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ORIGINAL RESEARCH

Impact of Duration of Adjuvant Therapy on Patients with Initially Unresectable Hepatocellular Carcinoma After Conversion Surgery: A Propensity Score Matching Study

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Background: This study aimed to assess the effect of adjuvant therapy with different durations in patients with initially unresectable hepatocellular carcinoma (uHCC) after conversion surgery.

Methods: This study included 85 patients with initially uHCC who received conversion surgery between May 2019 and November 2022. They were divided into the long duration group (n = 57) and short duration group (n = 28) based on postoperative medication duration. Recurrence-free survival (RFS) and overall survival (OS) were analyzed and compared between the cohorts.

Results: No significant difference in RFS or OS was found between the two groups [RFS: hazard ratio (HR) = 0.486; 95% confidence interval (CI), 0.229–1.034, P = 0.061; OS: HR = 0.377; 95% CI, 0.119–1.196, P = 0.098]. Patients without major pathologic response (MPR) in the long duration group had better RFS and OS results compared to those in the short duration group (RFS: HR = 0.242; 95% CI, 0.092–0.634, P = 0.004; OS: HR = 0.264; 95% CI, 0.079–0.882, P = 0.031). No significant difference was detected in RFS or OS between the two groups in patients with MPR (RFS: HR = 1.250; 95% CI, 0.373–4.183, P = 0.718; OS: HR = 7.389; 95% CI, 0.147–372.4, P = 0.317). After propensity score matching, 25 pairs of patients were selected and the results remained consistent.

Conclusion: At least 6 months of adjuvant therapy may be beneficial for patients without MPR after conversion surgery. However, in patients with MPR, the effect of adjuvant therapy remains unclear. Further studies are needed to confirm the optimal duration of adjuvant therapy.

Keywords: unresectable, hepatocellular carcinoma, conversion therapy, adjuvant therapy, recurrence-free survival, overall survival

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors and a primary factor in global cancer-related mortality.[1] To date, surgical resection remains the most effective treatment for HCC.[2,3] However, given the insidious nature of HCC, most patients are diagnosed at an intermediate or advanced stage and are ineligible for curative resection.[4] For patients with unresectable HCC (uHCC), conversion therapy is the mainstay of treatment.[5,6]

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Conversion therapy is a strategy that aims to convert unresectable tumors into resectable ones followed by surgery to remove the tumors. Sorafenib was approved for the therapy of advanced HCC in 2007. However, it has a low objective response rate (ORR) and conversion rate.[7–9] With the development of targeted drugs and immune checkpoint inhibitors, the conversion rate for uHCC has experienced a significant increase, and the overall survival (OS) and progression-free survival (PFS) of patients have improved.[10–12] IMbrave150 showed that the median OS, median PFS, and ORR were significantly better in the atezolizumab and bevacizumab groups than those in the sorafenib group (median OS: 19.2 months vs 13.4 months, $p < 0.001$; median PFS: 6.9 months vs 4.3 months, $p < 0.001$; and ORR: 30% vs 11%).[10] Meanwhile, we reported a high conversion rate of 53.2% and excellent long-term survival benefits in patients with uHCC who received the combination therapy of transarterial chemoembolization (TACE), lenvatinib, and anti-PD-1 antibodies.[11,13–15]

The ultimate goal of treatment is not conversion surgery, but rather to prolong patients' long-term survival. A recent study has shown that postoperative adjuvant hepatic arterial infusion chemotherapy improves disease-free survival in HCC patients with microvascular invasion.[16] Further, results from the IMbrave050 study indicate that adjuvant atezolizumab plus bevacizumab improves recurrence-free survival (RFS) in high-risk HCC patients following surgery.[17] In addition, Wang et al suggest that adjuvant sintilimab significantly prolongs RFS in resected high-risk HCC patients.[18] These findings indicate that effective adjuvant therapy after surgery may improve the prognosis of patients with HCC. Currently, many problems persist regarding adjuvant therapy after conversion surgery, including the absence of a uniform standard for the duration of postoperative adjuvant therapy. The Chinese expert consensus on conversion therapy for HCC recommends that adjuvant therapy after conversion surgery should last for at least 6 months;[19] however, there is insufficient data to support this recommendation. To better understand the effect of postoperative adjuvant therapy on survival after conversion surgery for uHCC, we conducted this study to compare the effect of adjuvant therapy with different durations in patients after conversion surgery.

Patients and Methods

Patients

This study included patients with uHCC who underwent conversion surgery at four high-volume institutions in China between May 2019 and November 2022 (Fujian Provincial Hospital, First Affiliated Hospital of Fujian Medical University, First Affiliated Hospital of Xiamen University, and Zhongshan Hospital of Xiamen University). Retrospectively collected and analyzed baseline data including demographics, pathological characteristics and survival outcomes. This study received approval from the Institutional Ethics Committees of each participating institution and was conducted in compliance with the principles outlined in the Declaration of Helsinki. All of the patients and their legal guardians provided written informed consent.

Inclusion and Exclusion Criteria

The eligibility criteria for inclusion were as follows: 1) age between 18 and 75 years; 2) uHCC treated with conversion therapy (lenvatinib plus anti-PD-1 antibodies combined with TACE) and salvage surgery (which was described in our previous study[14]); 3) R0 resection: a negative resection margin on pathological examination; no recurrence on radiological examination within 1 month after surgery; des-gamma-carboxy prothrombin (DCP) and alpha-fetoprotein (AFP) decreased to normal within 1 month after surgery; 4) Eastern Cooperative Oncology Group Performance status of 0–1; and 5) Child-Pugh class A or B.

The eligibility criteria for exclusion were as follows: 1) recurrence within 6 months after surgery; 2) Barcelona Clinic Liver Cancer (BCLC) stage A; 3) severe organ dysfunction; and 4) important data missing.

Treatment

Patients resumed lenvatinib and anti-PD-1 antibodies approximately 1 month after conversion surgery, as they had completely recuperated from the hepatectomy, patients received oral lenvatinib (Lenvima, Merck) 8 mg/day (for <60 kg body weight) or 12 mg/day (for ≥60 kg body weight) and anti-PD-1 antibodies (including sintilimab 200 mg, camrelizumab

200 mg, pembrolizumab 200 mg, toripalimab 240 mg, or tislelizumab 200 mg) intravenously every 3 weeks. Drug dose modification and interruption were determined by physicians based on the treatment-related adverse events (TRAEs) in the patients. Patients were divided into two groups based on the duration of postoperative adjuvant therapy: short duration group (≤6 months) and long duration group (>6 months). All patients with hepatitis B virus (HBV) infection received oral antiviral treatment.

Follow-Up and Endpoints

The first follow-up for all patients was 1 month after salvage hepatectomy, followed by every 3 months for the first 2 years, and then every 4 months after 2 years. Follow-up examinations included a physical examination, AFP and DCP levels, routine blood tests, routine urinalysis, liver and renal function tests, thyroid function tests, cortisol levels, troponin I, b-type natriuretic peptide, chest computed tomography (CT), and enhanced liver CT or magnetic resonance imaging (MRI). The recurrence of HCC was evaluated by identifying arterial phase hypervascularization and venous or delayed phase washout through MRI or CT images.[20] Once HCC recurrence, treatments, including resection, radiofrequency ablation, interventional therapy, and second-line systemic therapy, were selected according to the patient's condition.

The primary endpoint was RFS, which was defined as the duration from surgery to the diagnosis of recurrence or last follow-up. The secondary analysis endpoint was OS, which was defined as the duration from surgery to the date of death or last follow-up. Major pathologic response (MPR) was identified as the percentage of viable tumor cells ≤10% in the resected tumor tissue, lymph nodes, or tumor thrombus. The absence of viable tumor cells in the resected tumor tissue, lymph nodes, or tumor thrombus was defined as pathological complete response (PCR). TRAEs were evaluated and graded based on the Common Terminology Criteria for Adverse Events version 5.0.

Statistical Analysis

Continuous data was tested for normal distribution, and normally distributed continuous data was expressed as mean ± standard deviation and assessed utilizing Student's *t*-test. Categorical data were expressed as numbers (%) and assessed utilizing the chi-square test or Fisher's exact test. RFS and OS curves were constructed by the Kaplan–Meier method, and the differences between two groups were compared utilizing the Log rank test. The Cox proportional hazards model was used to estimate hazard ratios (HR) and their corresponding 95% confidence intervals (CI). Factors with a p-value <0.1 in the univariate analysis were considered for inclusion in the multivariate analysis. A propensity score matching (PSM) analysis was performed in this study to minimize potential selection bias. The nearest neighbor method with a caliper of 0.02 was utilized to match the short duration group and long duration group in a 1:1 ratio in this study. The variables included in the PSM analysis were sex, age, total bilirubin, HBsAg, alanine aminotransferase levels, serum AFP, serum DCP, tumor diameter, tumor number, liver cirrhosis, and BCLC stage. Statistical significance was defined as the two-tailed p-value <0.05. Considering the impact of the degree of pathologic response on survival outcomes, subgroup analyses were performed in patients with and without MPR. The SPSS software version 26.0 and GraphPad Prism software version 9.5 were used for statistical analyses.

Results

A total of 85 patients with uHCC who underwent conversion surgery were included in this study (Figure S1). Among these patients, the mean age was 55.41 ± 11.70 years, with 10 female and 75 male patients. A total of 76 patients had HBV, and 51 patients achieved MPR after conversion therapy. According to the BCLC staging system, 25.9% and 74.1% of patients had BCLC stage B and C, respectively. A total of 57 patients received adjuvant therapy for less than 6 months (median duration: 3.0 months; 95% CI: 2.6–3.8), and the remaining 28 patients underwent adjuvant therapy for more than 6 months (median duration: 11.5 months; 95% CI: 11.2–16.4). Before PSM, analysis by baseline comparison showed that no significant difference was found in the baseline characteristics between the two groups. After PSM, 25 pairs of patients were selected, and the baseline characteristics of the patients between the two groups were comparable and well balanced. The patient demographics and clinical characteristics are presented in Table 1.

During a median follow-up of 21.1 months (range, 6.3–35.3 months), recurrence was observed in 28 patients. Among them, 17 patients experienced intrahepatic recurrence, 4 patients experienced extrahepatic recurrence, and 7 patients

Table 1 Baseline Characteristics of the Short and Long Duration Groups Before and After PSM

Characteristics	Before PSM (n = 85)			After PSM (n = 50)		
	Short duration group (n=57)	Long duration group (n=28)	*p*-value	Short duration group (n=25)	Long duration group (n=25)	*p*-value
Sex			0.286			> 0.999
Male	52 (91.23%)	23 (82.14%)		22 (88.00%)	23 (92.00%)	
Female	5 (8.77%)	5 (17.86%)		3 (12.00%)	2 (8.00%)	
Age (years)	56.18 ± 12.99	53.86 ± 8.50	0.394	53.56 ± 13.87	54.28 ± 8.44	0.826
HBsAg			0.979			1.000
Positive	51 (89.47%)	25 (89.29%)		23 (92.00%)	23 (92.00%)	
Negative	6 (10.53%)	3 (10.71%)		2 (8.00%)	2 (8.00%)	
TBIL (μmol/L)			> 0.999			1.000
< 34	54 (94.74%)	27 (96.43%)		24 (96.00%)	24 (96.00%)	
≥ 34	3 (5.26%)	1 (3.57%)		1 (4.00%)	1 (4.00%)	
ALT (U/L)			0.318			1.000
< 40	31 (54.39%)	12 (42.86%)		10 (40.00%)	10 (40.00%)	
≥ 40	26 (45.61%)	16 (57.14%)		15 (60.00%)	15 (60.00%)	
AFP (ng/mL)			0.703			0.571
< 400	26 (45.61%)	14 (50.00%)		11 (44.00%)	13 (52.00%)	
≥ 400	31 (54.39%)	14 (50.00%)		14 (56.00%)	12 (48.00%)	
DCP (mAU/mL)			0.575			1.000
< 400	15 (26.32%)	9 (32.14%)		7 (28.00%)	7 (28.00%)	
≥ 400	42 (73.68%)	19 (67.86%)		18 (72.00%)	18 (72.00%)	
Diameter (cm)			0.593			1.000
< 10	32 (56.14%)	14 (50.00%)		13 (52.00%)	13 (52.00%)	
≥ 10	25 (43.86%)	14 (50.00%)		12 (48.00%)	12 (48.00%)	
Tumor number			0.580			0.544
Solitary	26 (45.61%)	11 (39.29%)		7 (28.00%)	9 (36.00%)	
Multiple	31 (54.39%)	17 (60.71%)		18 (72.00%)	16 (64.00%)	
Liver cirrhosis			0.680			0.382
Positive	34 (59.65%)	18 (64.29%)		11 (44.00%)	8 (32.00%)	
Negative	23 (40.35%)	10 (35.71%)		14 (56.00%)	17 (68.00%)	
BCLC stage			0.896			0.225
B	15 (26.32%)	7 (25.00%)		10 (40.00%)	6 (24.00%)	
C	42 (73.68%)	21 (75.00%)		15 (60.00%)	19 (76.00%)	
MPR			0.706			1.000
Yes	35 (61.40%)	16 (57.14%)		11 (44.00%)	11 (44.00%)	
No	22 (38.60%)	12 (42.86%)		14 (56.00%)	14 (56.00%)	
MVI			0.175			0.529
Yes	11 (19.30%)	9 (32.14%)		6 (24.00%)	8 (32.00%)	
No	46 (80.70%)	19 (67.86%)		19 (76.00%)	17 (68.00%)	
Satellite lesions			0.442			1.000
Yes	12 (21.05%)	8 (28.57%)		6 (24.00%)	6 (24.00%)	
No	45 (78.95%)	20 (71.43%)		19 (76.00%)	19 (76.00%)	
Surgical margins (cm)			0.473			0.564
< 1	32 (56.14%)	18 (64.29%)		14 (56.00%)	16 (64.00%)	
≥ 1	25 (43.86%)	10 (35.71%)		11 (44.00%)	9 (36.00%)	
Differentiation			0.166			0.093
Edmondson I–II	16 (28.07%)	9 (32.14%)		8 (32.00%)	9 (36.00%)	
Edmondson III–IV	22 (38.60%)	15 (53.57%)		9 (36.00%)	14 (56.00%)	
Unknown*	19 (33.33%)	4 (14.29%)		8 (32.00%)	2 (8.00%)	

Note: *pathological complete response.

Abbreviations: PSM, propensity score matching; HBsAg, Hepatitis B virus surface antigen; TBIL, total bilirubin; ALT, alanine aminotransferase; AFP, alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin; BCLC, Barcelona Clinic Liver Cancer; MPR, major pathologic response; MVI, microvascular invasion.

experienced both intrahepatic and extrahepatic recurrences. In addition, 12 patients died during the follow-up period. Among these patients, 11 died of tumor recurrence, and one patient died of non-tumor related causes (esophagogastric varices bleeding). The 1-year and 2-year rates of RFS were 77.3% and 59.1%, respectively, and the rates of OS were 91.1% and 83.5%, respectively (Figure S2).

Prognostic Factors for RFS and OS

Univariate analysis indicated that total bilirubin level ≥34 μmol/L (HR = 3.512; 95% CI, 1.052–11.721, P = 0.041), MPR (HR = 0.348; 95% CI, 0.162–0.744, P = 0.006), and >6 months duration (HR = 0.450; 95% CI, 0.191–1.062, P = 0.068) were potentially associated with RFS (Table 2). Meanwhile, MPR (HR = 0.056; 95% CI, 0.007–0.431, P = 0.006), satellite lesions (HR = 4.622; 95% CI, 1.465–14.585, P = 0.009), and total bilirubin level ≥34 μmol/L (HR = 4.653; 95% CI, 1.004–21.567, P = 0.049) were potentially associated with OS (Table 3).

Further multivariate analysis revealed that only MPR was significantly associated with better RFS (HR = 0.346; 95% CI, 0.157–0.764, P = 0.009; Table 2) and OS (HR = 0.080; 95% CI, 0.010–0.653; P = 0.018; Table 3). Adjuvant therapy duration of >6 months was not significantly associated with RFS (HR = 0.427; 95% CI, 0.178–1.027, P = 0.057; Table 2) or OS (HR = 0.298; 95% CI, 0.065–1.364, P = 0.119; Table 3).

Association of Adjuvant Therapy Duration with Survival Outcomes

Before PSM, the RFS rates at 1- and 2-year were 96.0% and 69.2% in the long duration group and 67.1% and 53.9% in the short duration group, respectively. The OS rates at 1- and 2-year were 100.0% and 94.7% in the long duration group and 85.9% and 76.8% in the short duration group, respectively. There were no significant differences in RFS (HR = 0.486; 95% CI, 0.229–1.034, P = 0.061) and OS (HR = 0.377; 95% CI, 0.119–1.196, P = 0.098) between the two groups (Figure 1A and B). However, we still assumed patients in the long duration group had better survival than those in the short duration group.

After PSM, there were also no significant differences in RFS (HR = 0.613; 95% CI, 0.236–1.591, P = 0.314) and OS (HR = 0.324; 95% CI, 0.056–1.876, P = 0.208) between the two groups (Figure 1C and D).

Table 2 Univariate and Multivariate Analysis for Recurrence-Free Survival in 85 Unmatched Patients

Variables	Univariate		Multivariate	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Sex (male vs female)	0.853 (0.296–2.462)	0.769		
Age (≥ 65 vs < 65 years)	0.462 (0.139–1.534)	0.208		
ALT (≥ 40 vs < 40 U/L)	0.782 (0.371–1.648)	0.519		
TBIL (≥ 34 vs < 34 μmol/L)	3.512 (1.052–11.721)	0.041	1.805 (0.505–6.443)	0.363
AFP (≥ 400 vs < 400 ng/mL)	1.779 (0.831–3.808)	0.138		
DCP (≥ 400 vs < 400 mAU/mL)	1.226 (0.519–2.898)	0.642		
BCLC stage (C vs B)	1.735 (0.701–4.295)	0.233		
Tumor diameter (≥ 10 vs < 10 cm)	1.210 (0.574–2.550)	0.616		
Tumor number (multiple vs solitary)	1.232 (0.568–2.672)	0.598		
Liver cirrhosis (yes vs no)	0.748 (0.354–1.584)	0.449		
MPR (yes vs no)	0.348 (0.162–0.744)	0.006	0.346 (0.157–0.764)	0.009
MVI (yes vs no)	1.430 (0.628–3.524)	0.394		
Satellite lesions (yes vs no)	1.677 (0.758–3.714	0.202		
Surgical margins (≥ 1 vs < 1 cm)	0.959 (0.449–2.052)	0.915		
Duration (> 6 vs ≤ 6 months)	0.450 (0.191–1.062)	0.068	0.427 (0.178–1.027)	0.057

Abbreviations: HR, hazard ratio; CI, confidence interval; ALT, alanine aminotransferase; TBIL, total bilirubin; AFP, alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin; BCLC, Barcelona Clinic Liver Cancer; MPR, major pathologic response; MVI, microvascular invasion.

Table 3 Univariate and Multivariate Analysis for Overall Survival in 85 Unmatched Patients

Variables	Univariate		Multivariate	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Sex (male vs female)	0.416 (0.112–1.540)	0.189		
Age (≥ 65 vs < 65 years)	0.847 (0.185–3.873)	0.831		
ALT (≥ 40 vs < 40 U/L)	0.443 (0.133–1.472)	0.184		
TBIL (≥ 34 vs < 34 μmol/L)	4.653 (1.004–21.567)	0.049	3.405 (0.710–16.323)	0.125
AFP (≥ 400 vs < 400 ng/mL)	1.445 (0.458–4.559)	0.530		
DCP (≥ 400 vs < 400 mAU/mL)	0.513 (0.161–1.632)	0.258		
BCLC stage (C vs B)	2.248 (0.492–10.275)	0.296		
Tumor diameter (≥ 10 vs < 10 cm)	1.373 (0.433–4.352)	0.591		
Tumor number (multiple vs solitary)	1.006 (0.318–3.185)	0.992		
Liver cirrhosis (yes vs no)	0.604 (0.193–1.888)	0.386		
MPR (yes vs no)	0.056 (0.007–0.431)	0.006	0.080 (0.010–0.653)	0.018
MVI (yes vs no)	2.341 (0.738–7.422)	0.149		
Satellite lesions (yes vs no)	4.622 (1.465–14.585)	0.009	2.710 (0.828–8.864)	0.099
Surgical margins (≥ 1 vs < 1 cm)	0.666 (0.200–2.222)	0.508		
Duration (> 6 vs ≤ 6 months)	0.298 (0.065–1.364)	0.119		

Abbreviations: HR, hazard ratio; CI, confidence interval; ALT, alanine aminotransferase; TBIL, total bilirubin; AFP, alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin; BCLC, Barcelona Clinic Liver Cancer; MPR, major pathologic response; MVI, microvascular invasion.

Survival Analysis of the Non-MPR Subgroup

Among the 34 patients without MPR, 17 patients experienced recurrence, and 11 patients died. Among them, 10 died of tumor recurrence, and one died of non-tumor related causes (esophagogastric varices bleeding). A total of 22 patients received adjuvant therapy for ≤6 months, and the remaining 12 patients underwent adjuvant therapy for >6 months. Before PSM, compared with the short duration group, the long duration group exhibited longer 1- and 2-year RFS rates (HR = 0.242; 95% CI, 0.092–0.634, P = 0.004) and OS rates (HR = 0.264; 95% CI, 0.079–0.882, P = 0.031) (Figure 2A and B). The 1-year and 2-year rates of RFS were 100.0% and 71.4% in the long duration group and 42.5% and 30.4% in the short duration group, respectively. The 1-year and 2-year rates of OS were 100.0% and 87.5% in the long duration group and 68.7% and 48.1% in the short duration group, respectively.

After PSM, RFS (HR = 0.231; 95% CI, 0.056–0.960, P = 0.044) and OS (HR = 0.115; 95% CI, 0.016–0.822, P = 0.031) were also significantly longer in the long duration group than those in the short duration group (Figure 2C and D). The 1-year and 2-year rates of RFS were 100.0% and 71.4% in the long duration group and 48.0% and 48.0% in the short duration group, respectively. The 1-year and 2-year rates of OS were 100.0% and 100.0% in the long duration group and 66.7% and 53.3% in the short duration group, respectively.

Survival Analysis of the MPR Subgroup

Among the 51 patients with MPR, 11 patients experienced recurrence, and one patient died of tumor recurrence 31.3 months after conversion surgery. A total of 35 patients received adjuvant therapy for ≤6 months, and the remaining 16 patients underwent adjuvant therapy for >6 months. Before PSM, no significant differences were detected in RFS rates (HR = 1.250; 95% CI, 0.373–4.183, P = 0.718) and OS rates (HR = 7.389; 95% CI, 0.147–372.4, P = 0.317) between the two groups (Figure 3A and B). The 1-year and 2-year rates of RFS were 93.3% and 67.8% in the long duration group and 85.7% and 72.3% in the short duration group, respectively. The 1-year and 2-year rates of OS were 100.0% and 100.0% in the long duration group and 100.0% and 100.0% in the short duration group, respectively. After PSM, there were also no significant differences in RFS (HR = 1.346; 95% CI, 0.362–5.001, P = 0.657) and OS (HR = 7.389; 95% CI, 0.147–372.4, P = 0.317) between the two groups (Figure 3C and D).

Furthermore, we used a 3-month duration of adjuvant therapy as the cutoff. The 1-year and 2-year rates of RFS were 84.3% and 67.7% in the >3 months group and 94.1% and 73.3% in the ≤3 months group, respectively. The 1-year and 2-year rates of OS were 100.0% and 100.0% in the >3 months group and 100.0% and 100.0% in the ≤3 months group,

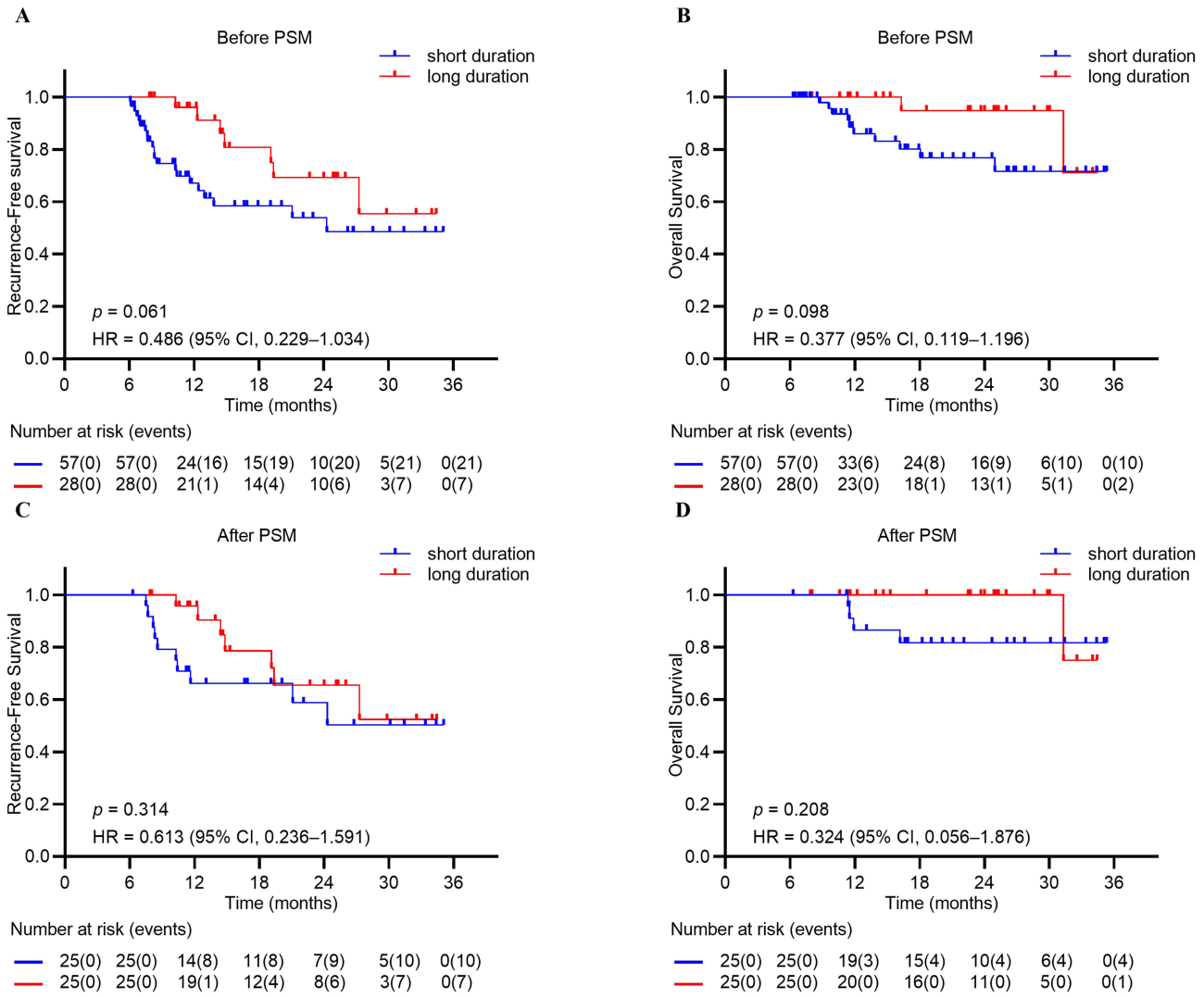

Figure 1 Kaplan–Meier curves of all patients in two duration groups. (**A**) RFS and (**B**) OS of all patients before PSM. (**C**) RFS and (**D**) OS for all patients after PSM.
Abbreviations: RFS, recurrence-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; PSM, propensity score matching.

respectively. No significant difference was detected in either RFS (HR = 1.704; 95% CI, 0.509–5.702, P = 0.387) or OS (HR = 7.389; 95% CI, 0.147–372.4, P = 0.317) (Figure S3).

Survival Analysis of Patients with MPR and Without MPR

Compared to patients without MPR, those with MPR had better RFS (HR = 0.322; 95% CI, 0.148–0.702, P = 0.004) and OS (HR = 0.101; 95% CI, 0.031–0.325, P = 0.000) (Figure S4). The 1- and 2-year RFS rates were 88.1% and 70.1% for patients with MPR and 62.1% and 43.6% for patients without MPR, respectively. The 1- and 2-year OS rates were 100.0% and 100.0% for patients with MPR and 79.6% and 61.9% for patients without MPR, respectively.

Safety of Treatment

The most common TRAEs in both groups in our study were abnormal liver function, fatigue, and hypertension. Table S1 showed that hypertension, abnormal liver function, and thrombocytopenia were the most common grade 3 or 4 adverse events in both groups, with 11 patients (19.30%) in the short duration group and 9 patients (32.14%) in the long duration group experiencing grade 3 or 4 TRAEs.

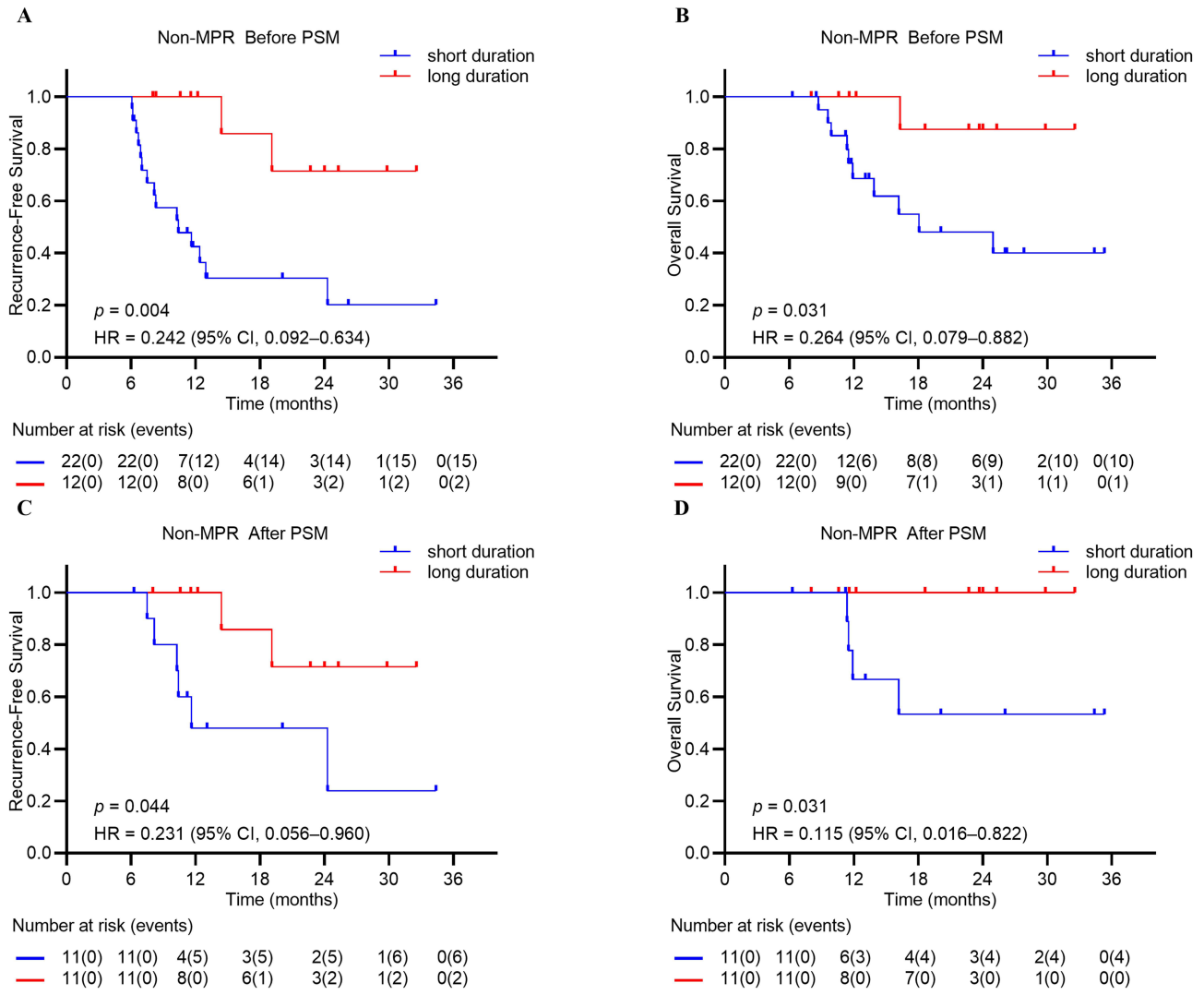

Figure 2 Kaplan–Meier curves of patients without MPR in two duration groups. (**A**) RFS and (**B**) OS of patients without MPR before PSM. (**C**) RFS and (**D**) OS of patients without MPR after PSM.

Abbreviations: MPR, major pathologic response; RFS, recurrence-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; PSM, propensity score matching.

Discussion

To the best of our knowledge, this is the first study to investigate the effect of adjuvant therapy duration on survival outcomes in patients with uHCC following conversion surgery. We found that there was no significant difference in either RFS or OS when comparing patients who received adjuvant therapy for more or less than 6 months. However, further analysis revealed that patients without MPR who received adjuvant therapy for >6 months had better RFS and OS than those who received it for ≤6 months. In patients with MPR, no survival benefits were found in those who received adjuvant therapy for >6 months compared to those who received it for ≤6 months. Even with a 3-month cutoff, no difference in survival was observed between the two duration groups.

Limited studies have been conducted on the association between a pathologic response and the postoperative prognosis in patients with HCC. Yang's study showed that in 1970 patients with HCC who underwent R0 resection, a pathologic response of ≥90% was identified as an independent protective factor against early recurrence.[21] Agopian et al conducted a study in which 501 HCC patients with pretransplant local treatment underwent liver transplantation. The results showed that, compared to patients without PCR, those who achieved PCR through local treatment had significantly better RFS rates at 1-, 3-, and 5-year.[22] Ho et al applied cabozantinib and nivolumab to convert locally advanced HCC to resectable HCC and found that the

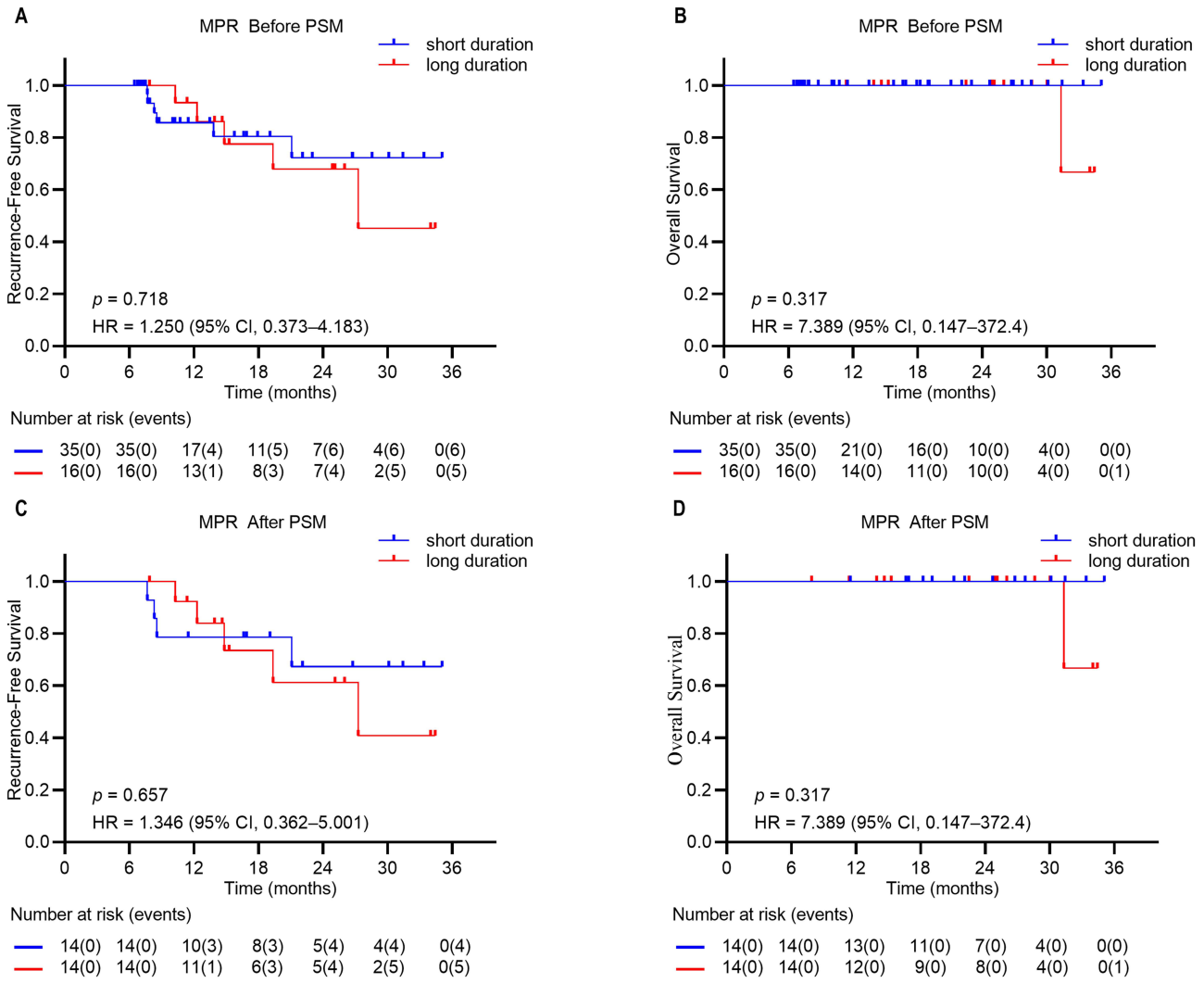

Figure 3 Kaplan–Meier curves of patients with MPR in two duration groups. (**A**) RFS and (**B**) OS of patients with MPR before PSM. (**C**) RFS and (**D**) OS of patients with MPR after PSM.

Abbreviations: MPR, major pathologic response; RFS, recurrence-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; PSM, propensity score matching.

patients with MPR had longer disease-free survival than those without MPR.[23] Additionally, in a study using tyrosine kinase inhibitors and anti-PD-1 antibodies for the treatment of initially uHCC, patients with PCR exhibited a tendency towards improved RFS compared to those who did not achieve PCR.[24] In this study, we also concluded that MPR was an independent protective factor for RFS and OS.

In the MPR subgroup, we observed no significant difference in survival between the two duration groups. Even when we used a 3-month duration as the cutoff point, we did not find a difference in RFS or OS between the two groups. This may be attributed to the lower risk of recurrence and metastasis resulting from deep tumor cell necrosis. These patients may not get additional benefits from long-term medication. Therefore, prolonging the postoperative medication duration for patients with MRP is not recommended so as to minimize TRAEs and the economic burden.

In the patients without MPR subgroup, there was a significant difference in survival between the two different duration groups. Considering the poorer prognosis of patients without MPR and our results suggesting that prolonging the duration of adjuvant therapy can be effective in improving the prognosis of patients, we recommend a medication duration of at least 6 months or more. The heterogeneity of HCC may lead to relative insensitivity to therapy in patients without MPR.[25] Further investigation is necessary to determine the exact duration.

There is a lack of recommendations in the current guidelines for adjuvant therapy in patients with uHCC after conversion surgery. In China, the Chinese expert consensus on conversion therapy for HCC recommends that the original conversion therapy regimen can be used as an adjuvant therapy for a duration of 6 months or more.[19] In a study on the combination of lenvatinib and sintilimab as conversion therapy in patients with uHCC, it was thought that eight cycles of perioperative treatment might be sufficient.[26] Determining the optimal duration of adjuvant therapy is a challenging task because an insufficient treatment duration may result in tumor recurrence. In contrast, a prolonged treatment duration may impose financial burdens on patients and increase the risk of TRAEs. Our results may provide evidence regarding the duration of adjuvant therapy in patients with uHCC after conversion surgery.

Postoperative adjuvant therapy was generally safe and tolerated. The most common TRAEs of any grade in both groups were abnormal liver function, fatigue, and hypertension. The majority were in grade 1 or 2 adverse events, with no grade 5 adverse events observed. Most of these symptoms were alleviated or disappeared following dose adjustment or symptomatic treatments.

This study had a few limitations. First, this was a retrospective study with a limited sample size; although we used PSM to reduce the selection bias, we still cannot completely avoid it. Second, the postoperative follow-up time was relatively short; therefore, the long-term prognosis remains unknown. Third, the conversion therapy regimen used in this study was a triple combination therapy of TACE, lenvatinib, and anti-PD-1 antibodies. Although it was very effective, it was not the first-line treatment for uHCC. Finally, this was a multicenter study in China, with most patients having a background of HBV infection. Whether the study results can be generalized to other countries or other etiologies of HCC needs to be explored in subsequent studies. Therefore, further prospective randomized controlled trials are required to confirm the optimal duration of adjuvant therapy.

In conclusion, at least 6 months of adjuvant therapy may be beneficial for patients without MPR. However, in patients with MPR, the effect of adjuvant therapy remains unclear. We suggest an individualized selection of the duration of adjuvant therapy for patients with uHCC after conversion surgery.

Data Sharing Statement

All data analyzed or generated in this study are presented in this article and its supplementary materials. For further information, please contact the corresponding author.

Ethical Approval

This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committees of Fujian Provincial Hospital (approval number: K2022-07-022).

Consent to Participate

All patients and their legal guardians provided written informed consent to participate in the study.

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Disclosure

The authors report no conflicts of interest in this work.

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