Original Article

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Conversion therapy followed by surgery and adjuvant therapy improves survival in Barcelona C stage hepatocellular carcinoma — A propensity score-matched analysis

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SUMMARY: Conversion therapy with a combination of tyrosine kinase inhibitor and anti-programmed death-1 antibody sequential surgery and postoperative adjuvant therapy has shown improved survival benefits in patients with Barcelona C stage (BCLC-C) hepatocellular carcinoma (HCC). We aimed to compare the survival benefits in a retrospective cohort of patients with BCLC-C HCC who underwent surgery after conversion therapy with adjuvant therapy and surgery alone. The conversion therapy group was derived from a prospective clinical study, and from January 2015 to September 2023, we selected patients diagnosed with BCLC-C HCC who underwent liver resection at Chinese PLA General Hospital as the surgical group. The primary endpoint in the comparison of survival benefits between conversion therapy and surgery-alone groups was recurrence-free survival. Propensity score matching was applied to reduce any potential bias in the study. By the end of follow-up, the conversion therapy group mRFS was 37.8 months, with postoperative 1-, 2- and 3-year RFS rates of 66.8%, 54.6%, and 48.3%. In the surgery group, the mRFS was 3.0 months, and postoperative 1- , 2- and 3-year RFS rates of 22.4%, 17.5%, and 15.0%, respectively. On multivariable Cox regression analyses, conversion therapy significantly reduced HCC-related mortality and HCC recurrence rates compared with surgery alone. For BCLC-C HCC patients, conversion therapy with adjuvant therapy is in relationship with increased survival in comparison with surgery alone.

Keywords: hepatocellular carcinoma, salvage surgery, tyrosine kinase inhibitor, anti-programmed death-1 antibody, portal vein tumor thrombosis, propensity score matching

1. Introduction

Liver cancer is the fourth leading cause of cancer-related death, and it is the second leading cause of cancer-related death in males (*1*). Approximately 70-80% of individuals with HCC are diagnosed during their progressive stage and have a poor prognosis (*2*). Barcelona Clinic Liver Cancer (BCLC) staging is the most commonly used international staging method for HCC. Individuals with BCLC–C-stage HCC have a short survival period (approximately 3-6 months) (*3,4*). Currently, there is no effective therapy to achieve a favorable prognosis for individuals with BCLC-C stage HCC. BCLC–C-stage HCC mainly presents with vascular invasion and extrahepatic metastasis. Individuals with HCC combined with portal vein tumor thrombus (PVTT) have a natural survival of 2.7-4 months, while patients with HCC combined with lymph node metastasis have a median disease-free survival (mRFS) and overall survival (mOS) of only 5.9 months and 11 months, with 1-year, 3-year, and 5-year OS rates were 36.4%, 13.6%, and 13.6% (*5,6*). An international consensus on treating individuals with BCLC–C-stage HCC combined with vascular invasion alone is unavailable. According to the EASL and NCCN guidelines, combined vascular invasion is a contraindication to surgical treatment for individuals with HCC (*7,8*). In addition, patient prognosis is not considerably improved after preoperative adjuvant therapy, and surgery is not the best treatment option for such individuals. However, Chinese guidelines indicate that patients with PVTT grade 2 or less can be treated surgically (*9*). Surgery is not recommended worldwide for patients with PVTT grade 3 or higher or with lymph node metastases alone, and systemic drug-based supportive therapy is preferred.

The advent of immunotherapy combined with targeted regimens has provided novel insights into treating advanced HCC. Numerous clinical trials suggest

that a combination regimen based on immunotherapy combined with targeted therapy effectively prolongs the survival duration of individuals with advanced HCC (*10*). Based on previous research, implementing immunotherapy combined with targeted regimens (conversion therapy) in patients with advanced HCC preoperatively and sequential surgical treatment after the patient has achieved oncologic benefit has become an effective practice, and postoperative adjuvant therapy based on pathologic findings may further prolong patient survival (*11*). Despite the initial effectiveness, further studies using large sample sizes are required to demonstrate its efficacy and safety. The current historical-prospective study explored the safety and efficacy of conversion therapy sequential surgical therapy to treat BCLC–C-stage HCC. Meanwhile, the previous research of our team pointed out that serum alpha-fetoprotein (AFP) level has a significant impact on the efficacy assessment and prognosis of HCC patients receiving conversion therapy, which was also given further exploration in this study (*12*).

2. Material and Methods

2.1. Sample sources

Individuals with BCLC–C-stage HCC received surgical treatment at the Department of Hepatobiliary and Pancreatic Surgery, General Hospital of the Chinese People's Liberation Army. Patients in the conversion therapy group of this study were derived from a prospective clinical study, registration number ChiCTR1900023914 (A Research of programmed death-1 (PD-1) Inhibitors Combined with Lenvatinib for Advanced Unresectable Liver Cancer as the Conversion Therapy: A Prospective Open-label Exploratory Clinical Study). Patients in the surgery group were selected from January 2015 to September 2023, which had a high degree of homogeneity in the study site and surgeon team in addition to the intervention. Patients were followed up till December 2024. Informed consent was obtained from all patients to be included in the study. We obtained written informed consent for treatment and the use of patient data for clinical research before treatment. Patients who received preoperative conversion therapy and sequential surgery with postoperative treatment served as the conversion therapy and postoperative treatment group, whereas patients who received no conversion therapy and were treated directly with surgery served as the surgery alone group. The major observational endpoint of this research was recurrence-free survival (RFS), and the secondary endpoint was overall survival (OS) because of the diverse treatments available to patients after postoperative recurrence. In addition, the association between the patient's serum AFP levels at the time of initial diagnosis and preoperatively and the treatment outcome was also studied as a secondary observational endpoint.

2.2. Selection criteria

The inclusion criteria for this research were as stated: (1) Age 18-80 years; (2) Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score of 0 ; (3) Diagnosis of HCC according to the guidelines of the American Association for the Study of Liver Diseases (AASLD) or postoperative pathology; (4) R_0 resection confirmed by postoperative pathology; (5) Administration of PD-1 antibody in combination with tyrosine kinase inhibitor (TKI) for sequential surgical resection; (6) Tumor stage of BCLC-C during initial diagnosis; the exclusion criteria were as stated: (1) Previous treatment with PD-1 antibody, TKI, or any other combination regimen; (2) Cancer history other than HCC in the last 5 years; (3) Concurrent major systemic diseases.

2.3. Data collection

Relevant information was collected from patients at the initial visit, including gender, age, viral hepatitis, initial liver function Child-Pugh score, ECOG-PS score, maximum tumor diameter, number of tumor lesions, serum AFP level (patients were differentiated into AFP high (AFPH) and AFP low (AFPL) groups based on whether or not the AFP was positive (> 20 μg/mL)), other local treatment received preoperatively, pre-combined therapy portal vein tumor thrombosis (PVTT), hepatic vein tumor thrombosis/inferior vena cava tumor thrombosis (HVTT/IVCTT), and lymph node metastasis.

The conversion therapy group received a combination of TKI and PD-1 antibody as the downstaging protocol. Conversion therapy is subjected to unresectable tumors, aiming to make surgery feasible and improve overall survival by local or systemic therapy (*13*). Conversion protocols are mainly made concerning achieving a high objective response rate (ORR) (Appendix Table S1). The postoperative therapy protocols were guided based on pathological examination findings: 1) Patients who reached a pathological complete response (PCR) would only receive initial PD-1 antibodies consistently for another 6 months, otherwise, 2) Patients would receive initial combination therapy protocol for 6–12 months depending on imaging examination findings by follow-up.

Intraoperative data were collected from patients, including the surgical approach (simple hepatectomy, superimposed thrombectomy or portal vein reconstruction, *etc*.), the extent of hepatectomy (≥ 3 Couinaud's segments were considered extensive hepatectomy), intraoperative bleeding, and perioperative blood transfusion. Information on postoperative complications included postoperative Clavein-Dindo score, postoperative biliary fistula (diagnosed by

bilirubin > 3 times serum bilirubin level in the operative area drainage fluid on postoperative day 3), postoperative bleeding, duration of postoperative hospitalization, and postoperative Child-Pugh score at 5 days (*14,15*).

Information on immunotherapy combined with a targeted regimen was collected from patients. Additionally, one infusion of PD-1 was used as 1 treatment cycle. Efficacy assessment by abdominal enhancement magnetic resonance imaging (MRI, urine routine, blood routine, thyroid function, coagulation function, liver and kidney function, cardiac enzyme profile, and tumor markers were carried out approximately every 3 months. The maximum diameter of the tumor after combined treatment was collected from patients. The tumor treatment effect was assessed by the modified Response Evaluation Criteria in Solid Tumors (m-Recist) (*16*). The proportion of residual tumor cells in the postoperative pathology was used to evaluate the response to tumor treatment. The absence of microscopically visible residual tumor cells in the pathology specimens indicated a pathological complete response (pCR). For pathological findings, the major pathological response (MPR) was defined as surviving tumor activity < 10% (*17,18*). Treatment-related adverse events were assessed by the common terminology criteria for adverse events (CTCAE 5.0) evaluation criteria (*19*). In this study, the JSH typing criteria were adopted to define the grade of post-conversion cancer emboli according to the location of emboli still present in the vasculature after combined treatment (regardless of their oncological activity) due to the absence of a uniform and clear definition (*20*).

2.4. Surgical evaluation and postoperative adjuvant medication and follow-up in the conversion therapy group

Surgical treatment was performed when the following indications were met: (1) Preoperative liver function Child-Pugh score grade A/B; (2) Postoperative residual liver volume ≥ 35% of standard liver volume during the lack of cirrhosis and ≥ 45% of standard liver volume in cirrhosis; (3) 15-min retention rate < 20% for indocyanine green; (4) Structural integrity of the planned preserved hepatic parenchymal inflow and outflow tracts; (5) Patent biliary drainage or an intra- and extra-hepatic biliary structure that can be completely reconstructed; (6) Eastern U.S. Oncology Collaborative Group score of 0 to 1; (7) ASA rating ≤ grade 3. (*21*)

2.5. Selection of surgical modality and procedures

(1) Hepatectomy: A reverse L-shaped incision was made in the right upper abdomen to open the tissue layer by layer or to establish a laparoscopic operating system. Subsequently, the abdominal cavity was explored for ascites, distant metastases in lymph nodes or other organ tissues, and local tumor infiltration. The liver segment where the tumor was located was targeted and the resection line was marked along > 2 cm beyond the tumor. Afterward, the liver parenchyma was fragmented by the Cavitation Ultrasonic Surgical Aspirator (CUSA)/ ultrasonic knife/clamp, and the exposed Glisson system and the veins of the hepatic venous system were ligated or sutured. The primary branches of the Glisson system or the main trunk of the hepatic venous system were dissected with a linear Endo-GIA stapler. The sections were covered with hemostatic material after energy instrumentation and suturing for hemostasis.

(2) Vascular thrombectomy and reconstruction: Vascular clamping was performed on both ends of the branches where the portal vein cancer embolus was located. Subsequently, the vessel wall was incised longitudinally along the direction of the vessel. The clamp was used to remove all the visually visible cancerous tissues to investigate whether the tumor invaded the contralateral vessel. After the examination, the distal vascular clamp was released to ensure proper blood flow. After confirming no residual tumor tissue in the vascular system, the vessel wall incision was closed with transverse plastic sutures using 4-0/5-0 prolene sutures. If the angle between the residual portal vein and the main trunk was still acute after suturing, the angle was straightened and adjusted to an obtuse angle by ligating again on the resected side to ensure a smooth flow signal within it.

(3) Abdominal lymph node dissection: according to the patient's preoperative imaging data and intraoperative exploration results, the metastatic lymph nodes with definite and suspicious metastases in the abdominal cavity were removed by dissection after ligation of lymphatic vessels and sent for pathological examination.

2.6. Statistical analysis

Comparison of continuous variables conforming to normal distribution between two groups was carried out using the *t*-test, whereas the Mann-Whitney *U*-test was utilized for comparing the continuous variables not conforming to normal distribution. The chi-square and Fisher's exact tests were used to compare categorical data. Survival status between the two groups was compared using the Kaplan-Meier method for the log-rank test. Univariate survival analysis was introduced in a multivariate Cox proportional risk model to explore important risk factors for recurrence. Continuous variables were dichotomized and then included in the analysis to determine adjusted risk ratios and 95% confidence intervals (CIs). Propensity score matching was applied in the two patient groups to reduce the potential bias in this study. Variables associated with long-term survival were chosen for propensity score generation, including age, gender, and hepatitis etiology; Child-Pugh score, ECOG-PS, and serum AFP level; other

local treatments; tumor diameters; multiple or single tumors; BCLC stage; and surgery procedures, major or minor hepatectomy, perioperative blood loss, and perioperative blood transfusion. All statistical analyses were performed using SPSS 26.0 and R 4.1.2. Statistical significance was obtained at $P < 0.05$.

3. Results

3.1. Patients' related basic information

In total, 88 patients from the prospective study were included in the study, 123 patients diagnosed with BCLC–C-stage HCC and subjected to surgery at the Department of Hepatobiliary and Pancreatic Surgery, General Hospital of the Chinese People's Liberation Army, from January 2015 to September 2023, were recruited into this study. Eventually, 211 individuals with BCLC–C-stage HCC were included in this research after screening by the inclusion and exclusion criteria, and 176 patients comprised the PSM cohort (patients in the conversion therapy group were completely matched) (Figure 1).

3.2. Baseline characteristics of patients

The baseline features of the two groups in this study are demonstrated in Table 1. In the total cohort, the group of patients receiving combination therapy had a higher rate of HBV infection ($P = 0.027$), previous local treatments ($P = 0.035$), multiple tumor number ($P = 0.003$) and minor hepatectomy ($P = 0.024$) at the initial diagnosis. No considerable variations were noted between the two groups in terms of all variables after PSM. All patients were diagnosed as BCLC–C-stage HCC by preoperative imaging or postoperative pathology.

3.3. Evaluation of the effect of immunotherapy combined with targeted therapy and toxic side effects in the conversion therapy group

The dosing regimens of the 88 patients receiving immunotherapy combined with the targeted therapy regimen are demonstrated in Table 2. These patients were given a dosing regimen of 3-20 cycles with a median of 5 cycles. According to the m-Recist criteria, 12 patients achieved complete response (CR), 58 achieved partial response (PR), 16 had stable disease (SD), and 2 had progressive disease (PD). Before the combined treatment, 75 individuals in the conversion therapy group developed vascular invasion, including 68 with PVTT, and 20 with HVTT. After conversion therapy, 68 patients had vascular invasion, including 61 with PVTT and 11 with HVTT. In addition, 27 patients had a decrease in PVTT of at least one grade, and 7 had complete disappearance of PVTT. In addition, the HVTT decreased by at least one grade in 15 patients, and the HVTT disappeared completely in 9 patients. Moreover, 34 patients in the conversion therapy group had lymph node metastases before the combined treatment, but this number decreased to 17 after the combined treatment. And postoperative pathological findings confirmed that the primary tumor foci eventually reached pCR in 21 patients, and MPR in 48 patients. During immunotherapy combined with targeted therapy, 64 individuals in the conversion therapy group experienced adverse events during treatment, 44 of whom had a CTCAE event grade ≥ 2 (Table 2). No patient abandoned the treatment regimen or failed to undergo surgery due to the side effects accompanying the treatment process.

3.4. Surgical procedures and postoperative complications

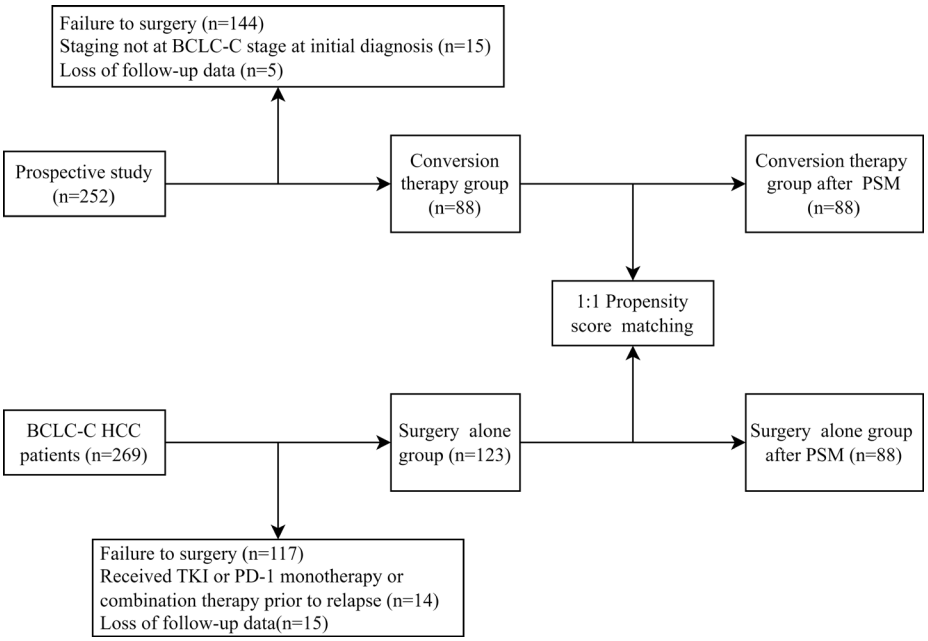

Figure 1. Flowchart of this research.

Table 1. Comparison of characteristics between BCLC-C HCC patients undergoing conversion therapy and postoperative treatment or surgery alone

Variables *n* (%)	Before PSM			After PSM		
	Conversion therapy (*n* = 88)	Surgery (*n* = 123)	*P*	Conversion therapy (*n* = 88)	Surgery (*n* = 88)	*P*
Age (years)	54 (24-73)	55 (29-80)	0.917	54 (24-73)	55 (30-80)	0.642
Gender			0.528			1.000
Male	77 (87.5)	111 (90.2)		77 (87.5)	77 (87.5)	
Female	11 (12.5)	12 (9.6)		11 (12.5)	11 (12.5)	
Etiology of hepatitis			0.027			0.551
HBV	76 (86.4)	94 (76.4)		76 (86.4)	80 (90.9)	
HCV	6 (6.8)	5 (4.1)		6 (6.8)	3 (3.4)	
No hepatitis	6 (6.8)	24 (19.5)		6 (6.8)	5 (5.7)	
Child-pugh grade			0.329			0.406
A	86 (97.7)	117 (95.1)		86 (97.7)	84 (95.5)	
B	2 (2.3)	6 (4.9)		2 (2.3)	4 (4.5)	
ECOG PS			1.000			1.000
0	88	123		88	88	
1	0	0		0	0	
2	0	0		0	0	
3	0	0		0	0	
4	0	0		0	0	
5	0	0		0	0	
AFP (ng/mL)			0.706			0.861
> 20	66 (75)	95 (77.2)		66 (75)	67 (76.1)	
≤ 20	22 (25)	28 (22.8)		22 (25)	21 (23.9)	
Previous local treatment			0.035			0.150
Yes	24 (27.3)	19 (15.4)		24 (27.2)	16 (18.2)	
No	64 (72.7)	104 (84.6)		64 (72.8)	72 (81.8)	
Tumor diameter (cm)	9.11±4.25	8.43±4.04	0.549	8.6 (2.7-19.9)	8.5 (2-25)	0.589
Tumor number			0.003			0.082
Single	61 (77.3)	106 (86.2)		61 (69.3)	71 (80.7)	
Multiple	27 (22.7)	17 (13.8)		27 (30.7)	17 (15.3)	
BCLC stage			1.000			1.000
A	0	0		0	0	
B	0	0		0	0	
C	88 (100)	123 (100)		88 (100)	88 (100)	
D	0	0		0	0	
Surgical procedure			0.152			0.364
Thrombectomy	37 (52.7)	64 (52.0)		37 (42.0)	43 (48.9)	
En-bloc	51 (47.3)	59 (48.0)		51 (58.0)	45 (51.1)	
Extent of resection			0.024			0.165
Major	49 (55.7)	87 (70.7)		49 (55.7)	58 (65.9)	
Minor	39 (44.3)	36 (29.3)		39 (44.3)	30 (34.1)	
Intraoperative blood loss (mL)	300 (50-2400)	300 (50-3000)	0.077	300 (50-2400)	300 (50-2500)	0.680
Perioperative blood transfusion			0.496			
Yes	37 (42.0)	46 (37.4)		37 (42.0)	30 (34.1)	0.277
No	51 (58.0)	77 (62.6)		51 (58.0)	58 (65.9)	

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha-fetoprotein; ECOG PS, Eastern Cooperative Oncology Group performance status.

In the conversion therapy group, 51 patients underwent hepatectomy alone, and 37 had hepatectomy combined with thrombectomy. In contrast, 59 patients underwent hepatectomy alone, and 64 had hepatectomy combined with thrombectomy in the surgery group. Considerable variations were not observed between the two groups ($P = 0.152$). The mean intraoperative bleeding volumes were 300 mL (50-2,400 mL) and 300 mL (50-3,000 mL) in the two groups, respectively. In addition, major variations were not observed between the two groups in terms of perioperative blood transfusion, postoperative hospital days, postoperative biliary fistula, bleeding, and other complications, Child-Pugh score, and Clavein-Dindo score (Table 3). In the cohort after PSM, there were no significant statistical differences in surgery-related complication indicators between the two groups of patients.

3.5. Follow-up results

By the end of follow-up, 38 patients in the conversion therapy group experienced recurrence and mRFS was 37.8 months, with postoperative 1-, 2- and 3-year RFS rates of 66.8%, 54.6%, and 48.3%, respectively. In the surgery group, 93 patients experienced recurrence, with an mRFS of 3.1 months and postoperative 1-, 2-

and 3-year RFS rates of 27.2%, 21.1%, and 18.5%, respectively. Sixteen patients in the conversion therapy group died and did not reach mOS yet, with 1-, 2-, 3-, and 5-year OS rates of 96.6%, 82.8%, 77.2%, and 58.1%, respectively. In the surgery group, 85 patients died, with a mOS of 26.8 months and 1-, 2-, 3-, and 5-year OS rates of 66.7%, 53.7%, 38.2%, and 28.9%, respectively. The survival curves for RFS and OS of patients in both groups are shown in Figure 2.

For patients with combined macrovascular invasion, the 1-, 2-, and 3-year RFS rates in the conversion therapy group compared with the surgery group were 66.6% *vs*. 27.0%, 52.1% *vs*. 20.9%, and 45.0% *vs*. 17.3%, respectively; the 1-, 2-, 3-, and 5-year OS rates in the two groups were 96.0% *vs*. 66.7%, 79.8% *vs*. 53.3%, 74.7% *vs*. 38.3% and 57.3% *vs*. 29.6%. As for patients with lymph node metastasis, the 1-, 2-, and 3-year RFS rates were 63.7 % *vs*. 20%, 57.0% *vs*. 20%, 50.6% *vs*. 20%, respectively; the 1-, 2-, 3-, and 5-year OS rates in both groups were 94.4% *vs*. 60%, 82.9% *vs*. 40%, 79.4% *vs*. 20% and 67% *vs*. 20% (Figure 2).

In the propensity model, 33 patients in the conversion therapy group developed recurrence and mRFS was 37.8 months, with postoperative 1-, 2- and 3-year RFS rates of 66.8%, 54.6%, and 48.3%, respectively. In the surgery group, 60 patients developed recurrence, with an mRFS of 3.0 months and 1-, 2- and 3-year RFS rates of 22.4%, 17.5% and 15.0%, respectively. Thirteen patients in the conversion therapy group died and did not attain mOS, with 1-, 2-, 3-, and 5-year OS rates of 96.6%, 82.8%, 77.2%, and 58.1%, respectively. In the surgery group, 55 patients died, with a mOS of 22.7 months and 1-, 2-, 3-, and 5-year postoperative OS rates of 63.6%, 48.9%, 33.5%, and 21.8%, respectively. Survival curves for RFS and OS of the PSM cohort and subgroup for combined macrovascular invasion and lymph node metastasis are illustrated in Figure 3.

Table 2. Tumor response and adverse events to conversion therapy

No. of patients	Conversion therapy cohort, No. (%)
Response to conversion therapy	
CR	12 (13.6)
PR	58 (65.9)
SD	16 (18.2)
PD	2 (2.3)
Tumor pathology	
PCR	21 (23.9)
MPR	48 (54.5)
Adverse events (CTCAE)	
Grade 0	24 (27.2)
Grade 1	20 (22.7)
Grade 2	29 (33.0)
Grade 3	15 (17.1)
Grade 4	0 (0)
Grade 5	0 (0)

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PCR, pathological complete response; MPR, major pathological response; CTCAE, common terminology criteria for adverse events.

3.6. Analysis of serum AFP levels with patient outcome and prognosis

Analysis of the relationship between AFP levels before and after treatment and patient prognosis in patients receiving conversion therapy revealed that OS (Figure 4A) and RFS (Figure 4B) were significantly higher in patients with negative AFP levels before conversion therapy than in patients with positive AFP levels before conversion therapy (P = 0.016/0.026). AFP-positive patients reached median relapse-free survival at 21.6 months. The efficacy of AFP level after conversion therapy was more significant (P = 0.0025/< 0.001) in suggesting OS (Figure 4C) and RFS (Figure 4D) of patients. No significant correlation was observed between the AFP level at the time of the initial diagnosis and the proportion of residual tumor (Figure 4E), and there was a significant correlation between the proportion of residual tumor in surgically resected specimens and AFP level after conversion therapy (Figure 4F, P = 0.0047, R^2= 0.089). However, among the other indicators of efficacy assessment, AFP levels at initial consultation and after

Table 3. Comparison of surgery-related complications in the conversion therapy or surgery group

Variables *n* (%)	Before PSM			After PSM		
	Conversion therapy (*n* = 88)	Surgery (*n* = 123)	*P*	Conversion therapy (*n* = 88)	Surgery (*n* = 88)	*P*
Postoperative Child-pugh grade on day 5			< 0.001			< 0.001
A	74 (84.1)	71 (56.3)		74 (84.1)	50 (56.9)	
B	14 (15.9)	50 (42.2)		14 (15.9)	37 (42.0)	
C	0 (0)	2 (27.8)		0 (0)	1 (1.1%)	
Postoperative hospital stays	9 (4-33)	9 (4-40)	0.756	9 (4-33)	9 (4-40)	0.691
Perioperative mortality	0 (0)	2 (1.6)	0.511	0 (0)	1 (1.1%)	0.316
Complications						
Clavien-Dindo classification			0.25			0.53
3	4	10		4	5	
4	14	20		14	12	
5	0	3		0	1	

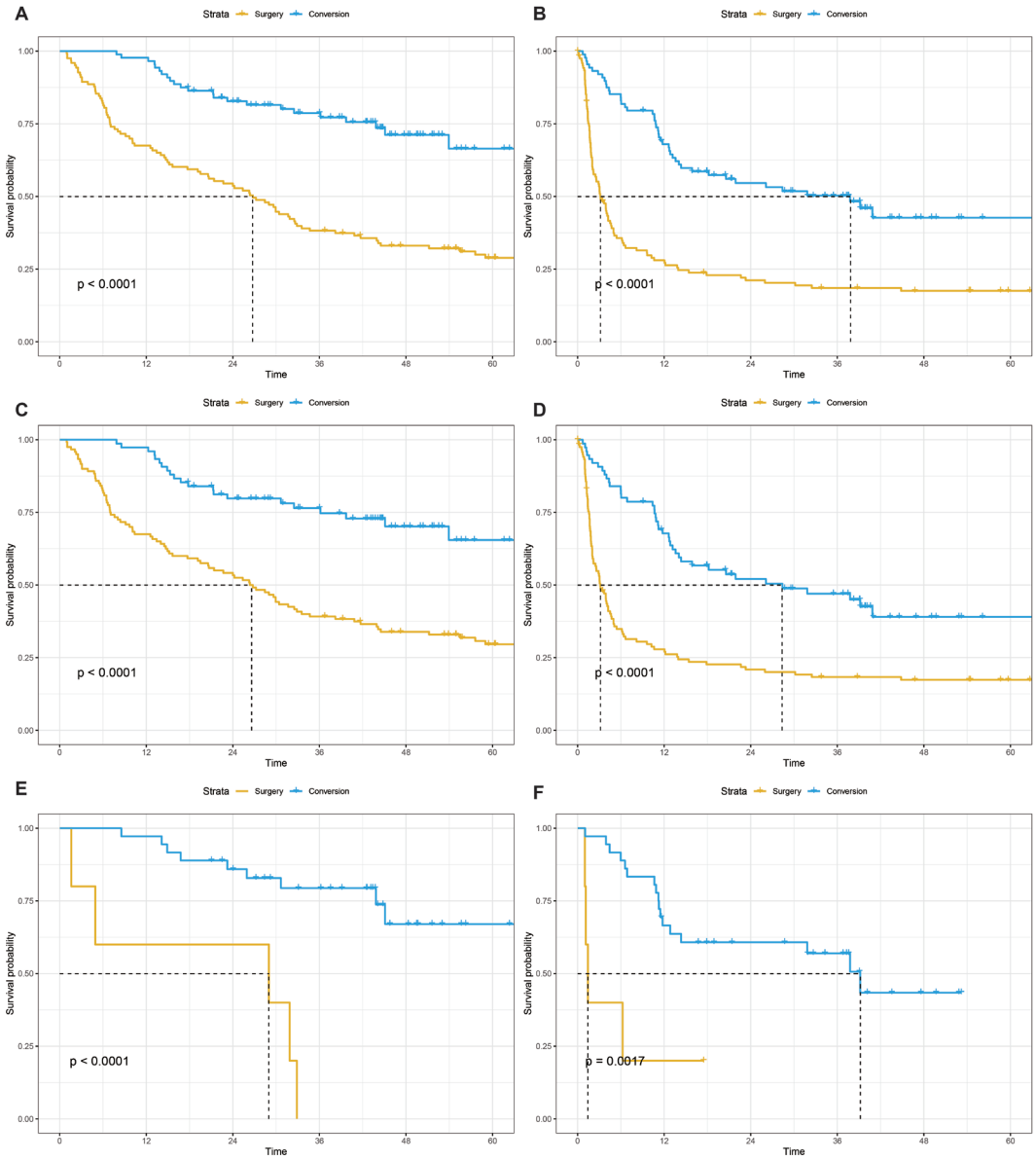

Figure 2. (A) Overall survival (OS) curves for the conversion therapy groups and surgery groups, (B) Recurrence-free survival (RFS) curves for the conversion groups and surgery-alone groups, (C) Overall survival (OS) curves for patients with macrovascular invasion in two groups, (D) Recurrence-free survival (RFS) curves for patients with macrovascular invasion in two groups. (E) Overall survival (OS) curves for patients with lymph node metastasis in two groups. (F)Recurrence-free survival (RFS) curves for patients with lymph node metastasis in two groups.

treatment were significantly correlated with the results of mRecist assessment and the results of pathologic assessment (Figures 4G-J).

3.7. COX analysis results

According to univariate COX regression analysis, preoperative CHILD grading, intraoperative blood loss, perioperative blood transfusion, and conversion therapy were correlated with postoperative recurrence of individuals with BCLC–C-stage HCC ($P < 0.1$) and were included in the COX multivariate analysis. The final results suggested a significant correlation between conversion therapy and postoperative OS in individuals with BCLC–C-stage HCC. Moreover, the above factors still exhibited a statistical correlation with OS in the cohort after PSM. Multivariate Cox analysis in the PSM cohort revealed that conversion therapy remains the only independent risk factor associated with postoperative survival in patients with BCLC-C stage HCC. The final results suggested that conversion therapy was remarkably linked to postoperative OS in individuals with BCLC–C-stage HCC (Table 4). In terms of postoperative recurrence in patients at the BCLC-C stage, univariate Cox analysis results from the overall cohort suggest that conversion therapy, tumor diameter, surgical procedure, intraoperative blood loss, and perioperative blood transfusion are associated with postoperative RFS. After incorporating these into a multivariate Cox analysis, it was found that only conversion therapy is an independent

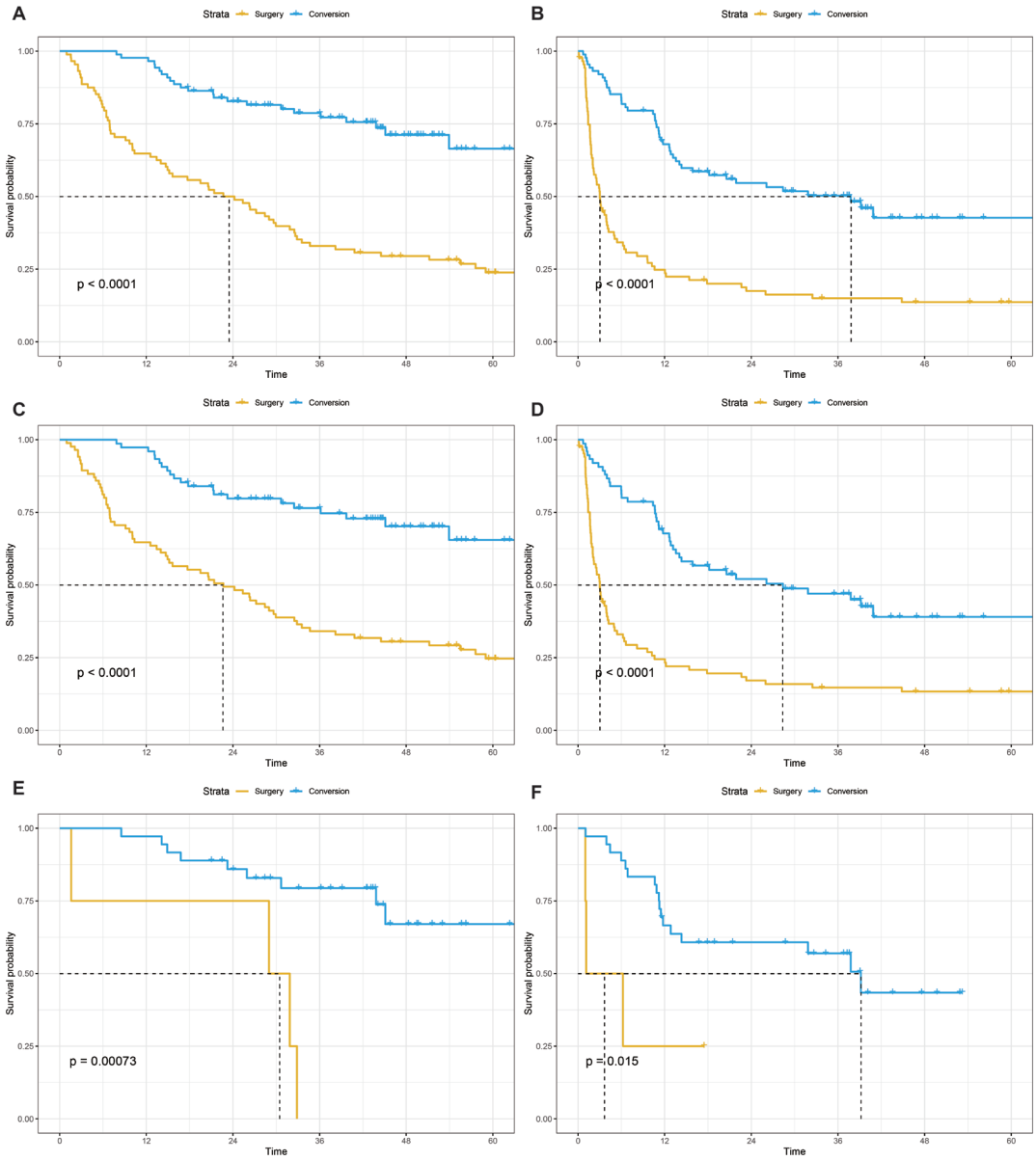

Figure 3. (A) Overall survival (OS) curves for the conversion therapy groups and surgery groups in propensity model, (B) Recurrence-free survival (RFS) curves for the conversion groups and surgery-alone groups in propensity model, (C) Overall survival (OS) curves for patients with macrovascular invasion in two groups in propensity model, (D) Recurrence-free survival (RFS) curves for patients with macrovascular invasion in two groups in propensity model. (E) Overall survival (OS) curves for patients with lymph node metastasis in two groups in the propensity model. (F)Recurrence-free survival (RFS) curves for patients with lymph node metastasis in the two groups in propensity model.

risk factor for postoperative recurrence. Similar results were observed in the cohort after PSM (Table 5).

4. Discussion

Individuals with BCLC–C-stage HCC have poor treatment outcomes and short survival duration. Surgery is the radical means to treat HCC (*22*). In previous clinical practice, patients with BCLC-C stage were recommended by most guidelines and consensus to undergo systemic combined treatment to delay tumor progression because of the poor outcome of surgical treatment (*8*). However, immunotherapy combined with targeted sequential surgical regimens significantly improved the prognosis of individuals with BCLC–C-stage HCC (*12,23*). In addition, the stage-reducing effect of conversion therapy furthered the opportunity for surgery in patients with stage BCLC-C. A total of 211 individuals with BCLC–C-stage HCC were included in this research. Among them, 88 patients received conversion therapy sequential surgical treatment before surgery, and 123 received surgery directly. The comparison of recurrence-free survival and survival rates between the two groups suggested that patients with BCLC–C-stage HCC treated with conversion therapy sequential surgery had a significantly better prognosis than their counterparts who underwent direct surgery. Therefore, conversion therapy may provide a significant

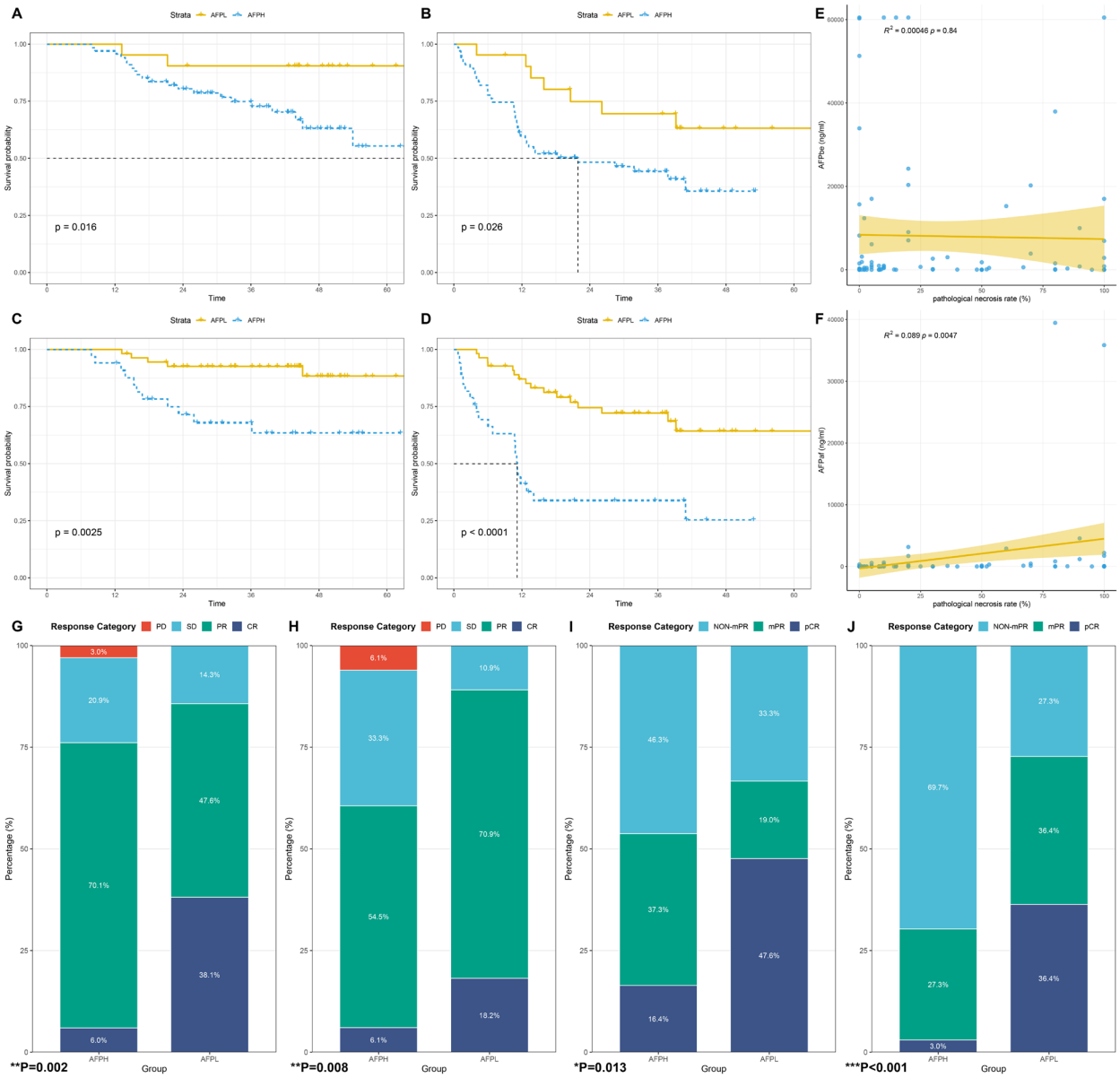

Figure.4 (A) Overall survival (OS) curves for the initial AFPH groups and AFPL groups, (B) Recurrence-free survival (RFS) curves for the initial AFPH groups and AFPL groups, (C) Overall survival (OS) curves for the AFPH groups and AFPL groups after conversion therapy, (D) Recurrence-free survival (RFS) curves for the AFPH groups and AFPL groups after conversion therapy. (E) Correlation between initial AFP levels and percentage of pathological necrosis. (F) Correlation between AFP levels after conversion therapy and percentage of pathological necrosis. (G) Relationship between initial AFP and mRecist assessment results. (H) Relationship between AFP after conversion therapy and mRecist assessment results. (I). Relationship between initial AFP and results of pathologic evaluation. (J). Relationship between AFP after conversion therapy and results of pathologic evaluation.

survival benefit for individuals with BCLC–C-stage HCC. According to the results of the COX multifactorial regression model, preoperative immunotherapy combined with targeted sequential surgical therapy was a significant protective factor for overall survival(HR = 0.212, $P < 0.001$) and recurrence-free survival (HR = 0.387, $P < 0.001$) in patients with BCLC–C-stage HCC. In contrast, individuals with BCLC–C-stage HCC underwent transhepatic artery chemoembolization with sorafinib to achieve mOS of 12 months, and 1- and 2-year OS rates were 47% and 24%, respectively (*24*). Whereas advanced hepatocellular carcinoma is treated by applying SBRT, the 6 and 12-month PFS was 58% and 40% (*25*). Therefore, conversion therapy with sequential surgical treatment protocols has better efficacy than previous combination therapies.

Macrovascular invasion is a common clinical condition in individuals with BCLC-C stage HCC. After conversion therapy, 27 patients had downgraded PVTT, 7 patients had complete disappearance of PVTT, and 15 patients had downgraded HVTT, 9 patients had complete disappearance of HVTT. PVTT is more likely to result in intrahepatic and hematogenous metastases, increasing portal vein pressure, and the risk of ruptured esophagogastric varices (*26*). Patients with hepatic vein thrombosis are not only at higher risk of pulmonary

Table 4. Univariate and multivariate Cox-regression analyses of overall survival in HCC patients with PVTT undergoing conversion therapy or surgery alone

Variables	UV HR (95% CI)	*P*	MV HR (95% CI)	*P*
Before PSM				
Age (> 60 *vs*. ≤ 60 years)	0.958 (0.620-1.483)	0.849		
Gender (Male *vs*. Female)	1.055 (0.549-2.028)	0.871		
HBsAg (Positive *vs*. Negative)				
No hepatitis	-	-		
HBV	1.065 (0.613-1850)	0.823		
HCV	0.744 (0.247-2.245)	0.600		
Child-pugh grade (B *vs*. A)	2.115 (0.925-4.835)	0.076	1.357 (0.573-3.209)	0.488
AFP (> 20 *vs*. ≤ 20 ng/mL)	1.317 (0.814-2.130)	0.262		
Previous local treatment (Yes *vs*. No)	0.828 (0.502-1.365)	0.459		
Tumor diameter (cm)	1.032 (0.986-1.080)	0.178		
Tumor number (Multiple *vs*. Single)	1.070 (0.656-1.747)	0.785		
Surgical procedure (Thrombectomy *vs*. En-bloc)	1.169 (0.791-1.729)	0.433		
Extent of resection (Major *vs*. Minor)	1.103 (0.722-1.685)	0.649		
Intraoperative blood loss (> 400 *vs*. ≤ 400 mL)	1.911 (1.290-2.830)	0.001	1.510 (0.965-2.362)	0.071
Perioperative blood transfusion (Yes *vs*. No)	1.670 (1.116-2.500)	0.013	1.352 (0.846-2.160)	0.207
Conversion therapy (Yes *vs*. No)	0.235 (0.138-0.403)	< 0.001	0.242 (0.141-0.415)	< 0.001
After PSM				
Age (> 60 *vs*. ≤ 60 years)	1.003 (0.590-1.705)	0.991		
Gender (Male *vs*. Female)	0.783 (0.400-1.533)	0.475		
HBsAg (Positive *vs*. Negative)				
No hepatitis	-	-		
HBV	2.216 (0.695-7.068)	0.179		
HCV	1.834 (0.370-9.096)	0.458		
Child-pugh grade (B *vs*. A)	4.355 (1.728-10.972)	0.002	4.212 (1.604-11.057)	0.004
AFP (> 20 *vs*. ≤ 20 ng/mL)	1.146 (0.668-1.966)	0.620		
Previous local treatment (Yes *vs*. No)	0.936 (0.526-1.664)	0.822		
Tumor diameter (cm)	1.024 (0.968-1.084)	0.403		
Tumor number (Multiple *vs*. Single)	1.126 (0.634-1.998)	0.686		
Surgical procedure (Thrombectomy *vs*. En-bloc)	0.913 (0.565-1.476)	0.710		
Extent of resection (Major *vs*. Minor)	1.132 (0.684-1.872)	0.630		
Intraoperative blood loss (> 400 *vs*. ≤ 400 mL)	1.750 (1.086-2.817)	0.021	1.267 (0.754-2.129)	0.372
Perioperative blood transfusion (Yes *vs*. No)	1.893 (1.158-3.094)	0.011	1.705 (0.988-2.941)	0.055
Conversion therapy (Yes *vs*. No)	0.225 (0.122-0.414)	< 0.001	0.212 (0.114-0.391)	< 0.001

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha-fetoprotein.

metastasis but also at risk of sudden death due to the dislodgment of the hepatic vein thrombus (*27*). A meta-analysis has noted that patients with microvascular invasion treated surgically have a median overall survival of 14.39 months, 1-year OS was 54.47% and 3-year OS was 23.20%, the 1- and 3-year RFS were 27.70% and 10.06%, respectively (*28*). Compared with the results reported in our study, it can be found that the application of the combined treatment regimen significantly prolonged the OS and RFS of the patients, providing a clear survival benefit for the patients. Conversion therapy effectively reduced tumor load and prolonged patient survival. Thus, a combination regimen to downgrade the tumor followed by sequential surgical procedures was effective. The reduction in tumor volume allows patients to complete radical resection of the tumor within a smaller resection area, and the larger residual liver volume provides sufficient opportunity to undergo other local treatment options or even secondary surgical treatment after tumor-resistant recurrence (*14*). And the retreating cancer embolus prepares an adequate length of blood vessels. Therefore, patients who would otherwise require cancer embolization or even portal vein resection and reconstruction can complete en-bloc resection through hepatectomy alone. This protocol simplifies the surgical procedure, ensures a higher percentage of en-bloc resection, and improves the procedure's safety (*29*).

A subset of individuals with BCLC–C-stage HCC will develop extrahepatic metastases. The vast majority of patients with extrahepatic lesions in this study had abdominal lymph node metastases, and only one patient in the surgery group had localized diaphragmatic invasion. Currently, non-surgical treatments, such as PD-1 antibodies, targeted agents, or other localized treatment options, are still recommended for patients with hepatocellular carcinoma combined with lymph node metastases. In this study, 34 patients in the conversion therapy group were diagnosed by imaging data with lymph node metastasis at the initial diagnosis. However, lymph node metastases were detected in only 17 individuals in the postoperative pathological specimen examination. During the conversion process, it was observed that several patients in the conversion therapy group showed shrinkage or even the disappearance

Table 5. Univariate and multivariate Cox-regression analyses of recurrence-free survival in HCC patients with PVTT undergoing conversion therapy or surgery alone

Variables	UV HR (95% CI)	*P*	MV HR (95% CI)	*P*
Before PSM				
Age (> 60 *vs*. ≤ 60 years)	1.048 (0.716-1.534)	0.809		
Gender (Male *vs*. Female)	0.884 (0.516-1.515)	0.653		
HBsAg (Positive *vs*. Negative)				
No hepatitis	-	-		
HBV	0.942 (0.583-1.520)	0.805		
HCV	0.711 (0.285-1.770)	0.463		
Child-pugh grade (B *vs*. A)	1.490 (0.656-3.384)	0.340		
AFP (> 20 *vs*. ≤ 20 ng/mL)	1.258 (0.828-1.911)	0.282		
Previous local treatment (Yes *vs*. No)	0.975 (0.638-1.490)	0.907		
Tumor diameter (cm)	1.040 (0.997-1.084)	0.066	1.037 (0.992-1.084)	0.106
Tumor number (Multiple *vs*. Single)	1.128 (0.734-1.734)	0.582		
Surgical procedure (Thrombectomy *vs*. En-bloc)	1.467 (1.040-2.070)	0.029	1.175 (0.822-1.679)	0.376
Extent of resection (Major *vs*. Minor)	1.332 (0.916-1.938)	0.133		
Intraoperative blood loss (> 400 *vs*. ≤ 400 mL)	1.604 (1.137-2.261)	0.007	1.310 (0.877-1.957)	0.187
Perioperative blood transfusion (Yes *vs*. No)	1.477 (1.028-2.122)	0.035	1.202 (0.789-1.831)	0.392
Conversion therapy (Yes *vs*. No)	0.391 (0.267-0.572)	< 0.001	0.394 (0.268-0.580)	< 0.001
After PSM				
Age (> 60 *vs*. ≤ 60 years)	1.043 (0.663-1.643)	0.855		
Gender (Male *vs*. Female)	0.748 (0.423-1.324)	0.319		
HBsAg (Positive *vs*. Negative)				
No hepatitis	-	-		
HBV	1.500 (0.654-3.436)	0.338		
HCV	1.063 (0.300-3.771)	0.924		
Child-pugh grade (B *vs*. A)	1.606 (0.589-4.384)	0.355		
AFP (> 20 *vs*. ≤ 20 ng/mL)	1.164 (0.731-1.853)	0.522		
Previous local treatment (Yes *vs*. No)	1.056 (0.649-1.717)	0.827		
Tumor diameter (cm)	1.031 (0.980-1.084)	0.238		
Tumor number (Multiple *vs*. Single)	1.212 (0.739-1.987)	0.447		
Surgical procedure (Thrombectomy *vs*. En-bloc)	1.287 (0.856-1.936)	0.225		
Extent of resection (Major *vs*. Minor)	1.298 (0.846-1.991)	0.223		
Intraoperative blood loss (> 400 *vs*. ≤ 400 mL)	1.417 (0.941-2.133)	**0.096**	1.108 (0.696-1.763)	**0.666**
Perioperative blood transfusion (Yes *vs*. No)	1.544 (1.001-2.382)	**0.050**	1.527 (0.935-2.495)	0.091
Conversion therapy (Yes *vs*. No)	0.390 (0.253-0.600)	**< 0.001**	0.387 (0.251-0.597)	**< 0.001**

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha-fetoprotein; ECOG PS, Eastern Cooperative Oncology Group performance status; PVTT, portal vein tumor thrombus.

of lymph nodes. The location of the lymph nodes present at the initial diagnosis was carefully explored intraoperatively, and some tissues were excised for pathological examination, suggesting that there were no definite tumor cells. Therefore, the immunotherapy combined with targeted therapy effectively attenuated the tumors metastasizing in local lymph nodes. However, the need for radical debulking of sites where lymph node lesions have disappeared after conversion therapy remains to be investigated.

Serum AFP levels have previously been used as a tumor marker for the diagnosis of hepatocellular carcinoma. More and more studies have pointed out that AFP levels may also indicate the effectiveness of treatment during tumor therapy in hepatocellular carcinoma (*30*). In this study, serum AFP levels were significantly associated with OS, RFS, mRecist, pathologic evaluation, and the percentage of pathologic tumor cell remnants in patients who underwent conversion therapy. This suggests that AFP levels after conversion therapy can be used to predict patient outcomes and evaluate the timing of surgery. At the same time, AFP levels at the time of initial diagnosis also correlated with these indicators, suggesting that serum AFP levels at the time of initial diagnosis can be used to predict the efficacy of immunotherapy and the prognosis of patients. However, no matter before or after treatment, patients in the high AFP group always showed shorter survival and poorer therapeutic effects, which we believe is related to the inhibitory tumor immune microenvironment caused by high AFP levels and further research is urgently needed to explore the related mechanisms (*31,32*).

Also of interest in this study was the postoperative adjuvant therapy that the patients received. In this study, patients will undergo postoperative targeted combination immunotherapy after surgery based on pathology findings. To date, 43 individuals in this cohort have completed postoperative adjuvant therapy. We believe that postoperative adjuvant therapy plays a positive role in preventing postoperative recurrence in patients, while its mechanism and efficacy still need to be revealed

by further research. A postoperative adjuvant program based on a combination of surgical and pathologic findings to guide the process provides a clear plan for discontinuation of the drug. This has helped to minimize adverse drug reactions and economic burden for patients.

Sixty-four patients in the conversion therapy group experienced adverse events during conversion therapy, 44 of whom had a CTCAE event grade ≥ 2. No patients discontinued the conversion regimen due to treatment-related adverse events and considerable variations were not observed between the two groups regarding bleeding volume, intraoperative blood transfusion, and postoperative hospitalization days. In the conversion therapy group, five patients developed postoperative biliary fistula, one developed postoperative bleeding, one suffered from pancreatitis, and one had postoperative secondary portal thrombosis (right anterior branch). The non-significant differences in Clavein-Dindo scores between the two groups suggest the safety of immunotherapy combined with targeted sequential surgical regimens. Compared with traditional surgical treatment of liver cancer, the difference in perioperative complication rates was not statistically significant, confirming the safety and feasibility of this protocol.

There are certain limitations to this study. The nature of this historical-prospective study leads to some bias and the sample size included in the subgroup was small. Moreover, statistically positive outcomes were difficult to obtain in some patients. Nevertheless, this study contains the largest cohort and assesses the efficacy and safety of immunotherapy combined with targeted sequential surgical therapy in individuals with advanced HCC. It provides a detailed analysis of the efficacy and safety of treatment in multiple subgroups of patients.

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Appendix Data

Table S1. Conversion therapy protocols

Conversion therapy protocols	No. of patients, No. (%)
Sintilimab+lenvatinib	66 (75.0)
pembrolizumab+lenvatinib	8 (9.1)
Tislelizumab+lenvatinib	5 (5.7)
Toripalimab+lenvatinib	5 (5.7)
Camrelizumab+apatinib	1 (1.1)
Toripalimab+apatinib	1 (1.1)
Camrelizumab + lenvatinib	1 (1.1)
Navulizumab+lenvatinib	1 (1.1)