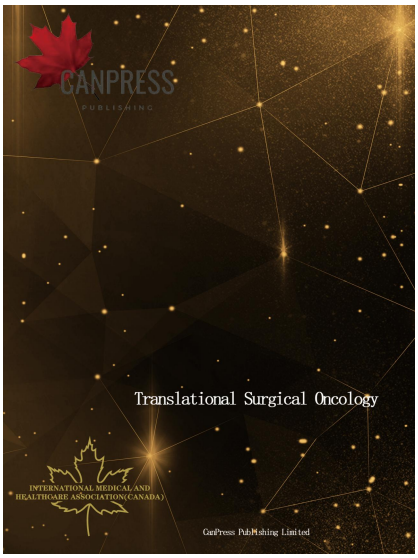
Surgical Conversion for Initially Unresectable Locally Advanced Hepatocellular Carcinoma: case series



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Abstract

Conversion therapy has been established as a strategy that combines chemotherapy and additional surgical resection for the treatment of live cancer with unresectable metastases. Patients with potentially resectable or even unresectable advanced hepatocellular carcinoma (HCC) can undergo radical surgical resection after conversion therapy, and the postoperative treatment effect is good. Here we reported 4 cases of unresectable HCC who underwent radical surgical resection after conversion therapy. We also performed literature review of conversion therapy for HCC. We found that success rate of conversion therapy for patients with advanced HCC was low. Most of the patients with successful conversion therapy were patients younger than 60 years old. We need explore better strategies of conversion therapy for clinical treatment of liver cancer.

Keywords: Conversion therapy; Hepatocellular carcinoma; PD-1; Hepatic functional reserve

Introduction

The number of liver cancer in China accounts for 46.7% of the total number of liver cancer patients in the world, and the 5-year survival rate was less than 15%[1-3]. Comprehensive treatment based on surgery is the main treatment method for liver cancer. Because the onset of liver cancer is insidious and there are no obvious symptoms in the early stage, the patients are usually in the middle and late stages at the time of treatment, and the opportunity of surgical resection is lost, resulting in a median survival of only about 2 years [4,5]. With the advent of liver cancer targeted drugs and immune checkpoint inhibitors such as programmed death protein 1 (PD-1), more treatment options are available for liver cancer and clinical treatment efficacy and prognosis of liver cancer are significantly improved. Recent studies have shown that PD-1 combined antiangiogenic drug can achieve a response rate of 30% and a median survival of more than 20 months in HCC patients[6-9] . Conversion therapy has been established as a strategy that combines chemotherapy and additional surgical resection for the treatment of gastrointestinal cancers with unresectable metastases. However, it is unclear whether patients who cannot undergo surgical resection can undergo surgical resection after neoadjuvant treatment. A study reported that patients with potentially resectable or even unresectable advanced liver cancer can undergo radical surgical resection after conversion therapy, and the postoperative treatment effect was good[10]. Therefore, here we reported 4 cases of selected patients who underwent conversion therapy successfully. The details of patient condition, treatment and prognosis are described below.

Patients and Methods

The general information of four patients was list in Table 1. The inclusion criteria: Patients were all diagnosed as liver cancer before operation. After multidisciplinary team (MDT) discussion, they received a conversion therapy. Patients reveive operation finally. The exclusion criteria: Patients who

are ultimately inoperable. Patients with distant metastasis of tumor. Follow-up time from operation to Jun 1,2022.

Case Presentation

Case 1

A 45 years old women came to our department with upper abdominal discomfort for 2 weeks. The laboratory examinations showed that Hepatitis B virus-deoxyribonucleic acid (HBV-DNA) and AFP were high (Table 1 and 2), albumin was 29 g/L, platelet count (PLT) was 63×109/l, ALT, AST and blood cell count were normal. Enhanced magnetic resonance imaging (MRI) of upper abdomen suggested the possibility of HCC accompanied with inferior vena cava tumor thrombus. The right branch of portal vein was compressed, with thickened trunk (Figure 1 A, B). Conventional transcatheter arterial chemoembolization (c-TACE) treatment was given for 4 times: at initial visit, 2 months, 4 months and 6 months later, respectively. Lenvatinib (12 mg, once a day) and camrelizumab (200 mg, once every 3 weeks, a total of 8 times) were used by oral and intravenous infusion respectively. At the 7th month, she was transferred to surgery department to evaluate the surgical indications. Another MRI examination showed that the tumor was liquefied and necrotic, according to the RECIST criteria, the tumor volume was reduced, and the inferior vena cava tumor thrombus had regressed (Figure 1 C, D). The change of blood AFP dropped significantly to 45 ng/ml before operation. Blood HBV-DNA was normal. The liver function was child-Pugh grade A. Preoperative three-dimensional (3D) reconstruction showed that the tumor was close to the right branch of portal vein, invaded the right hepatic vein and was close to the middle hepatic vein (Figure 1 E, F). It was planned to perform the resection of liver segments S7 and S8, and the remaining liver volume was 67% (if the right hemihepatectomy was performed, the remaining liver volume was only 40%, considering that the tumor had been necrotic, local tumor resection could retain more liver volume). The result of indocyanine green retention test (ICG-r15) was 9.3%. Then open hepatectomy of segments S7 and S8 + cholecystectomy + dissection of abdominal adhesions was performed. During the operation, the liver showed sclerosis and volume atrophy. The tumor was located in segments VII and VIII, protruding from the diaphragmatic surface of the liver. The right hepatic vein was cut off, the middle hepatic vein and the right branch of portal vein were preserved, and the tumor was resected. The patient was discharged from the hospital on the eighth day after operation. No recurrence was found in the follow-up for 11 months after operation, and AFP was normal. Prophylactic use of PD-1 for treatment was continued for half a year after operation and then discontinued.

Case 2

A 40 years old male come to our hospital for the reason of finding a tumor by physical examination. The ALT, AST and blood cell count were normal (table 1 and 2). CT and 3D showed that a tumor invaded the end of the right anterior branch and the right posterior branch of the portal vein, and was accompanied by arterial phase enhancement (Figure 2 A, B, C). Right hepatectomy should be performed, but the remaining liver volume was only 35%, and the risk of postoperative liver failure was high. C-TACE treatment was performed twice (first visit and 2 months later). The patient received targeted drug and immunotherapy drug therapy (lenvatinib 12 mg daily and camrelizumab 200 mg, once every 3 weeks). The possibility of surgery was reassessed after 3 months. Laboratory examination: blood AFP was 96 ng/ml, liver function of Child-Pugh was class A, normal HBV-DNA, and the ICG test result was 5%. CT and 3D reconstruction showed that the tumor volume was significantly reduced, according to the RECIST criteria, the tumor and the right anterior branch of the portal vein became more distant (Figure 2 D, E, F). We proposed a new surgical method: resection of segments S5, 6, and 7 of the liver, and the remaining liver volume was 79.4%. Fluorescence laparoscopic hepatic segments S5+S6+S7 resection + cholecystectomy was performed. During the operation, the middle hepatic vein was preserved, and the right branch of portal vein and the right hepatic artery were cut off. The operation lasted 3.5 hours. The first hepatic portal was blocked 6 times during the operation (15 min each time), and the intraoperative bleeding was about 300 ml. The patient was discharged safely on the 7th day after operation. The postoperative pathological examination showed cholangiocarcinoma. Oral lenvatinib was continued two weeks after operation. No tumor recurrence was found during the follow-up of about 16 months, and the blood AFP was normal.

Case 3

A 50 years old male come to our hospital for the reason of finding a tumor by physical examination. He received surgery for appendicitis 10 years ago and received surgery for Budd-Chiari syndrome 20 years ago. Laboratory examination: blood AFP was 12500 ng/ml, HBV-DNA was normal, and liver function of Child-Pugh was class A. CT and 3D reconstruction showed that a huge tumor in the right liver invaded the right branch of portal vein, the root of the right hepatic vein, and the middle hepatic vein (Figure 3 A, B, C, D). Right hemihepatectomy was planned, but the remaining liver volume was only 41%. The conversion therapy protocol was: c-TACE + targeted lenvatinib + camrelizumab. TACE was performed 5 times during 8 months, camrelizumab was injected intravenously 9 times (once every three weeks), and 8 mg lenvatinib was administrated orally every day. After 8 months, re-examination of CT and 3D reconstruction showed that the tumor volume decreased significantly (Figure 3 E, F, G, H), according to the RECIST criteria, The distance

between tumor and portal vein became further. AFP dropped significantly to 2,100 ng/ml. ICG result was 4.8%. It was found that the tumor was located in S7+S8 and invaded the diaphragm during the operation, and "liver S7 + S8 resection + partial resection of diaphragm + diaphragm repair + cholecystectomy" was performed to keep the right branch of portal vein and the right posterior inferior hepatic vein. The operation lasted for 5 hours and the first hilar was blocked 10 times (15 minutes each time). Intraoperative bleeding was about 2,000 ml. The postoperative pathological analysis showed that the tumor was hepatocellular carcinoma. Liver function and other indexes were examined every day after the operation. The transaminase gradually increased to 10,000 U/L and then decreased, bilirubin increased from 40 umol/L to 65 umol/L, and Pt increased to 29s and then decreased. Creatinine gradually increased to 515 umol/L after operation and decreased after CRRT treatment. The patient died of multiple organ failure on the 10th day after operation, perhaps due to immune system collapse and liver failure.

Case 4

A 55 years old male come to our hospital for the reason of finding a tumor by physical examination. Laboratory examination (Table 1 and 2): blood cell count and ALT, AST were normal. MRI showed that the diameter of the right liver tumor was about 5.5 cm. The formation of tumor thrombus in the main and right branches of portal vein was judged as type III according to Cheng's classification (Figure 4 A, B). ICG R15 was 4.1%. C-TACE was performed once at the first visit; 8 mg lenvatinib was administrated orally for 3 months; 200 mg camrelizumab was injected intravenously for 4 cycles (once every 3 weeks); Radiotherapy was mainly used to treat portal vein tumor thrombus (54 Gy/18F). The tumor was evaluated after 3.5 months. Laboratory examination: leukocyte 2.92×109/L, platelet 111×109/L, AFP 383 ng/ml, HBV-DNA normal, liver function index normal (Child A class). According to the RECIST criteria, MRI showed that the enhancement of liver tumor was weakened, the portal vein tumor thrombus was smaller, and regressed to the right branch of portal vein (Figure 4C, D). The result of ICG R15 was 14.3%. The proposed operation method was right hemihepatectomy + cholecystectomy, and the remaining liver volume was 70%. The operation time was about 3 hours, and the first hilar was blocked for 5 times (15 minutes each time). Moderate ascites occurred after operation, which improved after liver protection and diuretic treatment, and the patient was hospitalized for 2 weeks. After discharge, he continued to take lenvatinib and PD-1, and discontinued PD-1 half a year later. No tumor recurrence was found after 16 months of follow-up.

Discussion

With the development of non-surgical treatment such as drugs, the overall median survival of patients with inoperable liver cancer has improved to 20 months after comprehensive treatment [10-12]. In contrast, the median survival of liver cancer patients with macrovascular invasion is only 12-15 months after surgical resection[13], less than that of patients with non-surgical treatment. Therefore, it is considered that direct surgical treatment is not the first choice for these patients. Instead, conversion therapy has been proposed to reduce tumor load and volume, improve R0 resection rate and reduce surgical risk. At present, there is no unified opinion on the scheme selection of conversion therapy and the advantages and disadvantages of various schemes. The following schemes could be important in the treatment of liver cancer: lenvatinib combined with pabolizhu monoclonal antibody, bevacizumab combined with atilizhu monoclonal antibody, bevacizumab analogue combined with cindili monoclonal antibody, and apatinib combined with carrelizhu monoclonal antibody[11,12,14]. Interventional therapy in liver cancer treatment mainly includes two methods: the traditional TACE, and the more popular hepatic artery infusion chemotherapy (HAIC). These two methods are effective in the comprehensive treatment of unresectable liver cancer[15-17]. HAIC combined with target free systemic therapy has shown good curative effect[18]. In addition, HAIC is better than TACE in conversion treatment of large liver cancer, especially liver cancer with large vessel invasion[19]. Radiotherapy is effective in the treatment of liver cancer with portal vein tumor thrombus. Studies have shown that preoperative intravenous tumor thrombus radiotherapy for patients with potentially resectable liver cancer can reduce the stage of tumor thrombus from Cheng's type III to type II or even to type I. The prognosis and survival of patients who underwent conversion therapy were significantly higher than those who underwent direct surgery[20,21]. In addition, TACE combined with portal vein particle strip implantation for local radiotherapy of liver cancer complicated with portal vein tumor thrombus achieved good curative effect, and the OS of patients (9.8 months) was significantly longer than that of patients treated with TACE alone (5.2 months)[22]. The survival of patients with portal vein stent implantation was better than that of patients with portal vein stent implantation alone Therefore, radiotherapy plays an important role in the comprehensive treatment of liver cancer, especially for large vessel tumor thrombus[23]. In this report, all 4 cases with portal vein tumor thrombus underwent surgery.

Our experience with conversion therapy for liver cancer in our center indicated that the success rate of conversion therapy was low (about 20%). The 4 cases reported in this study were only patients who had successfully performed the operation. However, there are still some patients who failed conversion therapy, including a 60-year-old female with lung metastasis after 4 months of treatment with TACE + lenvatinib + camrelizumab; and a 65-year-old male with huge tumor in the right liver who developed intrahepatic metastasis after 3 cycles of TACE + lenvatinib + camrelizumab treatment because of insufficient residual liver volume, and so on. In our

study, all 4 patients were treated with lenvatinib and camrelizumab. Although they were not the first-line drugs recommended by the guidelines at that time. But there have some clinical trial to show benefit of lenvatinib and camrelizumab in treating liver cancer. And they have now been recommended for the first-line treatment of liver cancer. It is important to take the opportunity for operation after conversion therapy. Generally, it is about 4-6 months based on the reduction of tumor volume, the reduction of AFP, the change of liver function and other indicators. Most patients who fail to undergo surgery after conversion treatment for more than 6 months are more difficult to get the opportunity for conversion therapy. Moreover, most of the patients with successful conversion therapy are patients younger than 60 years old. We believe that young patients may respond better to PD-1 or targeted drugs to activate the autoimmune system to inhibit tumor. Some studies showed that the patients achieved remission based on imaging after target immunotherapy, the tumor was obviously liquefied and necrotic, and cancer cells could not be detected by pathological examination. However, cancer could recur and metastasize within 1 to 1.5 years, so it is still recommended to select the appropriate time for surgical resection after conversion therapy. Moreover, some patients can achieve remission based on pathological analysis[10,24,25]. Whether such patients can benefit from continued target immunotherapy in the long term need to be further explored. We believe that pathological remission may be incomplete, and surgical resection should be performed. For treatment time of targeted immune drugs, we stopped targeted drugs (antiangiogenic drugs) at least 2 weeks before operation, and PD-1 was stopped 4 weeks before operation, similar to the experiences of other researchers [26-28]). After operation, targeted drugs were used for more than 1 year, and PD-1 was used for more than half a year. For postoperative complications, we found high risk of postoperative liver failure in case 3. Although the preoperative examination of the patient was consistent with hepatectomy, there was acute liver failure after operation. The reason may be that the preoperative liver function evaluation strategy is not suitable for the patients who underwent reoperation after target immunotherapy, such as liver volume, ICG measurement and other indicators. As we all know, PD-1 causes damage to liver function. Patients who undergo surgical resection after treatment may suffer two liver blows and increase the risk of postoperative liver failure. At present, there are few studies on the evaluation strategy of liver function in patients with liver cancer after target immunotherapy. It may be necessary to find new indicators for hepatic functional reserve. In case 4, the ICG was 4.1% before drug treatment and 14.3% after drug treatment (preoperative), which indicates that the liver function is significantly weakened, and the impact of drugs on the liver is large. Therefore, the impact of surgical resection on the liver leads to a higher postoperative risk than that of patients without conversion therapy.

One important aspect of conversion therapy of liver cancer is to select appropriate drugs for the patients after operation. If a patient is insensitive to the drugs during conversion therapy, are there any drugs available for the patient if the tumor relapses after the operation? In contrast, if conversion therapy is successful, it indicates that the patient is sensitive to first-line treatment drugs and can achieve better prognosis after operation. This is similar to the experience of neoadjuvant therapy for pancreatic cancer. If neoadjuvant therapy cannot be continued, it is better to give up surgery because it is difficult for the patients to benefit from surgery.

Conclusion

There are still controversies on conversion therapy of liver cancer. We need explore better strategies of conversion therapy for clinical treatment of liver cancer. How to select the combination of treatment can improve the success rate of conversion and reduce the incidence of complications.

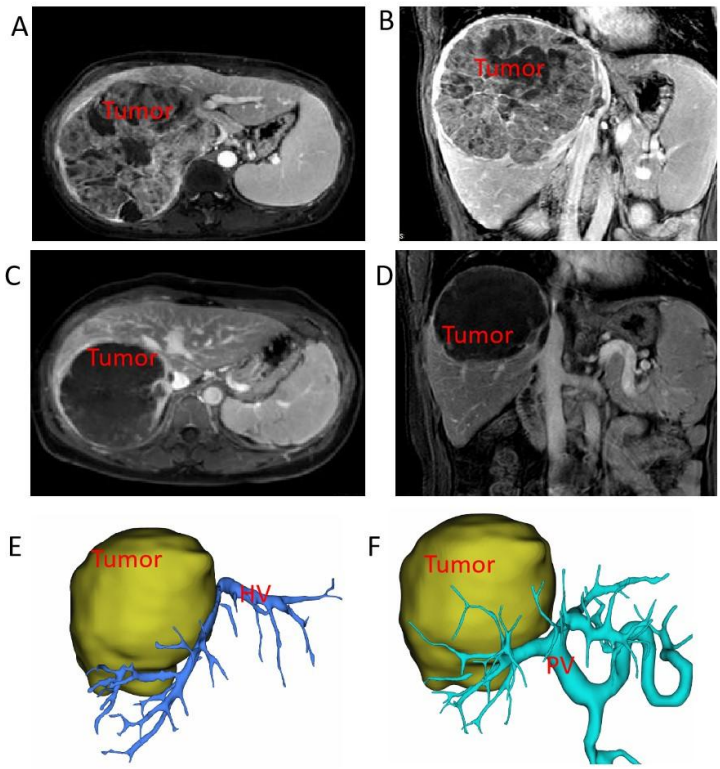

Figure 1. Comparison of MIR before and after conversion therapy. MRI images at the first visit showed that the tumor volume was large and the enhancement in arterial phase was obvious (A, B); MRI image before operation showed that the tumor was obviously liquefied and necrotic, and the inferior vena cava tumor thrombus had no arterial phase enhancement (C, D); preoperative 3D reconstruction to clarify the relationship between tumor and portal vein and hepatic vein (E, F).

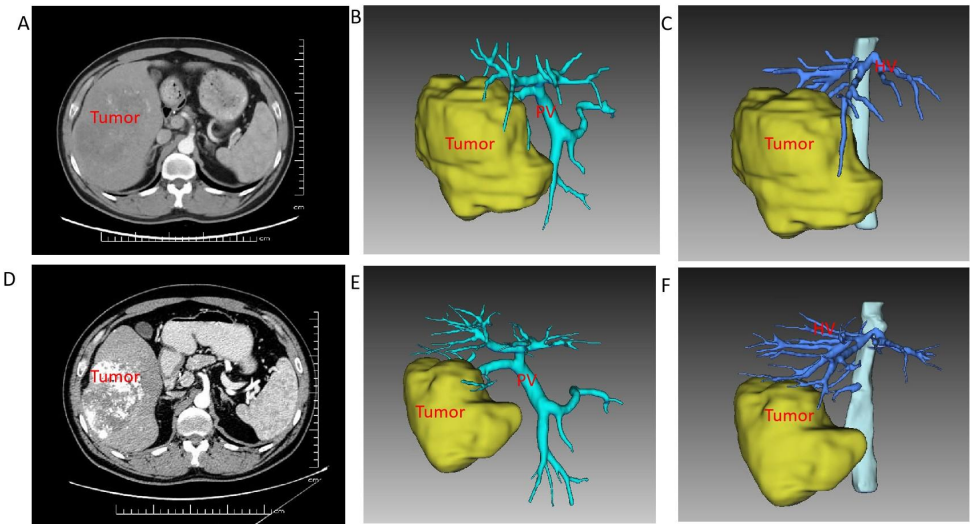

Figure 2. CT findings at the initial visit showed obvious enhancement in the arterial phase of the tumor, and the 3D reconstruction showed that the tumor invaded the end of the right anterior branch and the right posterior branch of the portal vein (A, B, C); CT findings and 3D reconstruction after conversion therapy showed lipiodol deposition in the tumor, weakened tumor enhancement and reduced volume (D, E, F).

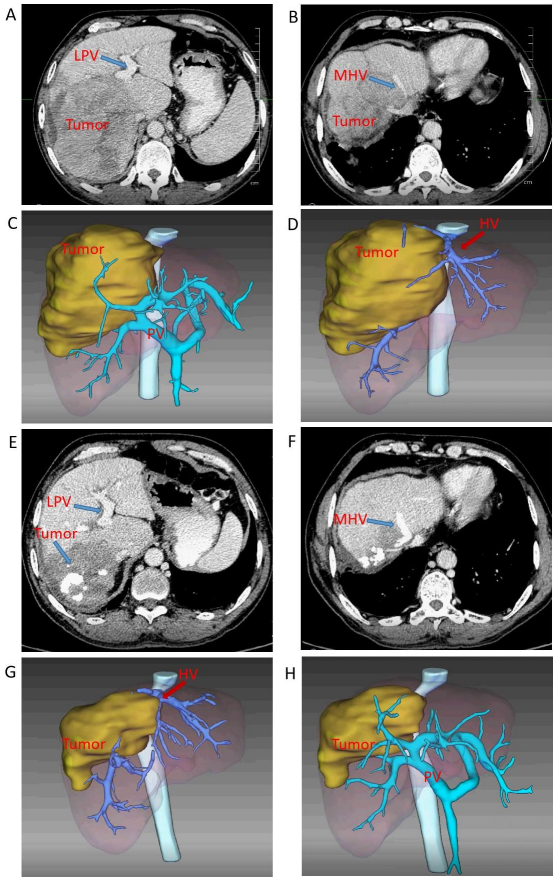

Figure 3. Enhanced CT before operation showed that the tumor was enhanced in venous phase and invaded the right branch of portal vein, right hepatic vein and middle hepatic vein, and the 3D reconstruction further determined the relationship between the tumor and portal vein and hepatic vein (A, B, C, D); Enhanced CT before operation showed that the enhancement of the tumor was weakened, the tumor volume was reduced, and the tumor was far away from the right branch root of portal vein (E, F, G, H). LPV: Left hepatic portal vein. MHV: Middle hepatic vein.

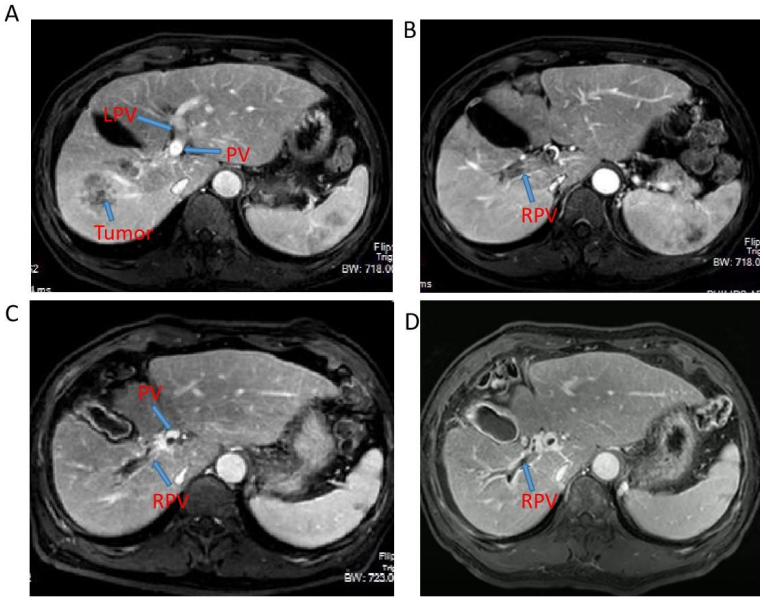

Figure 4. MRI examination at the initial treatment found that the tumor was located in the right liver, showing multi-nodule type, with obvious enhancement in arterial phase, accompanied by cancer thrombus in the main portal vein and right branch (A-B);After conversion therapy, the preoperative MRI showed tumor necrosis, weakened enhancement, obvious necrosis of portal vein tumor thrombus. The tumor thrombus in the main trunk regressed to the right branch (C-D). PV: portal vein. LPV: Left hepatic portal vein. RPV: Right hepatic portal vein.

Table 1 The clinical data of four patients. Bef: before surgical resection; Aft: after sugical resection.

Case	Clinical data				Disease description (initial)			Treatment (initial)	Outcome
	Age	Sex	HBV-DNA (copies/ml)		Child-pugh	Symptom	Tumor diameter (cm)	BCLC stage A/B/C	
			Bef	Aft					
1	45	Female	6.9×10^5	<200	A	upper abdominal discomfort	18	C	c-TACE +lenvatinib +camrelizumab	The operation was successfully performed. No recurrence after follow-up for 11 months.
2	40	Male	2.2×10^3	<200	A	None	15	C	c-TACE +Apatinib +camrelizumab	The operation was successfully performed.No recurrence after follow-up for 16 months.
3	50	Male	<200	<200	A	None	14	C	c-TACE +lenvatinib +camrelizumab	The operation was successfully performed.Perioperative death.
4	55	Male	2.1×10^3	<200	A	None	5.5	C	c-TACE +lenvatinib +camrelizumab +radiotherapy	The operation was successfully performed.No recurrence after follow-up for 16 months.

c-TACE: Conventional transcatheter arterial chemoembolization; AFP: alpha-fetoprotein; HBV: Hepatitis B virus; BCLC: Barcelona Clinic Liver Cancer.

Table 2 The AFP (ng/ml) value before and after surgical resection. 0 indicate the month of surgical resection.

Time (Months)	Case 1	Case 2	Case 3	Case 4
-8			12500	
-7	2500		10020	
-6	1800		9978	
-5	1001		6200	
-4	620		5113	
-3	113	316.16	3801	10538
-2	101		4151	
-1	51	211	2100	783
0	45	96	2102	383
1	20		15	36
2				
3	15	16	11	17

Conflict of interest

The authors declare no conflict of interest.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author contribution

ZDY and SWL: manuscript writing. WQ: pathological review. WDD, ZS, LiuZ: Image picture review and acquisition of data. LuZ: conception and critical review. All authors contributed to the article and approved the submitted version.

Ethics approval

The study was approved by the Ethics Committee of Bengbu Medical College (No. 20211123) and all patients provided signed consent.

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