Original Article

Factors influencing the prognosis patients with Barcelona Clinic Liver Cancer stage C hepatocellular carcinoma undergoing salvage surgery after conversion therapy

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Background: The aim of this study was to investigate the prognostic factors influencing the outcome of patients with Barcelona Clinic Liver Cancer stage C hepatocellular carcinoma (HCC) receiving salvage surgery after conversion therapy based on tyrosine kinase inhibitors (TKIs) and anti-programmed death-1 (PD-1) antibodies.

Methods: From June 2018 to December 2022, patients receiving salvage surgery after conversion therapy based on PD-1 and TKIs at the Faculty of Hepato-Pancreato-Biliary Surgery, Chinese PLA General Hospital were retrospectively recruited for this study. Overall survival (OS) and recurrence-free survival (RFS) were observed as the primary end point in the Cox analysis of prognostic factors among this study.

Results: The 6- and 12-month RFS rates were 77.0% and 64.8%, respectively, while the 6-, 12-, 24-, and 36-month OS rates were 98.4%, 93.4%, 76.8%, and 69.8%, respectively. The median OS and RFS were not reached. On multivariable Cox regression analyses, low serum alpha fetoprotein (AFP) level (≤20 ng/mL) after conversion therapy [hazard ratio (HR) 0.186, 95% CI: 0.039–0.887; P=0.035) and microvascular invasion (MVI) grade II (HR 3.054, 95% CI: 1.000–9.329; P=0.050) were independent factors associated with a higher OS and RFS.

Conclusions: For patients with Barcelona Clinic Liver Cancer stage C (BCLC-C) HCC, lower AFP level after conversion therapy (<20 ng/mL) and MVI II were associated with a higher OS and lower RFS rate, respectively.

Keywords: Hepatocellular carcinoma (HCC); tyrosine kinase inhibitor (TKI); anti-programmed death-1 (PD-1) antibody; conversion therapy; salvage surgery

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common tumor worldwide and ranks third in cancer-related death (1). Moreover, 70–80% of patients with HCC are initially diagnosed with Barcelona Clinic Liver Cancer (BCLC) stage C, and the prognosis of these patients is dismal, with a median overall survival (mOS) of a mere 2.7–4 months without any treatment (2,3). The 5-year survival rate of patients with BCLC-C HCC undergoing hepatectomy alone is 23.8–39.1% (4,5). However, a new therapeutic paradigm of advanced HCC has emerged in recent years. Several trials based on tyrosine kinase inhibitor (TKI) and anti-programmed death-1 (PD-1) antibody combinations have shown a remarkable effect in improving the survival benefits for patients with BCLC-C, with an mOS reaching 22–24 months (6-8). Salvage surgery after conversion therapy has become a reasonable practice owing of the effect of downstaging yielded from combined protocols, and previous studies have already demonstrated the improvement of survival rate compared with those previously reported (9-13).

However, few studies have thus far examined the factors associated with the prognosis of salvage surgery after conversion therapy. Identifying the factors related the survival time of patients with BCLC-C HCC treated with salvage surgery after conversion therapy can help us predict the prognosis of these patients and select those most suited for this type of therapy. Since previous studies have not included a sufficient number of patients and discussed factors associated with survival benefit, we conducted this research to investigate the factors influencing survival benefits in a retrospective cohort of patients with BCLC-C HCC who received salvage surgery after conversion therapy. We present this article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-70/rc).

Highlight box

Key findings

- For patients with Barcelona Clinic Liver Cancer stage hepatocellular carcinoma (HCC) undergoing salvage surgery after conversion therapy based on tyrosine kinase inhibitors (TKIs) and anti-programmed death-1 (PD-1) antibodies, lower alpha fetoprotein (AFP) level after conversion therapy and microvascular invasion (MVI) II were associated with overall survival (OS) and recurrence-free survival (RFS).

What is known and what is new?

- What is known: Salvage surgery after conversion therapy has become a reasonable practice, and previous studies have demonstrated the development in survival rate.
- What is new: We found that lower AFP level after conversion therapy <20 ng/mL) and MVI II were associated with OS and RFS rate.

What is the implication, and what should change now?

- The results reveal the association between AFP levels and MVI grade after conversion therapy and the prognosis of these patients. This suggests that AFP levels and MVI II are related to the survival benefit of patients receiving conversion therapy.

Methods

Patient enrollment

This retrospective cohort study was conducted with patients who underwent hepatectomy after conversion therapy based on PD-1 antibody and TKIs after being diagnosed with BCLC-C stage HCC at the Chinese PLA General Hospital from June 2018 to December 2022. The criteria for inclusion were as follows: (I) age of 18 to 80 years, (II) Child-Pugh class A liver function, (III) HCC with portal vein tumor thrombus (PVTT) diagnosed by the American Association for the Study of Liver Diseases (AASLD) guidelines or postoperative pathological examination, (IV) R0 resection confirmed by postoperative pathological examination, (V) no previous treatment with PD-1 antibody, TKIs or any other combination protocols, (VI) no history of other malignant tumors in the previous 5 years, and (VII) Eastern Cooperative Oncology Group performance status (ECOG PS) score <2.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Chinese People's Liberation Army (PLA) General Hospital (Beijing, China; Approval No. S2018-111-01), and individual consent for this retrospective analysis was waived.

Data collection and patient follow-up

The following data were collected from individual medical records: age, gender, etiology of hepatitis [hepatitis B was defined as hepatitis B surface antigen (HBsAg) positive], serum alpha fetoprotein (AFP) at initial diagnosis and after conversion therapy, other local therapy [transarterial chemoembolization (TACE), Hepatic Artery Infusion Chemotherapy (HAIC) etc.], tumor diameter (the largest tumor diameter was taken as the size of HCC, regardless of the number of tumors), tumor number, portal vein tumor

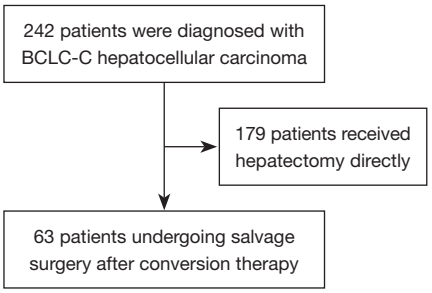

Figure 1 Flowchart of this study. BCLC-C, Barcelona Clinic Liver Cancer stage C.

thrombosis classification(Classification based on JSH typing, VP0, no PVTT; VP1, PVTT confined to portal branches distant from secondary branches; VP2, PVTT involving secondary branches of portal vein; VP3, PVTT involving primary branches of portal vein; VP4, PVTT invading main trunk of portal vein or contralateral primary branches), hepatic vein tumor thrombosis classification [classification based on JSH typing, tumor thrombosis in a peripheral hepatic vein (pHVTT, Vv1), in a major hepatic vein (mHVTT, Vv2), or in the inferior vena cava (IVCTT, Vv3)], lymph node metastasis, assessment of modified Response Evaluation Criteria in Solid Tumors (m-RECIST), pathological complete response (PCR; no residual viable tumor after conversion therapy), satellite nodules, microvein invasion, surgery procedure, extent of resection, intraoperative blood loss, perioperative blood transfusion, and cycles of conversion therapy (14-16). The classification of microvascular invasion (MVI) was associated with the recurrence-free survival (RFS) of these patients according to the report by Sumie *et al.* on the classification of MVI (no MVI; mild MVI, 5 or fewer total blood vessels involved; severe MVI, more than 5 total blood vessels involved) (17). Adverse events were assessed with the use of the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Postoperative complications were evaluated according to the Clavein-Dindo classification (18). Liver function was assessed using Child-Pugh score. The primary end point was RFS, and the secondary end point was overall survival (OS). Follow-up using telephone interview or outpatient examination was performed up to April 2022.

Downstaging protocol and efficacy assessment

The patients received TKI combined PD-1 antibody as conversion therapy protocols. Protocols were selected mainly with reference to achieving a high objective response rate (ORR) (Table S1). Postoperative treatment was guided by the results of histological examination: (I) patients who achieved PCR received only initial PD-1 antibody for 6 months; (II) patients who did not achieve PCR received the initial combination therapy for 6–12 months according to the follow-up imaging results. Efficacy was assessed every 3 months.

Indications for hepatectomy

Indications for salvage surgery were the following: (I) Child-Pugh score of 5 to 6 before hepatectomy; (II) sufficient postoperative residual functional liver volume. The residual liver volume accounted for ≥35% of the standard liver volume in patients without cirrhosis and ≥45% in patients with cirrhosis; (III) a retention rate of indocyanine green at 15 min of less than 20%; (IV) intact inflow and outflow tracts of liver parenchyma; (V) an ECOG score 0–1; (VI) American Society of Anesthesiologists Rating ≤3; (VII) written informed consent (19).

Statistical analysis

The independent samples *t*-test, Mann-Whitney test, chi-squared test, or Fisher exact test were used for comparison between groups. The Kaplan-Meier method was used for survival analysis. The factors associated with survival in univariate analysis ($P<0.1$) were included in the Cox proportional hazards regression model. $P<0.05$ was considered statistically significant. SPSS 26.0 software (IBM Corp.) was used for statistical analysis

Results

Baseline characteristics

From June 2018 to December 2022, 242 patients diagnosed with BCLC-C HCC who received hepatectomy were recorded, among whom 63 met the inclusion criteria (*Figure 1*). Of the 63 patients, 55 were male (87.3%) and 8 were female (12.7%), and the average age at the time of initial diagnoses was 53.7 years. Hepatitis B infection was the most common cause of existing liver disease in 55 patients (87.3%), which was followed by other causes in 8 patients (12.7%). Moreover, 13 patients (20.6%) received other local therapy (TACE, etc.) combined with our conversion therapy. The initial serum AFP value was high (>20 ng/mL) in 49 patients (77.8%). After conversion

therapy, serum AFP level decreased to normal in 27 patients and remained high in 22 patients, and 14 patients were negative for serum AFP during the conversion therapy. The PVTT classification value was VP0 for 14 (22.2%) patients, VP1 for 0 (0.0%), VP2 for 8 (12.7%), VP3 for 22 (34.9%), and VP4 for 19 (30.2%) patients. Additionally, 50 (79.4%), 0 (0.0%), 8 (12.7%), and 5 (7.9%) patients were assessed with grade 0, I, II, and III hepatic vein tumor thrombus (HVTT). In addition, 15 patients (23.8%) were observed with lymph node metastasis. According to the m-RECIST, 15 (23.8%) patients had complete response (CR), 38 (60.3%) had partial response (PR), 5 (7.9%) had stable disease (SD), and 5 (7.9%) had progressive disease (PD). Moreover, 15 patients (23.8%) reached major pathologic response (MPR) according pathological examination. There were 55 (87.3%) specimens with satellite nodules and microvein invasion. Regarding MVI classification, 15 (23.8%) patients were MVI, 6 (9.5%) were MVI I, and 9 (14.3%) were MVI II. Furthermore, 27 (42.9%) patients underwent thrombectomy during surgery, and 34 (54.0%) patients received major hepatectomy. There were 25 patients whose intraoperative blood loss was less than 400 mL (39.7%), and 21 patients (33.3%) underwent perioperative blood transfusion. The duration of treatment ranged from 3 to 20 cycles, with a median of 5 cycles (*Table 1*). The patients' conversion therapy protocols were as follows: 50 patients were given sintilimab + lenvatinib (79.4%), 4 patients were given pembrolizumab + lenvatinib (6.3%), 4 patients were given tislelizumab + lenvatinib (6.3%), 3 patients were given tislelizumab + lenvatinib (4.8%), 3 patients were given toripalimab + lenvatinib (4.8%), 1 patient was given camrelizumab + apatinib (1.6%), 1 patient was given toripalimab + apatinib1 (1.6%), and 1 patient was given toripalimab + sorafinib1 (1.6%).

Follow-up data

The median follow-up time was 23 months (range, 18.28–27.72) in the cohort, recurrence was found in 20 patients (31.7%), and 14 HCC-related deaths occurred (22.2%). The 6- and 12-month RFS rates were 77.0% and 64.8%, respectively, while the 6-, 12-, 24-, and 36-month OS rates were 98.4%, 93.4%, 76.8%, and 69.8%, respectively. The median RFS and OS were not reached (*Figures 2,3*).

Factors influencing survival rate after hepatectomy

In the univariate analysis, the survival rate was higher among patients with low serum AFP level (≤20 ng/mL) after conversion therapy [hazard ratio (HR) 0.156, 95% CI: 0.034–0.713; P=0.017]. MVI grade II assessed by pathological examination was also a significantly associated with a poor survival rate (HR 3.917, 95% CI: 1.277–12.008; P=0.017) (*Table 2*). The RFS rate was associated with low serum AFP level (≤20 ng/mL) after conversion therapy (HR 0.246; 95% CI: 0.087–0.693; P=0.008), low serum AFP level (≤20 ng/mL) at initial diagnose (HR 0.163, 95% CI: 0.036–0.726; P=0.017), MVI grade II (HR 5.419, 95% CI: 1.950–15.062; P=0.001), and satellite nodules (HR 3.095, 95% CI: 1.118–8.571; P=0.030) (*Table 3*).

In the multivariate analysis performed with variables that were significant in the univariate analysis of OS, low serum AFP level (≤20 ng/mL) after conversion therapy (HR 0.186, 95% CI: 0.039–0.887; P=0.035) was an independent factor associated with a higher OS (*Table 2*). In the multivariate analysis performed with significant variables from the univariate analysis of RFS, MVI grade II assessed by pathological examination was independent factor associated with a higher survival rate (HR 3.054; 95% CI: 1.000–9.329; P=0.050) (*Table 3*).

Discussion

Principal results

Patients with BCLC-C HCC are considered difficult to cure, and the OS of these patients is 2.7–6 months (2,3). Fortunately, an increase in the long-term survival rate has been reported in patients with BCLC-C HCC undergoing new conversion therapy based on PD-1 antibodies and TKIs. Additionally, conversion therapy has led to a significant reduction in the tumor burden, leading to a greater number of hepatectomies as curative treatment for these patients (19). Salvage surgery after conversion therapy might further improve patients' survival benefit. Previous studies have reported that the 1-year RFS rate and OS rate after salvage hepatectomy from BCLC-C HCC is 74.7–92.9% and 92.6%, respectively (9-11,20). However, few studies have reported on those factors associated with the prognosis of these patients. In the present study, we recruited 64 patients undergoing salvage surgery after conversion therapy, and the 6-, 12-, 24-, and 36-month OS rates were 98.4%, 93.4%, 76.8%, and 69.8%, respectively, while the 6- and 12-month RFS rates were 77.0% and 64.8%, respectively. Patients received a similar survival benefit as that mention in our previous research (13).

Table 1 Baseline characteristics

Variable, n (%)	Value (n=63)
Age, years (mean ± SD)	53.7±10.6
Sex, male/female	55 (87.3)/8 (12.7)
Underlying liver disease, HBV/other	55 (87.3)/8 (12.7)
Initial AFP, >20/≤20 ng/mL	49 (77.8)/14 (22.2)
AFP after conversion	
>20 ng/mL after conversion	22 (34.9)
≤20 ng/mL after conversion	27 (42.9)
≤20 ng/mL Initially	14 (22.2)
Local therapy, yes/no	50 (79.4)/13 (20.6)
Tumor diameter, cm	8.9 (2.8–19.0)
Tumor numbers, multiple/single	44 (69.8)/19 (30.2)
PVTT classification, VP0/VP1/VP2/VP3/VP4	14 (22.2)/0 (0.0)/8 (12.7)/22 (34.9)/19 (30.2)
HVTT classification, 0/I/II/III	50 (79.4)/0 (0.0)/8 (12.7)/5 (7.9)
Lymph node metastasis, yes/no	15 (23.8)/48 (76.2)
m-RECIST assessment, CR/PR/SD/PD	15 (23.8)/38 (60.4)/5 (7.9)/5 (7.9)
PCR, yes/no	15 (23.8)/48 (76.2)
Satellite nodules, yes/no	55 (87.3)/8 (12.7)
Microinvasion, yes/no	
0	48 (76.2)
1	6 (9.5)
2	9 (14.3)
Surgery procedure, thrombectomy/en bloc	27 (42.9)/36 (57.1)
Extent of resection, major/minor	34 (54.0)/29 (46.0)
Intraoperative blood loss, >400/≤400 mL	25 (39.7)/38 (60.3)
Perioperative blood transfusion, yes/no	21 (33.3)/42 (66.7)
Cycle of conversion therapy, >5/≤5 cycles	22 (34.9)/41 (65.1)

SD, standard deviation; HBV, hepatitis B virus; AFP, alpha-fetoprotein; PVTT, portal vein tumor thrombus; HVTT, hepatic vein tumor thrombus; PCR, pathological complete response; m-RECIST, modified Response Evaluation Criteria in Solid Tumors version.

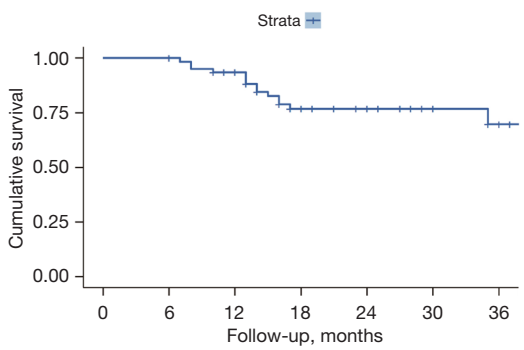

Figure 2 Overall survival in patients undergoing salvage surgery after conversion therapy.

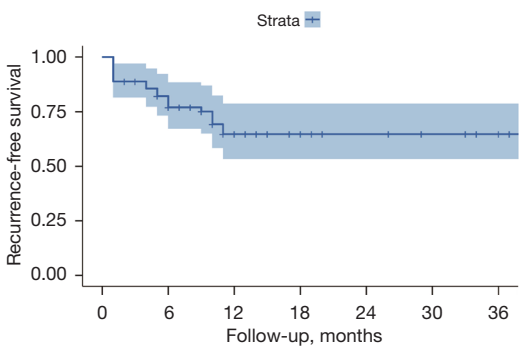

Figure 3 Recurrence-free survival in patients undergoing salvage surgery after conversion therapy.

Table 2 Factors affecting overall survival in patients undergoing salvage surgery after conversion therapy

Variable	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Age (>60 *vs.* ≤60 years)	0.796 (0.222–2.858)	0.727		
Gender (male *vs.* female)	1.332 (0.298–5.955)	0.708		
Underlying liver disease (HBV *vs.* other)	0.864 (0.193–3.864)	0.848		
AFP at initial diagnosis (>20 *vs.* ≤20 ng/mL)	2.381 (0.528–10.730)	0.259		
AFP after conversion therapy				
>20 ng/mL	1			
≤20 ng/mL after conversion therapy	0.156 (0.034–0.713)	0.017	0.186 (0.039–0.887)	0.035
≤20 ng/mL at initial diagnosis	0.223 (0.049–1.024)	0.054		
Other local therapy (yes *vs.*no)	0.182 (0.033–1.971)	0.251		
Tumor diameter (>10 *vs.* ≤10 cm)	2.346 (0.818–6.731)	0.113		
Tumor number (multiple *vs.* single)	1.724 (0.596–4.993)	0.315		
PVTT classification (VP0 + VP2 *vs.*VP3 + VP4)	1.273 (0.399–4.063)	0.683		
HVTT classification (0 *vs.* II + III)	1.525 (0.477–4.872)	0.477		
Lymph node metastasis (yes *vs.* no)	1.067 (0.296–3.845)	0.921		
m-RECIST (CR + PR + SD *vs.* PD)	1.379 (0.179–10.600)	0.758		
PCR (yes *vs.* no)	0.240 (0.031–1.838)	0.170		
Satellite nodules (yes *vs.* no)	2.925 (0.915–9.351)	0.070		
Microvein invasion				
0	1			
1	1.13 (0.141–9.054)	0.908		
2	3.917 (1.277–12.008)	0.017	2.177 (0.649–7.302)	0.208
Surgery procedure (thrombectomy *vs.* en bloc)	1.313 (0.459–3.751)	0.612		
Extent of resection (major *vs.* minor)	1.130 (0.391–3.263)	0.821		
Intraoperative blood loss (>400 *vs.* ≤400 mL)	1.387 (0.485–3.965)	0.542		
Perioperative blood transfusion (yes *vs.* no)	2.095 (0.734–5.981)	0.167		
Cycle of conversion therapy (>5 *vs.* ≤5 cycles)	0.639 (0.200–2.041)	0.449		

HR, hazard ratio; CI, confidence interval; HBV, hepatitis B virus; AFP, alpha-fetoprotein; PVTT, portal vein tumor thrombus; HVTT, hepatic vein tumor thrombus; PCR, pathological complete response; m-RECIST, modified Response Evaluation Criteria in Solid Tumors version; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Univariate and multivariate analyses

In this study, we analyzed the factors influencing OS and RFS in patients who underwent salvage hepatectomy after conversion therapy for BCLC-C HCC by investigating patient age, gender, hepatitis etiology, clinical and laboratory data, assessment of imagine material, postoperative pathological examination, surgery information, and perioperative indicators. In the univariate analysis, patients with low serum AFP level (≤20 ng/mL) after conversion therapy and MPR had a higher OS than did those without these features, whereas patients with preoperative AFP <20 ng/mL, MVI grade II, and satellite nodules had a higher RFS. In the multivariate analysis, low

Table 3 Factors affecting recurrence-free survival in patients undergoing salvage surgery after conversion therapy

Variable	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Age (>60 *vs.* ≤60 years)	0.459 (0.134–1.565)	0.213		
Gender (male *vs.* female)	0.816 (0.189–3.518)	0.785		
Underlying liver disease (HBV *vs.* other)	1.293 (0.299–5.587)	0.730		
AFP at initial diagnose (>20 *vs.* ≤20 ng/mL)	3.518 (0.816–15.166)	0.091		
AFP after conversion therapy				
>20 ng/mL	1			
≤20 ng/mL after conversion therapy	0.246 (0.087–0.693)	0.008	0.339 (0.113–1.012)	0.053
≤20 ng/mL at initial diagnose	0.163 (0.036–0.726)	0.017	0.258 (0.053–1.249)	0.092
Other local therapy (yes *vs.* no)	1.334 (0.484–3.673)	0.578		
Tumor diameter (>10 *vs.* ≤10 cm)	1.180 (0.470–2.959)	0.725		
Tumor number (multiple *vs.* single)	2.250 (0.931–5.443)	0.072		
PVTT classification (VP0 + VP2 *vs.* VP3 + VP4)	2.373 (0.793–7.104)	0.122		
HVTT classification (0 *vs.* II + III)	0.988 (0.330–2.956)	0.982		
Lymph node metastasis (yes *vs.* no)	0.571 (0.167–1.950)	0.371		
m-RECIST (CR + PR + SD *vs.* PD)	0.456 (0.133–1.556)	0.210	1.039 (0.321–3.361)	0.949
PCR (yes *vs.* no)	0.139 (0.019–1.040)	0.055		
Satellite nodules (yes *vs.* no)	3.095 (1.118–8.571)	0.030	1.782 (0.570–5.570)	0.321
Microvein invasion				
0	1		1	-
1	2.585 (0.720–9.287)	0.145	2.170 (0.576–8.179)	0.252
2	5.419 (1.950–15.062)	0.001	3.054 (1.000–9.329)	0.050
Surgery procedure, (thrombectomy *vs.* en bloc)	0.862 (0.352–2.113)	0.746		
Extent of resection (major *vs.* minor)	1.309 (0.535–3.203)	0.555		
Intraoperative blood loss (> 400 *vs.* ≤400 mL)	1.507 (0.627–3.622)	0.359		
Perioperative blood transfusion (yes *vs.* no)	1.531 (0.624–3.752)	0.352		
Cycle of conversion therapy (>5 *vs.* ≤5 cycles)	0.898 (0.358–2.253)	0.818		

HR, hazard ratio; CI, confidence interval; HBV, hepatitis B virus; AFP, alpha-fetoprotein; PVTT, portal vein tumor thrombus; HVTT, hepatic vein tumor thrombus; PCR, pathological complete response; m-RECIST, modified Response Evaluation Criteria in Solid Tumors version; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

serum AFP level (≤20 ng/mL) after conversion therapy was the only factor associated with OS, while MVI grade II was associated with RFS.

Serum AFP level

Alpha fetoprotein level is a widely used tumor marker in HCC diagnosis although serum AFP level remains controversial in this regard; moreover, the decline in serum AFP levels through conversion therapy based on PD-1 or other local therapies has been shown to be associated with tumor response in several studies (21,22). Shao *et al.* and Sun *et al.* reported results illustrating the relation of tumor response with serum AFP level, with AFP response

reflecting a higher OS rate (23,24). Similarly, in the RESORCE (Regorafenib after Sorafenib in Patients with Hepatocellular Carcinoma) study, 232 patients had an improved OS with an AFP response, which was defined as a decrease of ≥20% in AFP level from baseline at the start of cycle 3 (25). In the present study, serum AFP level decreased to normal after conversion therapy in 27 patients (42.9%), 22 patients (34.9%) had high preoperative levels, and 14 patients (22.2%) had low serum AFP levels during the conversion therapy. We found that among patients whose serum AFP level was high at initial diagnose, those whose AFP level reduced to normal after conversion therapy had an improved survival rate, which is in line with previous research (23,24). In addition, Zhu *et al.* found that the overall prognosis is well reflected by serum AFP level measured at initial diagnosis (25). In our study, low serum AFP level at initial diagnosis was associated with a higher RFS rate in the univariate analysis but not in multivariate analysis. The mechanism underlying the association between a decrease in AFP and tumor response may be the simultaneous reduction of tumor burden and serum AFP level caused by conversion therapy based on PD-1 antibodies and TKIs. It may also be that serum AFP level is a marker for the timing of surgery in patients receiving conversion therapy. We also believe lower AFP level after conversion therapy may be associated with RFS rate; however, the *P* value was slightly higher than 0.05 (P=0.053) and thus failed to meet the threshold of significance, possibly due to our small sample size.

Microvascular invasion

Microvascular invasion is considered to be a critical determinant of the early recurrence of HCC and its prognosis (26,27). One study that examined patients who underwent hepatectomy for HCC suggested that microvascular invasion in these patients is a risk factor of recurrence after hepatectomy (27). MVI appears as small thrombi of malignant cells in the portal and hepatic venous systems and is usually detected by postoperative pathological examination (28). In the study of Li *et al.*, MVI was detected in 38.7–48.6% of the patients through pathological examination after surgery (29). However, in our study, MVI was found in 15 patients (23.8%), account for a smaller proportion. Moreover, the classification of MVI did not have the same association to the RFS of these patients as that reported in the study by Sumie *et al.* in which both mild MVI (MVI I, 5 or fewer total blood vessels involved) and severe MVI (MVI II, more than 5 total blood vessels involved) were independent predictors of poor outcome (17). In the present study, MVI I was not significantly associated with a worse survival rate either in univariate analysis or multivariate analysis. Of the patients with MVI, 9 patients (14.3%) had MVI II, and the RFS rate was apparently lower in the univariate analysis and multivariate analysis for these patients. This result may be attributable to the tumor-reducing effect caused by conversion therapy, similar to the decline in serum AFP level. It was demonstrated that MVI I patients can benefit more from conversion therapy than can MVI II patients. MVI II patients may experience more drug resistance to conversion therapy, leading to a relatively poor response. Appropriate prolongation of postoperative medication administration or superimposing of other local treatments in MVI II patients should be encouraged and may improve the RFS rate among these patients. Furthermore, many studies indicate that high serum AFP level is a risk factor for MVI (30,31). The decline in serum AFP levels may point to the disappearance of MVI, a phenomenon which could be explained by the sensitively of response to conversion therapy. However, more prospective studies should be conducted to confirm these conclusions.

Pathological complete response

Pathological complete response refers to no residual viable tumor detected in pathological examination. PCR has been demonstrated to be a significant factor in predicting the prognosis in many other cancers owing to its relationship with tumor activity (32,33). Several studies have reported that the proportion of PCR in patients with HCC undergoing conversion therapy based on PD-1 antibodies and TKIs was 23.5–60% (9,12). In our study, 15 patients (23.8%) were assessed with PCR through pathological examination, which is consistent with previously reported data (9,12). However, in our study, PCR did not show an association with survival rate in either univariate or multivariate analysis. A similar result was reported by Xia *et al.* in 17 patients undergoing hepatectomy, 4 of whom experienced PCR (12). Although PCR represents the best response to conversion therapy, patients who receive an excellent conversion effect through conversion therapy may not be evaluated as PCR due to a lower cycle of conversion, less sensitivity to the combined protocol, or other reasons. PCR in patients may not reflect the difference in survival benefit in those treated with conversion therapy compared to those not treated. In some studies, MPR (a certain

proportion or less residual viable tumor after conversion therapy) has been used as a new pathological response index to evaluate preoperative treatment effect (34-36). MPR screens out potential patients who experience an improved survival benefit but have not reached PCR. In most types of tumor, MPR refers to a 10% or less residual viable tumor after conversion therapy, but the proportion in patients with HCC has not been determined. Larger sample, prospective research should be conducted to determine the boundary value of MPR in HCC to more critically evaluate the conversion therapy effect.

Limitations

Several limitations of the present study should be taken into consideration: (1). A retrospective cohort design was employed which might have introduced potential bias (2). Studies with a greater number of patients should be conducted to confirm and extend our findings. In spite of the above-mentioned limitations, our study has 2 main strengthens: (I) since salvage surgery after conversion therapy is a new field in the treatment of BCLC-C HCC, the size of our cohort can be considered large in this regard; (II) the results in this study may guide clinical practice to a certain extent.

In general, indicators reflecting the efficacy of conversion therapy show the most relevant relationship with survival benefit in present study. Oncology benefits yielded from conversion therapy were significantly associated with improved survival benefit.

Conclusions

Since salvage surgery after conversion therapy based on PD-1 antibodies and TKIs improve survival time, factors associated with this protocol were identified in this study. A lower AFP level (<20 ng/mL) was associated with a higher OS rate, and a relationship between MVI II and lower RFS was revealed. These results provide guidance for the timing of surgery and support a more active postoperative use of the combined regimen. However, more prospective, and large-scale studies of conversion therapy and subsequent surgery still need to be conducted to ensure a greater proportion of patients with BCLC-C HCC benefit from this therapy.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-70/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Chinese People's Liberation Army (PLA) General Hospital (Beijing, China; Approval No. S2018-111-01) and individual consent for this retrospective analysis was waived.

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