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Prognostic Value of Pathological Response for Patients with Unresectable Hepatocellular Carcinoma Undergoing Conversion Surgery

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Keywords

Hepatocellular carcinoma · Conversion surgery · Pathological response · Overall survival · Recurrence-free survival · Predictive factor

Abstract

Introduction: Transarterial chemoembolization combined with lenvatinib and PD-1 inhibitor (triple therapy) has displayed encouraging clinical outcomes for unresectable hepatocellular carcinoma (uHCC). We aimed to explore the prognostic value of pathological response (PR) in patients with initially uHCC who underwent conversion surgery following triple therapy and identify predictors of major pathological response (MPR). ***Methods:*** A total of 76 patients with initially uHCC who underwent conversion surgery following triple therapy were retrospectively analyzed. PR was calculated as the proportion of nonviable tumor cell surface area of the whole tumor bed surface area. MPR was identified when PR was ≥90%. Pathological complete response (pCR) was defined as the absence of viable tumor cells. ***Results:*** MPR and pCR were identified in 53 (69.7%) and 25 (32.9%) patients, respectively. The 1- and 2-year overall survival in patients with MPR were significantly higher than in those without MPR (100.0% and 91.3% vs. 67.7% and 19.4%; $p < 0.001$). The corresponding recurrence-free survival was also improved in patients with MPR compared to those without (75.9% and 50.8% vs. 22.3% and 11.2%; $p < 0.001$). Similar results were observed among patients with pCR and those without. Patients who achieved MPR without pCR exhibited survival rates comparable to those of patients who achieved pCR. Baseline neutrophil-to-lymphocyte ratio ≥2.6 ($p = 0.016$) and preoperative alpha-fetoprotein level ≥400 ng/mL ($p = 0.015$) were independent predictors of MPR. ***Conclusion:*** The presence of MPR or pCR could improve prognosis in patients with initially uHCC who

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underwent conversion surgery following triple therapy. The PR may become a surrogate marker for predicting the prognosis of these patients.
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Plain Language Summary

The combination of transarterial chemoembolization, lenvatinib, and PD-1 inhibitor is an efficacious conversion therapy for uHCC. In this multicenter retrospective study, we discovered that PR was associated with the prognosis of patients who underwent conversion surgery. Predictors of MPR included neutrophil-to-lymphocyte ratio and alpha-fetoprotein levels.
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Introduction

Hepatocellular carcinoma (HCC) is ranked as the sixth most common malignancy and the third most prevalent cause of cancer-related mortality worldwide [1]. Although surgical resection is a curative treatment option for patients with HCC, most of them are ineligible for radical surgery upon initial diagnosis [2–4]. Conversion therapies, such as systemic or locoregional treatment strategies, are adopted to downstage or alleviate the tumor burden in patients with initially unresectable HCC (uHCC) to provide them with an opportunity for curative surgery [5–8].

Transarterial chemoembolization (TACE) is a commonly used locoregional conversion strategy in the management of uHCC [9–11]. Several studies have revealed that the degree of TACE-induced pathologic tumor necrosis has a prognostic impact in patients with HCC [12–14]. Allard et al. [14] demonstrated that achieving a pathological complete response (pCR) or nearly pCR to preoperative TACE could improve postoperative overall survival (OS) and recurrence-free survival (RFS) in patients with HCC. Notably, in patients with breast cancer, gastric cancer, colorectal cancer, or colorectal liver metastases who received preoperative chemotherapy, the pathological response (PR) has been established as a crucial determinant of prognosis [15–18]. These findings indicated that conversion therapies may confer prognostic benefits by inducing pathologic tumor necrosis.

Recently, accumulating studies have revealed that combining locoregional and systemic therapy may enhance the antitumor activity and improve the conversion resection rate in patients with initially uHCC [19–24]. In a phase 2 clinical trial, sequential TACE and stereotactic body radiotherapy followed by immunotherapy were proven to be an effective conversion therapy for patients with locally advanced uHCC [25]. Furthermore, our previous study discovered that the combination of TACE, lenvatinib, and PD-1 inhibitor (triple therapy) demonstrated promising clinical outcomes for uHCC, with a major pathological response (MPR) rate of 84.3% [26]. The 2-year OS and RFS rates of patients who underwent conversion surgery were 94.4% and 54.4%, respectively [26]. Nevertheless, the relationship between the PR to triple therapy and the postoperative prognosis remains unclear. Therefore, we conducted this multicenter retrospective study to explore the prognostic value of PR in patients with initially uHCC who underwent conversion surgery following triple therapy. Furthermore, we identified preoperative predictors for achieving MPR.

Methods

Study Population

In this retrospective study, we collected medical records of consecutive patients with initially uHCC who underwent conversion surgery following triple therapy at seven centers in China (the Fujian Provincial Hospital, First Affiliated Hospital of Fujian Medical University, The Second Affiliated Hospital of Nanchang University, Zhangzhou Affiliated Hospital of Fujian Medical University, First Affiliated Hospital of Xiamen University, Zhongshan Hospital of Xiamen University, and Affiliated Hospital of Guilin Medical University) between June 2018 and October 2022. The study was conducted according to the Declaration of Helsinki and approved by the Ethics Committee of each center.

The inclusion criteria were as follows: (1) patients with initially uHCC who underwent conversion surgery following triple therapy; (2) individuals aged between 18 and 75 years old; (3) diagnosed with Barcelona Clinic Liver Cancer (BCLC) stage B or C. The exclusion criteria were as follows: (1) accompany by other malignancies; (2) death related to surgery within 30 days; (3) lack of important data.

HCC was diagnosed and staged according to the China Liver Cancer staging and the BCLC staging system, respectively [3, 4]. Tumor unresectability was evaluated by a multidisciplinary team and defined as lesions not amenable to curative resection because of extensive bi-lobar liver involvement, extrahepatic metastases, inadequate hepatic functional reserve, or insufficient remnant liver volume (ratio of the future liver remnant to the whole liver volume <40% in patients with liver cirrhosis and <30% in patients without liver cirrhosis). To further evaluate the survival benefit of conversion surgery, patients with resectable HCC with the same tumor stage who underwent upfront surgery at the Fujian Provincial Hospital during the same period were included as a control group.

Triple Therapy Procedure

Conventional TACE was performed on all patients. After puncturing the right femoral artery, a catheter was used to locate the feeding artery of the tumor. Super-selective chemoembolization of the feeding artery was performed via a microcatheter by injecting a mixture of pirarubicin and iodized oil. Finally, the feeding artery of the tumor was embolized with gelatin sponge particles. TACE was repeated at an interval of 4–6 weeks based on the assessment of the target tumor (especially evidence of supplying arteries) and the recovery of liver function.

The administration of lenvatinib and PD-1 inhibitor began within 3–14 days after the first TACE treatment. Lenvatinib was taken orally once a day at a dosage of 8 mg for individuals with a body weight <60 kg, or 12 mg for those with a body weight ≥60 kg. PD-1 inhibitor (toripalimab 240 mg, camrelizumab 200 mg, sintilimab 200 mg, pembrolizumab 200 mg, tislelizumab 200 mg, or penpulimab 200 mg) was administered intravenously every 3 weeks. Lenvatinib and PD-1 inhibitor were discontinued 3 days before each TACE session. Both medications would be resumed 3 days later if there were no severe TACE-related adverse events. The toxicity profile of triple therapy was evaluated based on treatment-related adverse events, which were monitored and graded based on the Common Terminology Criteria for Adverse Events version 5.0 [27].

Surgical Procedure

Tumor resectability assessment was performed every 4–6 weeks following the initiation of triple therapy. Once the tumor met the criteria for resectability, conversion surgery was considered after the discussion by the multidisciplinary team. The criteria for converting to resectable HCC were the same as in our previous study. Briefly, the criteria included having sufficient remnant liver volume for R0 resection, well-preserved liver function, good performance status, and no extrahepatic metastasis [26].

Before and after surgery, lenvatinib was temporarily discontinued for 1 week, and PD-1 inhibitor was temporarily discontinued for 4 weeks. The scope and method of liver resection were determined based on the stage and location of tumors, evaluation of the remaining liver function, and patient's overall performance. According to Brisbane 2000 terminology [28], liver resections were categorized as major hepatectomy (involving ≥3 anatomical segments) or minor hepatectomy (involving <3 anatomical segments).

Pathologic Examination

Tumor size, tumor number, satellite nodules, surgical margins, microvascular invasion (MVI), and the degree of necrosis were assessed during pathologic examination. Surgical liver specimens were sliced (5 mm thick) and stained with hematoxylin-eosin for microscopic evaluation. MVI was defined as the presence of tumor cells within a portal vein, hepatic vein, or a large capsular vessel in the surrounding hepatic tissue, which can only be visible through microscopy [29]. Satellite nodules were defined as tumors with a diameter <2 cm and located <2 cm from the primary tumor [29]. PR was defined as the proportion of nonviable tumor cell surface area (necrosis or fibrosis) of the whole tumor bed surface area. The mean percentage was adopted when multiple tumors were present. MPR was identified when the percentage of nonviable tumor cells was ≥90% of the whole tumor. The absence of viable tumor cells in any nodule was defined as pCR.

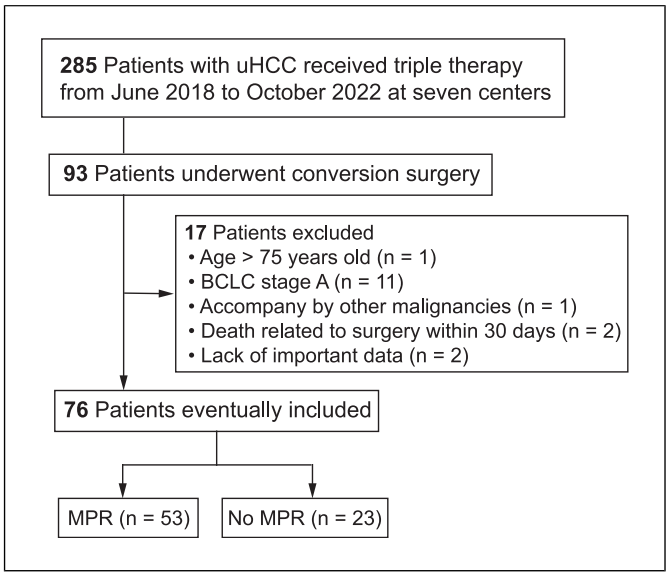

Fig. 1. Patient flowchart. BCLC, Barcelona Clinic for Liver Cancer; MPR, major pathological response; uHCC, unresectable hepatocellular carcinoma.

Follow-Up and Endpoints

All patients were followed up every 3–6 months and monitored for any signs of recurrence after discharge. During each follow-up session, contrast-enhanced abdominal computed tomography or magnetic resonance imaging, chest computed tomography, and laboratory tests were performed. The duration for administering lenvatinib and PD-1 inhibitor as a postoperative systemic therapy ranged from 3 to 12 months, depending on the postoperative pathological findings, radiographic evaluation during follow-up, and patient tolerance. Recurrence was diagnosed based on the radiological evidence of new intra- or extrahepatic tumor lesions, with or without an elevated serum alpha-fetoprotein (AFP) level. Upon the diagnosis of tumor recurrence, suitable treatments such as systematic therapy, TACE, radiofrequency ablation, or hepatectomy were administered based on the characteristics of recurrent tumors, liver function, and patient's general condition.

The primary study endpoint was OS, calculated as the time interval from surgery to death from any cause or the last follow-up. The secondary study endpoints were RFS and the predictors for MPR. RFS was defined as the time interval from surgery to the first recurrence, or death from any cause, or the last follow-up. The deadline for the follow-up was June 1, 2023.

Statistical Analysis

Continuous variables were compared using Student's t test (normally distributed) and Wilcoxon rank-sum tests (non-normally distributed). Categorical variables were compared using Pearson's χ^2 test or Yates's correction for continuity. Wilcoxon signed-rank tests were used for paired two-sample comparisons. The Kaplan-Meier method was used to estimate survival, and the log-rank test was employed to compare survival among different groups. Cox proportional hazards regression models were used for univariate and multivariate analyses to determine predictors

Table 1. Baseline demographic and clinical characteristics of patients

Characteristic	Overall (n = 76)	No MPR (n = 23)	MPR (n = 53)	p value
Age, mean years (±SD)	55.1±12.0	51.4±15.0	56.7±10.2	0.128
Age, *n* (%)				>0.999
<65 years	60 (78.9)	18 (78.3)	42 (79.2)	
≥65 years	16 (21.1)	5 (21.7)	11 (20.8)	
Sex, *n* (%)				0.949
Female	8 (10.5)	3 (13.0)	5 (9.4)	
Male	68 (89.5)	20 (87.0)	48 (90.6)	
Child-Pugh class, *n* (%)				0.989
A	71 (93.4)	22 (95.7)	49 (92.5)	
B	5 (6.6)	1 (4.3)	4 (7.5)	
BCLC stage, *n* (%)				0.351
B	24 (31.6)	9 (39.1)	15 (28.3)	
C	52 (68.4)	14 (60.9)	38 (71.7)	
HBV infection, *n* (%)				0.770
No	6 (7.9)	1 (4.3)	5 (9.4)	
Yes	70 (92.1)	22 (95.7)	48 (90.6)	
Baseline AFP, *n* (%)				0.116
<400 ng/mL	30 (39.5)	6 (26.1)	24 (45.3)	
≥400 ng/mL	46 (60.5)	17 (73.9)	29 (54.7)	
Macrovascular invasion, *n* (%)				0.351
Absent	24 (31.6)	9 (39.1)	15 (28.3)	
Present	52 (68.4)	14 (60.9)	38 (71.7)	
Maximum tumor size, *n* (%)				0.609
<10 cm	43 (56.6)	12 (52.2)	31 (58.5)	
≥10 cm	33 (43.4)	11 (47.8)	22 (41.5)	
Tumor number, *n* (%)				0.312
Single	19 (25.0)	4 (17.4)	15 (28.3)	
Multiple	57 (75.0)	19 (82.6)	38 (71.7)	
MVI, *n* (%)				<0.001
Absent	49 (64.5)	6 (26.1)	43 (81.1)	
Present	27 (35.5)	17 (73.9)	10 (18.9)	
Satellite nodules, *n* (%)				0.036
Absent	62 (81.6)	15 (65.2)	47 (88.7)	
Present	14 (18.4)	8 (34.8)	6 (11.3)	
Major reason for unresectability				0.615
Extensive bi-lobar tumors	15 (19.7)	6 (26.1)	9 (16.9)	
Insufficient future liver remnant	16 (21.1)	5 (21.7)	11 (20.8)	
Not amenable to R0 resection	45 (59.2)	12 (52.2)	33 (62.3)	

MPR, major pathological response; SD, standard deviations; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic for Liver Cancer; HBV, hepatitis B virus.

of OS and RFS. Schoenfeld residuals were used to verify the proportional hazards assumption. Logistic regression analysis was conducted to investigate predictors of MPR. Variables with a p value <0.05 in the univariate analysis were included in each multivariate analysis.

The neutrophil-to-lymphocyte ratio (NLR) was calculated as the ratio of neutrophil-to-lymphocyte count. The median of NLR was used as the cutoff value for dichotomization. Conventional cutoff values in clinical applications were adopted for grouping age, alanine transaminase, albumin, AFP, and tumor size. The present study complies with the STROBE reporting guidelines. Statistical analyses were performed using R (version 4.2.2). A p value <0.05 was considered statistically significant.

Results

Patient Characteristics

Among the 285 patients who received triple therapy at seven centers in China, 76 patients who underwent conversion surgery were eventually included in this study (Fig. 1). Table 1 summarizes the demographic and clinical characteristics of patients. Overall, the median age of the patients was 55.1 ± 12.0 years, and 68 patients (89.5%) were male. At diagnosis, 24 patients (31.6%) were classified as BCLC stage B, while 52 (68.4%) were BCLC stage C. Most patients had a hepatitis B virus (HBV) infection ($n = 70$; 92.1%), and all of them received oral antiviral therapy. According to the radiological evaluation, macrovascular invasion was identified in 52 patients (64.8%), and multiple lesions were detected in 57 patients (75.0%). Upon pathological examination, all patients had negative surgical margins. MVI was identified in 27 patients, while satellite nodules were observed in 14 patients.

MPR after conversion surgery was identified in 53 patients (69.7%). The MPR group had a lower percentage of patients with MVI (18.9% vs. 73.9%; $p < 0.001$), and satellite nodules were less frequent in this group (11.3% vs. 34.8%; $p = 0.036$). There were no statistical differences between the groups of patients with and without MPR regarding age, sex, Child-Pugh class, BCLC stage, HBV infection, baseline AFP level, macrovascular invasion, maximum tumor size, tumor number, and the major reason for unresectability.

Twenty-five patients (32.9%) were identified with pCR after conversion surgery. According to preoperative magnetic resonance imaging, 25 patients exhibited a complete radiological response based on the modified Response Evaluation Criteria in Solid Tumors [30]; of these, 18 (72.0%) also achieved pCR. A representative case of successful pCR after conversion surgery is provided in online supplementary Figure S1 (for all online suppl. material, see https://doi.org/10.1159/000536376).

Medication Details of Triple Therapy

The PD-1 inhibitors used during this study were camrelizumab ($n = 39$), sintilimab ($n = 12$), tislelizumab ($n = 11$), toripalimab ($n = 7$), pembrolizumab ($n = 5$), and penpulimab ($n = 2$). During the follow-up, the median duration of lenvatinib administration was 84 days (interquartile range, 56.5–159.5 days). The PD-1 inhibitors and TACE were administered for a median of three cycles (range, 1–18 cycles) and one time (range, 1–9 times), respectively.

Changes in Tumor Characteristics

Changes in tumor characteristics before and after triple therapy are summarized in online supplementary Table S1. Overall, the median number of tumors at baseline and preoperatively were 4 (range, 1–6) and 3 (range, 1–6), respectively ($p < 0.001$). The median tumor size was significantly smaller after triple therapy than at baseline (7.6 vs. 9.0 cm; $p < 0.001$). Moreover, compared with the median AFP level at baseline, there was a significant decrease after triple therapy (14.3 vs. 1,105.0 ng/mL; $p < 0.001$). The MPR and no MPR groups did not differ significantly regarding the baseline and preoperative tumor number or size. The baseline median AFP level was also similar between the two groups ($p = 0.462$). Nonetheless, the MPR group exhibited a lower median AFP level after triple therapy than the no MPR group (8.1 vs. 49.5 ng/mL; $p = 0.012$).

Toxicity Profile of Triple Therapy

Treatment-related adverse events occurred in 68 patients (89.5%), and the most common grade 3/4 adverse events were abnormal liver function (10.5%), hypertension (3.9%), hand-foot syndrome (2.6%), diarrhea (1.3%), and proteinuria (1.3%) (online suppl. Table S2). Four (5.3%) and 3 (3.9%) patients discontinued lenvatinib and PD-1 inhibitors, respectively, because of grade 3/4 adverse events. Dose reduction or interruption of lenvatinib was observed in 7 patients (9.2%). Additionally, dose interruption of PD-1 inhibitor was identified in 5 patients (6.6%).

Survival Outcomes after Conversion Surgery

The median follow-up period for all patients was 13.1 months (95% CI, 9.8–16.4). Death occurred in 14 (18.4%) patients, and tumor recurrence was observed in 36 (47.4%) patients (online suppl. Fig. S2). The median OS was not reached, and the 1- and 2-year OS rates were 90.3% and 66.9%, respectively. In addition, the median RFS was 12.5 months (95% CI, 6.9–18.2). The survival outcomes for patients who failed to receive conversion surgery are presented in online supplementary Figure S3.

Comparison with the Upfront Surgery Group

To further investigate the survival benefit of conversion surgery following triple therapy, 126 patients with resectable HCC who underwent surgery without any preoperative antitumor therapy were included in the upfront surgery group. The demographic and clinical characteristics of the patients are listed in online supplementary Table S3. More patients with later tumor stage were observed in the conversion surgery group than in the upfront surgery group (68.4% vs. 42.1% of patients with BCLC stage C; $p < 0.001$).

A stage-by-stage survival analysis was performed between the two groups. For patients with BCLC stage B, the

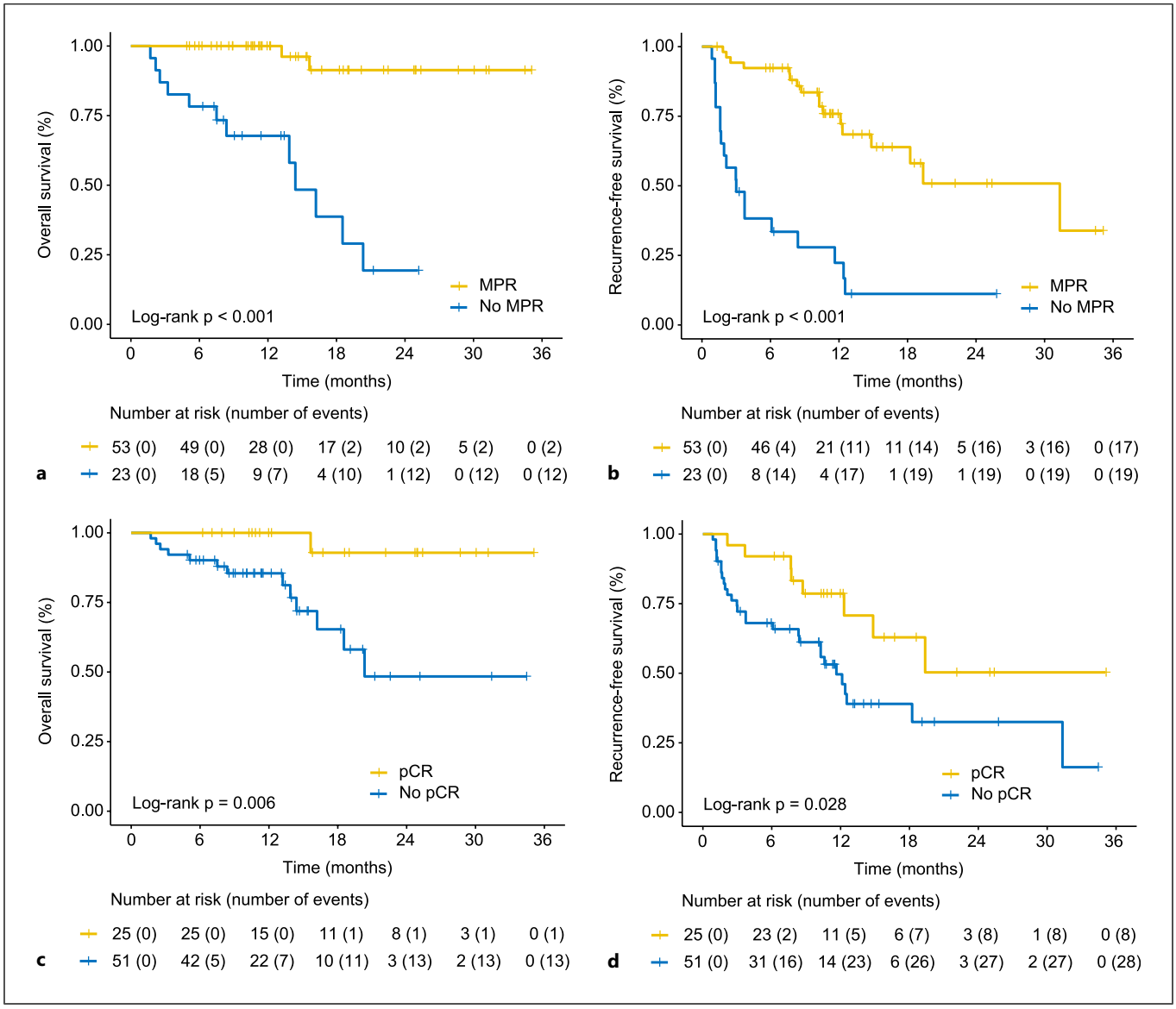

Fig. 2. Kaplan-Meier curves according to the PR. OS (**a**) and RFS (**b**) according to MPR. OS (**c**) and RFS (**d**) according to pCR. MPR, major pathological response; pCR, pathological complete response.

1- and 2-year OS rates of the conversion surgery group were better than those of the upfront surgery group (95.8% and 70.3% vs. 78.8% and 43.9%; $p = 0.047$) (online suppl. Fig. S4a). The corresponding RFS rates of the conversion surgery group were also higher than those of the upfront surgery group (54.3% and 54.3% vs. 30.3% and 19.8%; $p = 0.043$) (online suppl. Fig. S4b). Similarly, for patients in BCLC stage C, those who received conversion surgery showed improved OS ($p = 0.004$) and RFS ($p = 0.008$) compared to those who underwent upfront surgery (online suppl. Fig. S4c, d).

Prognosis according to the PR

Patients with MPR were found to have better OS than those without MPR. The 1- and 2-year OS rates after surgery were 100.0% and 91.3% in patients with MPR, which were significantly higher than the 67.7% and 19.4% rates in patients without MPR ($p < 0.001$) (Fig. 2a). Recurrence was observed later in patients with MPR, with a median RFS of 31.3 months compared with 3.0 months in patients without MPR. The 1- and 2-year RFS rates were also higher in patients with MPR than in those without (75.9% and 50.8% vs. 22.3% and 11.2%; $p < 0.001$) (Fig. 2b).

Table 2. Univariate and multivariate analysis for OS

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age, years (≥65/<65)	0.25	0.03–1.90	0.179			
Sex (male/female)	0.41	0.11–1.49	0.177			
Child-Pugh class (B/A)	1.10	0.14–8.42	0.927			
Baseline ALT, IU/L (≥40/<40)	1.07	0.37–3.09	0.899			
Baseline ALB, g/L (≥35/<35)	0.61	0.17–2.18	0.445			
Baseline NLR (≥2.6/<2.6)	5.09	1.41–18.41	0.013	5.53	1.36–22.52	0.017
Baseline AFP, ng/mL (≥400/<400)	8.34	1.09–63.87	0.041	6.14	0.79–47.80	0.083
Preoperative AFP, ng/mL (≥400/<400)	1.87	0.58–6.01	0.294			
Macrovascular invasion (yes/no)	1.59	0.49–5.11	0.436			
Maximum tumor size, cm (≥10/<10)	1.55	0.53–4.52	0.420			
Tumor number (multiple/single)	1.00	0.28–3.58	0.995			
Hepatectomy (major/minor)	0.66	0.23–1.93	0.453			
MVI (yes/no)	4.38	1.37–14.02	0.013	1.03	0.27–2.03	0.962
Satellite nodules (yes/no)	1.68	0.55–5.09	0.361			
MPR (yes/no)	0.05	0.01–0.23	<0.001	0.07	0.01–0.31	0.001

HR, hazard ratio; CI, confidence interval; ALT, alanine transaminase; ALB, albumin; NLR, neutrophil-to-lymphocyte ratio; AFP, alpha-fetoprotein.

Similar findings were found between patients with pCR and those without. Patients with pCR achieved 1- and 2-year OS rates of 100% and 92.9%, respectively, versus 85.5% and 48.4% in patients without pCR (p = 0.006) (Fig. 2c). Furthermore, the corresponding RFS rates were 78.6% and 50.3% in patients with pCR, compared to 49.6% and 32.5% in patients without pCR (p = 0.028) (Fig. 2d).

Association between MPR and pCR

To investigate whether the prognostic impact of MPR was influenced by pCR, MPR was subdivided into two categories: pCR (PR = 100%) and MPR without pCR (90%≤ PR <100%). The 1- and 2-year OS rates of patients with pCR (100% and 92.9%) and MPR without pCR (100% and 91.7%) were similar (p = 0.725) (online suppl. Fig. S5a). Moreover, the 1- and 2-year OS rates of patients who achieved MPR without pCR were significantly higher than those of patients without MPR (100% and 91.7% vs. 67.7% and 19.4%; p < 0.001) (online suppl. Fig. S5a).

Similar results were obtained when analyzing RFS. The 1- and 2-year RFS rates were 78.6% and 50.3% in patients with pCR, which were comparable to the 73.7% and 53.0% achieved by patients with MPR without pCR (p = 0.861) (online suppl. Fig. S5b). Similarly, patients who achieved MPR without pCR exhibited superior 1- and 2-year RFS rates compared with those without MPR (73.7% and 53.0% vs. 22.3% and 11.2%; p < 0.001) (online suppl. Fig. S5b).

Predictors of OS

In univariate analysis, variables associated with worse OS were baseline NLR ≥2.6, baseline AFP level ≥400 ng/mL, MVI, and absence of MPR (Table 2). In multivariate analysis, baseline NLR ≥2.6 (HR, 5.53; 95% CI, 1.36–22.52; p = 0.017) and MPR (HR, 0.07; 95% CI, 0.01–0.31; p = 0.001) emerged as independent predictors of OS.

Predictors of RFS

In univariate analysis, four variables were associated with poor RFS after conversion surgery: baseline NLR ≥2.6, MVI, satellite nodules, and absence of MPR (Table 3). In multivariate analysis, only satellite nodules (HR, 2.11; 95% CI, 1.04–4.29; p = 0.039) and MPR (HR, 0.20; 95% CI, 0.10–0.41; p < 0.001) remained as independent predictors of RFS.

Predictors of MPR

The results of univariate and multivariate analyses of the predictors of MPR are presented in Table 4. The baseline NLR ≥2.6 (OR, 0.24; 95% CI, 0.07–0.73; p = 0.016) and preoperative AFP level ≥400 ng/mL (OR, 0.17; 95% CI, 0.04–0.68; p = 0.015) were identified as independent negative predictors of MPR.

Table 3. Univariate and multivariate analysis for RFS

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age, years (≥65/<65)	1.04	0.48–2.30	0.914			
Sex (male/female)	2.98	0.71–12.53	0.136			
Child-Pugh class (B/A)	1.82	0.55–6.04	0.330			
Baseline ALT, IU/L (≥40/<40)	0.96	0.50–1.84	0.893			
Baseline ALB, g/L (≥35/<35)	0.52	0.22–1.21	0.129			
Baseline NLR (≥2.6/<2.6)	2.04	1.04–4.01	0.039	1.28	0.63–2.63	0.494
Baseline AFP, ng/mL (≥400/<400)	1.47	0.74–2.95	0.275			
Preoperative AFP, ng/mL (≥400/<400)	1.45	0.63–3.32	0.385			
Macrovascular invasion (yes/no)	1.14	0.55–2.34	0.730			
Maximum tumor size, cm (≥10/<10)	1.07	0.55–2.08	0.830			
Tumor number (multiple/single)	1.38	0.60–3.15	0.450			
Hepatectomy (major/minor)	0.67	0.34–1.31	0.239			
MVI (yes/no)	2.23	1.16–4.30	0.016	0.97	0.43–2.20	0.940
Satellite nodules (yes/no)	2.94	1.48–5.85	0.002	2.11	1.04–4.29	0.039
MPR (yes/no)	0.18	0.09–0.35	<0.001	0.20	0.10–0.41	<0.001

HR, hazard ratio; CI, confidence interval; ALT, alanine transaminase; ALB, albumin; NLR, neutrophil-to-lymphocyte ratio; AFP, alpha-fetoprotein.

Table 4. Univariate and multivariate analysis of factors associated with MPR

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age, years (≥65/<65)	0.94	0.30–3.35	0.923			
Sex (male/female)	1.44	0.27–6.45	0.639			
Child-Pugh class (B/A)	1.80	0.25–36.22	0.610			
Baseline ALT, IU/L (≥40/<40)	1.20	0.44–3.21	0.721			
Baseline ALB, g/L (≥35/<35)	0.84	0.17–3.27	0.816			
Baseline NLR (≥2.6/<2.6)	0.31	0.10–0.85	0.028	0.24	0.07–0.73	0.016
Baseline AFP, ng/mL (≥400/<400)	0.43	0.14–1.20	0.121			
Preoperative AFP, ng/mL (≥400/<400)	0.24	0.06–0.85	0.028	0.17	0.04–0.68	0.015
Macrovascular invasion (yes/no)	1.63	0.57–4.56	0.353			
Maximum tumor size, cm (≥10/<10)	0.77	0.29–2.09	0.610			
Tumor number (multiple/single)	0.53	0.14–1.71	0.318			

OR, odds ratio; CI, confidence interval; ALT, alanine transaminase; ALB, albumin; NLR, neutrophil-to-lymphocyte ratio; AFP, alpha-fetoprotein.

Discussion

More than a decade ago, Blazer et al. [18] reported that pCR induced by preoperative chemotherapy in patients with hepatic colorectal metastases was related to a superior 5-year OS of 75%, compared with 56% and 33% in patients with major response or minor response. This study revealed the promising prognostic value of PR, which is increasingly appreciated in more malignancies [15–17, 31–33]. Regarding patients with HCC who received preoperative TACE, previous studies have demonstrated that PR was independently associated with OS and RFS following surgery [12–14]. Recently, Zhu et al. [34] discovered that achieving pCR after systematic therapy (tyrosine kinase inhibitors plus PD-1 inhibitor) resulted in a more favorable RFS after resection for patients with uHCC. A similar finding was reported by Yi et al. [35], who revealed that

pCR was associated with longer tumor-free survival in patients with uHCC who received lenvatinib and PD-1 inhibitor.

During this study, triple therapy was adopted as a conversion strategy for patients with uHCC and exhibited promising efficacy with acceptable toxicity. Notably, after successful conversion surgery following triple therapy, patients with initially uHCC could experience survival superior to that of patients with resectable HCC who underwent upfront surgery. Furthermore, promising pathological outcomes were observed following conversion surgery. Overall, despite a significant tumor burden in a substantial number of cases, this study observed relatively high rates of MPR (69.7%) and pCR (32.9%). The following mechanisms may explain these findings: TACE can induce tumor ischemic necrosis through its embolic effect, and lenvatinib inhibits tumor revascularization induced by TACE [36–39]. Additionally, lenvatinib has an immunomodulatory effect and can enhance the efficacy of PD-1 inhibitor [40, 41]. In conclusion, the potential synergistic effects of triple therapy may boost antitumor activity and promote the tumor response.

This study discovered that MPR was associated with superior OS and RFS in patients with initially uHCC who received triple therapy. Similarly, individuals who achieved pCR also exhibited a more favorable prognosis. Moreover, we found that the prognostic impact of MPR was not influenced by pCR, suggesting that the post-surgery prognosis after triple therapy could be significantly improved as long as "near-pCR" is achieved. In further multivariate Cox regression analysis, MPR was identified as an independent predictor for both OS and RFS. These findings are consistent with previous studies, further confirming the hypothesis that the postoperative prognosis of solid tumors may greatly depend on the PR induced by preoperative treatments [14]. These results indicate that PR can potentially serve as a surrogate endpoint for predicting the postoperative prognosis, and efforts to increase the extent of PR are merited.

Given the prognostic value of MPR, we further identified that the NLR and AFP levels could independently predict MPR. NLR, an index of systemic inflammation, has recently emerged as a significant prognostic predictor in patients with HCC [42, 43]. Additionally, evidence suggested that NLR was associated with tumor angiogenesis and immune evasion [44]. Thus, NLR may potentially predict the response to antitumor therapy. For instance, Schobert et al. [45] found that a higher baseline NLR predicts poorer radiological tumor response in HCC after drug-eluting bead TACE. AFP, a significant biomarker of HCC, is crucial in promoting tumor growth while simultaneously impeding antitumor immunity [46]. A study conducted by Yang et al. [12] revealed that an AFP level <100 ng/mL predicted a higher likelihood of achieving pCR in patients with HCC who underwent curative surgery after TACE. Furthermore, an analysis from the US multicenter HCC transplant consortium demonstrated that the AFP and NLR were predictors of pCR after pretransplant locoregional therapy [47]. These findings suggest that the NLR and AFP level play significant roles in predicting PR in patients with HCC.

There were several limitations to this study. First, this was a retrospective study with the potential for selection bias, and the follow-up periods were limited. However, to our knowledge, this is the first study to confirm the prognostic value of PR in patients with uHCC who underwent combined locoregional and systemic therapy. Further prospective studies with longer follow-up duration are warranted to validate these findings. Second, the multicenter design of the study resulted in incomplete pathological features, including missing information on tumor capsule status or the degree of liver cirrhosis. Third, owing to the epidemiological characteristics of patients with HCC in China, most individuals in the present study were young male patients with HBV infection. Therefore, further prospective studies with larger populations are warranted to confirm the findings in this study.

In conclusion, this study has demonstrated that MPR or pCR improves prognosis in patients with initially uHCC who undergo conversion surgery following triple therapy, and the NLR and AFP levels can serve as predictors of MPR. The PR may become a surrogate marker for predicting the prognosis of patients with uHCC after conversion surgery.

Statement of Ethics

This study protocol was reviewed and approved by the Institutional Review Board of Fujian Provincial Hospital, approval number K2020-029-02. Written informed consent was obtained from all participants or their legal guardians to participate in the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author upon reasonable request.

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