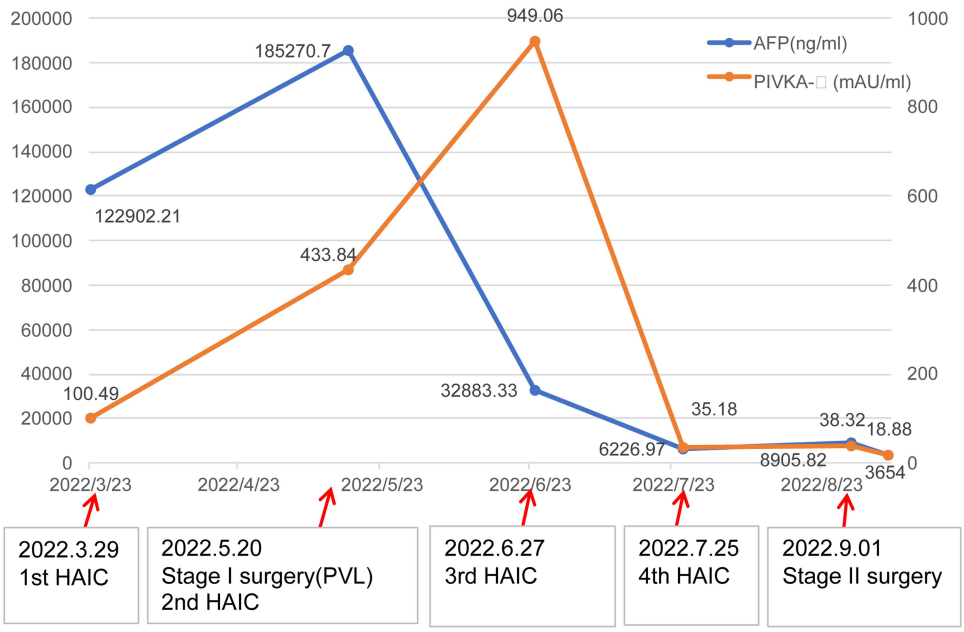

Figure 2 Dynamic changes in tumor markers during the treatment. A significant concurrent decrease in both abnormal prothrombin (PIVKA-II) and alpha-fetoprotein (AFP) levels. The red arrows point to the corresponding timeline.

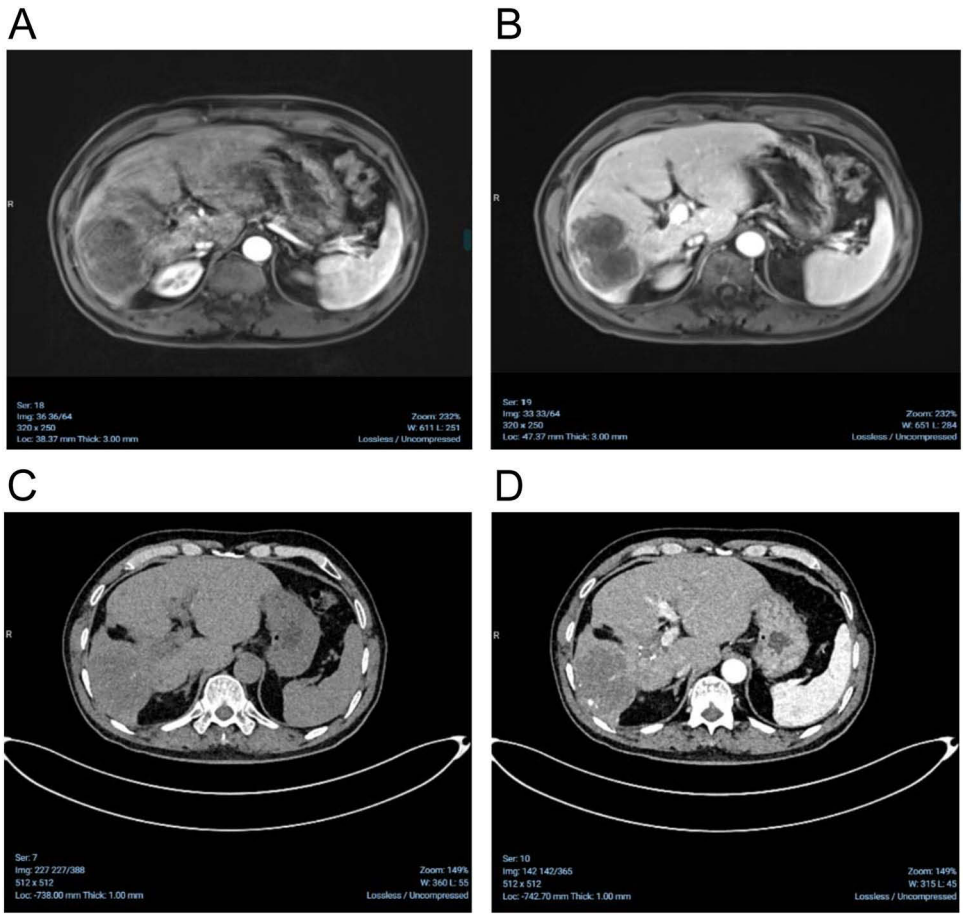

Figure 3 (**A** and **B**). Magnetic resonance imaging(MRI) after the second formal cycle of conversion therapy (**C** and **D**). Computed tomography (CT) after the third formal cycle of conversion therapy. The red arrow points to the target lesion.

Stage II Surgery

On 27 August, 2022, the patient was readmitted. An enhanced CT scan revealed that the original lesion had shrunk to 6.8×5.0×5.9cm (Figure 3C and D). The second contrast-enhanced ultrasound (CEUS) indicated that the focal liver lesion was still classified as LR-5 according to the Liver Imaging Reporting and Data System (LI-RADS). Two focal lesions were newly identified in segment IV, with a characteristic "fast-in and slow-out" enhancement pattern on contrast-enhanced CT scans, while the lesion appears as a hypodense shadow on plain CT scans. Thus hemangioma considered as a possible diagnosis. After 3D reconstruction of the liver, the calculated future liver remnant volume (FLR/SLV ratio after right hepatectomy was 65%) indicated an improved conversion response, with an ICG R15 of 6.2% following right hepatic inflow occlusion. Peripheral blood CD4+ T cells and CD8+ T cells had increased compared to previous levels (CD4+ T cells: 38.88% to 43.69%; CD8+ T cells: 15.99% to 21.28%). After obtaining surgical consent from the patient and their family, a right hepatectomy was performed on 1 September, 2022. Intraoperative findings included no ascites, slight atrophy of the right hepatic lobe, no signs of cirrhosis, a red color, sharp margins, a smooth surface, and soft texture. During the initial exploration, the ischemic demarcation line between the right and left lobes was observed. After releasing adhesions and intermittently occluding the first hepatic hilum, the right hepatic lesion was completely resected using an ultrasonic scalpel. Subsequently, the right hepatic pedicle and right hepatic vein were individually divided using a linear stapler. After tumor resection, the remaining liver showed no signs of ischemia or congestion. Finally, absorbable gelatin sponges and a surgical drain were placed on the transverse section. The operation lasted 285 minutes, with an intraoperative blood loss of 350 mL and an autologous blood transfusion of 300 mL. Pathological examination revealed extensive necrosis of the tumor tissue, with residual viable tumor cells (approximately 30%) surrounding it. The

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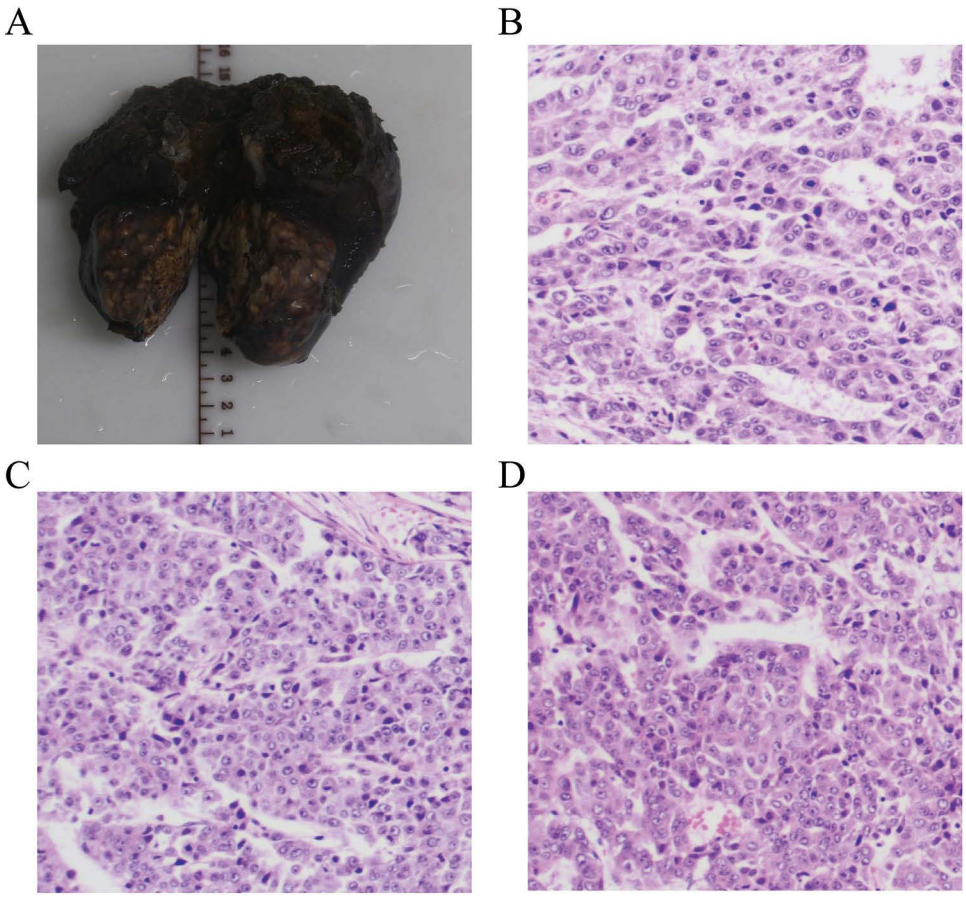

Figure 4 Surgical specimen and histopathological images. (**A**).The open resected specimen with HCC; (**B**–**D**).Pathological examination of tissue section.

microvascular invasion (MVI) grade was M0. The surrounding liver tissue exhibited chronic inflammatory changes (G2S1), with an Ishak score of 4 for inflammation and 2 for fibrosis. Immunohistochemical results showed Arginase-1 (weakly positive), Glypican-3 (positive), Hepatocyte (focally positive), CD34 (indicating capillarization, >50 vessels/200x field), CK7 (negative), CK19 (positive), CDX-2 (focally weakly positive), Ki-67 (70% positive in hotspots), NM23 (positive), P21 (partially positive), P53 (30% positive), and VEGF (negative). The mass in liver segment S4 was consistent with a cavernous hemangioma. Postoperative laboratory tests showed AFP: 3654.00 ng/mL, CA125: 42.8 U/mL, alpha-fetoprotein variant (AFP-L3): 734.9 ng/mL, AFP-L3 ratio: 20.12%, while abnormal prothrombin, CEA, CA199, and CA153 showed no significant abnormalities (Figure 4). A postoperative CT scan revealed fluid and air accumulation in the surgical area. The patient improved and was discharged 8 days after surgery. Liver function indicators returned to normal within 1 month postoperatively. The patient continued to receive sintilimab injection (200mg Q3W) on 28 September, 2022, 22 October, 2022, 17 November, 2022, and 19 December, 2022 combined with lenvatinib (12mg QD). Lenvatinib was discontinued in March 2025 (Figure 5). Laboratory and imaging examinations conducted at a local hospital as of September 1, 2025, showed no evidence of disease recurrence while HBV DNA remains at a low level (<100 IU/mL), and the patient is currently in good general condition.

Discussion

HCC is a highly heterogeneous malignant tumor with an insidious onset. At present, radical resection remains the preferred treatment for early-stage HCC. However, many patients require extensive liver resection due to factors such as large tumor size, multiple tumors, or inadequate resection margins due to the tumor is adjacent to vital vascula.[18,19] Yet, they cannot undergo one-stage radical resection owing to insufficient future liver remnant (FLR) volume, decreased hepatic functional tolerance, and poor overall physical conditi[4] on that renders them unable to withstand radical resection.

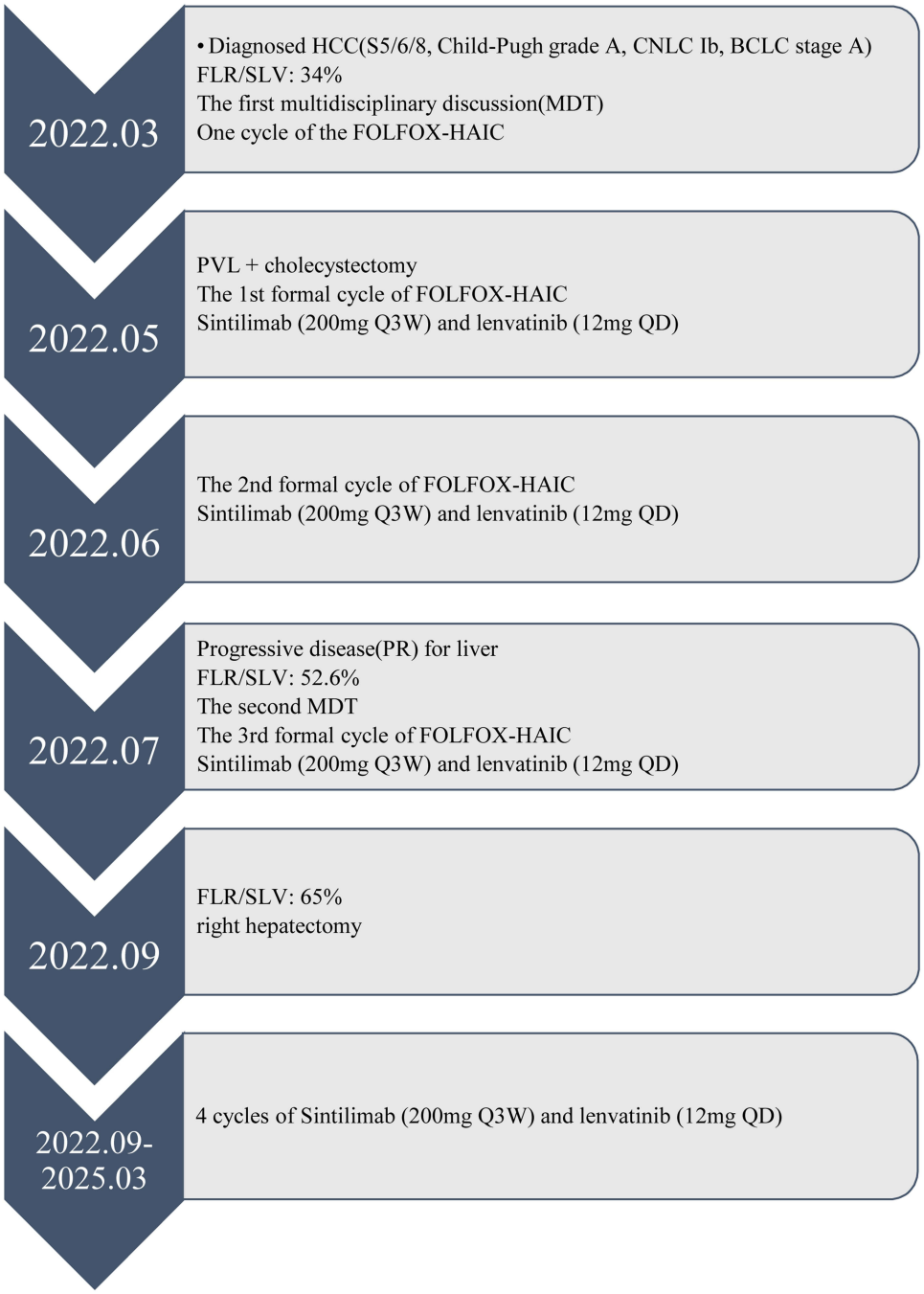

Figure 5 Timeline of the patient's disease progression.

In the past, these patients could only receive non-surgical treatments, which offered a very limited survival.[20] Therefore, increasing the FLR in HCC patients with insufficient residual liver volume—that is, conversion therapy of HCC with inadequate residual liver volume—holds significant importance for the long-term prognosis.

Conversion therapy encompasses both the surgical transformation of unresectable HCC into resectable HCC and the conversion of patients with a poor prognosis (CNLC stage IIb—IIIa) into those with a better prognosis after resection.[21] It represents one of the crucial avenues for patients with potentially resectable HCC to achieve radical resection and long-term survival. The China "Standard for diagnosis and treatment of primary liver cancer (2024 edition)"[4] recommend

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adopting a multimodal, high-intensity anti-tumor treatment strategy to facilitate conversion, while simultaneously ensuring treatment safety and maintaining quality of life.

Conversion therapy includes functional FLR conversion and oncological conversion. The former primarily involves portal vein ligation and embolization to induce compensatory hypertrophy of the remaining liver volume, thereby enhancing liver reserve function to meet the criteria for second-stage resection. The latter mainly controls tumor progression through local treatments (TACE;[22,23] HAIC;[24] radiotherapy[25–27]).

Lenvatinib has been recommended as a first-line treatment drug for HCC by guidelines for the Diagnosis and Treatment of HCC worldwide,[3–5] and clinical trials related to Lenvatinib have demonstrated positive outcomes.[12,28,29] A real-world study on a triple regimen combining systemic therapy (lenvatinib plus a PD-1 inhibitor) and radiation therapy in patients with HCC and portal vein tumor thrombus (PVTT) reported a 2-year OS of 15.4%, with no severe adverse reactions.[30] A single-arm, prospective study demonstrated that for advanced and intermediate-stage uHCC, the combination of lenvatinib and Anti-PD-1 therapy exhibited favorable efficacy as conversion therapy (conversion success rate:55.4% (31/56); ORR:53.6% per mRECIST and 44.6% per RECIST 1.1; mPFS: 8.9 months, mOS: 23.9 months; R0 resection rate: 85.7%) with controllable safety profile.[29] Additionally, results from a Chinese multicenter Phase III study (ORIENT-32) showed that the combination of sintilimab monoclonal antibody and a bevacizumab monoclonal antibody analog significantly outperformed the sorafenib group, with a 43% reduction in the risk of death and a 44% reduction in the risk of disease progression compared to the sorafenib group.[14] This regimen has also been recommended as one of the first-line treatment options for HCC in " Standard for diagnosis and treatment of primary liver cancer (2024 edition)"[4] Therefore, we believe that Lenvatinib-sintilimab can achieve the goals of controlling tumor progression and even reducing tumor size in the conversion therapy for HCC.

The main feature of this study lies in our successful implementation of conversion therapy for a case of massive HCC (8.1×11.5×8.7 cm), with immunohistochemistry revealing CK19 (+) expression indicative of dual hepatocellular and cholangiocarcinoma characteristics. Through a combination of PVL, HAIC, and sequential ICI-TKI therapy, the lesion achieved partial response (PR) according to mRECIST criteria after 3 formal cycles (9 weeks) of treatment, accompanied by an increase in left liver volume and hepatic reserve function, meeting the criteria for second-stage surgical resection. Furthermore, no recurrence in the patient until the follow-up of August 15, 2025. We believe that during the conversion therapy process, PVL promoted left liver lobe regeneration, while FOLFOX-HAIC combined with ICI-TKI provided local tumor control and systemic treatment. This tripartite collaboration effectively promoted compensatory hypertrophy of the remaining liver while precisely treating the tumor, yielding expected conversion outcomes. In addition, Govaere et al[31] demonstrated that CK19 could advance through the PDGFRα-LAMB1-CK19 axis. Lenvatinib, as an inhibitor of PDGFRα, might exert specific effects on CK19-positive HCC,[32] which could potentially serve as a direction for further subsequent research. And the patient's long-term and regular administration of Lenvatinib-sintilimab after surgery may also be the reason for the patient's prolonged survival despite the pathological result not achieving major pathological response (MPR) after conversion therapy. This may, to a certain extent, also reflect the importance of postoperative adjuvant therapy in the treatment of HCC.

The PLACES study[33] that was published by our team in 2025 demonstrated that, under the PVL combined with camrelizumab-apatinib regimen, 66.7% of patients met the criteria for second-stage resection, with an ORR of 26.7% and a 1-year event-free survival (EFS) rate of 63.3%. Compared to the traditional conversion therapy surgery associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), the PLACES study showed lower rates of surgical complications, reduced overall treatment costs, and improved short-term survival rates. In this case, we added HAIC to the PLACES regimen and replaced the ICI-TKI drugs with sintilimab-lenvatinib, which we believe played a similar role during the conversion process. We hope that the inclusion of HAIC can better control the tumor and shorten the interval between PVL surgery and radical resection. In the PLACES cohort, patients received an average of 5.25 cycles (Q3W) of conversion therapy before undergoing radical resection,[33] and prolonged treatment duration may lead to progressive disease (PD) during treatment. In this case, the patient met the criteria for radical resection after the 2 cycle of conversion therapy (post-PVL surgery), with a FLR/SLV ratio of 52.6% resulting in a shorter conversion therapy duration compared to the PLACES study (an additional cycle was added to enhance surgical safety). In addition, the ICGR15 after the PVL surgery was 6.2% (<19.8%), and no grade B/C PHLF was observed postoperatively, which are also consistent with the findings of our team's previous research.[34]

Conclusion

This case report exhibited a safe and effective conversion therapy of TSH plus HAIC and TKI-ICI in treatment of massive HCC, building upon our team's research to explore more efficient conversion therapy outcomes. The inclusion of local therapy with HAIC has significantly shortened the duration of conversion therapy. Therefore, we wish to share this novel method for treating early stage unresectable HCC and looking forward to large-sample prospective studies to further explore the efficacy and safety of this treatment regimen.

Data Sharing Statement

Correspondence and requests for materials should be addressed to Hao Su.

Ethics Declarations

The authors are accountable for all aspects of this work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Ethics Committee of Guangxi Medical University, First Affiliated Hospital (approval number: 2025-E0754). The patients provided their written informed consent to participate in this study. All procedures were performed in accordance with the principles of the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that taking part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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