ORIGINAL RESEARCH

The Role of Timing of Progression and Early Salvage Surgery in Unresectable Hepatocellular Carcinoma Treated with TACE Plus TKIs and PD-1 Inhibitors

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Background: The prognosis of initially unresectable hepatocellular carcinoma (iuHCC) has been improved by TACE with TKIs and PD-1 inhibitors (TTP). However, the role of timing of tumor progression and and early salvage surgery during TTP therapy remains unclear.

Patients and Methods: The data of 151 patients who received TTP for iuHCC consecutively between November 2019 and December 2022 were retrospectively analyzed. The X-Tile software was used to determine the optimal threshold of progression timing to differentiate the post-progression survival (PPS) for patients with tumor progression, ultimately yielding 9 months as the optimal cut-off time. Early tumor progression was defined as patients with tumor recurrence (surgical patients) or progressive disease by mRECIST (nonsurgical patients) within 9 months of initial treatment. Accordingly, early salvage surgery was defined as salvage surgery performed within 9 months of the initial treatment.

Results: Out of all the patients, 55 (36.4%) patients showed early tumor progression, 33 (34.4%) showed late tumor progression, and 63 (41.7%) showed non-progression. Patients who experienced early tumor progression had a median PPS of 5.2 months, while those with late tumor progression had a median PPS of 16.8 months ($P < 0.001$). Multivariable analysis revealed a robust independent correlation between early tumor progression and PPS (HR = 3.279, 95% CI: 1.591–6.756; $P = 0.001$). Patients who received early salvage surgery showed a considerably lower early tumor progression rate when compared with patients who did not receive early surgery (12.5% vs 42.9%, $P = 0.002$). The multivariable analysis revealed that early salvage surgery was an independent factor influencing early tumor progression (OR = 0.246; 95% CI: 0.078–0.773; $P = 0.016$).

Conclusion: Early tumor progression is associated with worse PPS in patients with iuHCC receiving TTP therapy. Early salvage surgery can further improve patient outcomes by lowering the incidence of early progression.

Keywords: Hepatocellular carcinoma, salvage surgery, early tumor progression, post-progression survival, real-world

Introduction

Globally, hepatocellular carcinoma (HCC) remains the third most common malignant neoplasm in terms of cancer-related death.[1,2] Resectable HCC can have a favorable survival through curative treatment, especially liver resection.[3–5] However, because of advanced stage and technological unresectability, several patients with HCC are not suited for resection.[6] In real-world practice, immune-combination therapy has been extensively used in initially unresectable HCC (iuHCC). Positive survival outcomes in iuHCC have been demonstrated when

1641

transcatheter arterial chemoembolization (TACE), tyrosine kinase inhibitors (TKIs), and programmed cell death protein-1 (PD-1) inhibitors (TTP) are combined.[7–10] More encouragingly, the high objective response rate following TTP therapy allowed some patients to plan for salvage surgery.[11–13] As such, TTP therapy may be used as the first line of therapy for iuHCC.[14]

Because HCC is heterogeneous, TTP therapy does not work for every patient in the same manner, leaving a sizable portion of patients with unsatisfactory prognoses. A significant reaction to this heterogeneity is differences in the characteristics of tumor progression among patients. One important feature of tumor progression is the patterns of progression. Tumor progression patterns have been linked with post-progression survival (PPS) in patients with HCC receiving TKIs, radiotherapy, or immunotherapy.[15–17] The timing of progression is another crucial factor in tumor progression. A strong correlation exists between early recurrence and survival following recurrence in patients with HCC undergoing hepatectomy.[18] This is explained by the fact that early recurrent tumors have immune escape mechanisms and a distinct immunological microenvironment.[19] Similarly, early progressing tumors following TTP therapy might show poorer biological behavior and a different tumor microenvironment. Consequently, these tumor-progression-responsive parameters may serve as markers of the efficacy of TTP therapy. Nevertheless, it is still unknown how important tumor progression patterns and timing are for prognosis in TTP therapy. Furthermore, although salvage surgery has produced some positive outcomes in TTP therapy, its significance warrants further investigation and elaboration from a perspective on tumor progression.

Here, we conducted a retrospective real-world analysis to assess the role of tumor progression patterns and timing in patients with iuHCC who received TTP therapy. Meanwhile, our research provides further insight into the role of early salvage surgery during TTP therapy.

Material and Methods
Study Design and Patients

A retrospective analysis was conducted on patients with iuHCC who received TTP therapy following departmental discussion at the Department of Hepatobiliary Surgery, Guangxi Medical University Cancer Hospital, between November 2019 and December 2022. Based on the Chinese guidelines, HCC was diagnosed through clinicoradiological assessment (CT, MRI, or both) or histological examination.[20,21] Tumors were considered unresectable due to the following factors: substantial tumor burden and insufficient volume of residual liver; the proximity of the tumor to major macrovascular structures may hinder the achievement of an R0 resection, as determined through departmental discussion; the presence of extrahepatic metastases or major vascular invasion contribute to the unsuitability of hepatectomy as a preferred treatment option. Additional inclusion criteria were the age of 18–80 years, no history of antitumor therapy for HCC, Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0–1, Child–Pugh A or B liver function, and a quantifiable target lesion as determined by modified Response Evaluation Criteria in Solid Tumors (mRECIST).

Tumor progression in this study included progressive disease (PD) in patients who did not undergo salvage surgery as assessed according to mRECIST criteria and tumor recurrence in patients who underwent salvage surgery. The X-Tile software (Yale University 2003–05, USA; Version: 3.6.1) was used to determine the optimal threshold of progression timing to differentiate the PPS for patients with tumor progression, ultimately yielding 9 months as the optimal cut-off time. Patients whose tumors progressed within 9 months of initial treatment were considered to have early tumor progression. One example of non-early progression was non-progression during follow-up, while another was late tumor progression. As a result, clarifying the progression statistics within 9 months was required. Patients with a follow-up period of < 9 months who did not progress were excluded. Other exclusion criteria were follow-up in another center, incomplete radiological data, and incomplete clinical data. The study protocol was scrutinized and approved by the ethics committee at Guangxi Medical University Cancer Hospital, and complied with the Declaration of Helsinki. Written informed consent was obtained from every patient.

TTP Therapy and Salvage Surgery

TACE was conducted as described previously and details in <u>Supplementary Methods</u>.[13] Based on liver function recovery, TKIs and PD-1 inhibitors were administered to patients 7 days following TACE. TKIs used in this study followed the first-line treatment protocol recommended by the Chinese guidelines for advanced HCC.[21] TKIs included donafenib (200 mg twice a day) or lenvatinib (8 mg or 12 mg daily, depending on body weight) taken orally. The patient's financial status, drug availability, and guideline recommendations all played a role in selecting PD-1 inhibitors. Every 3 weeks, 200 mg of camrelizumab, sintilimab, or tislelizumab was used to provide PD-1 inhibitors. All patients were receiving treatment until the point of PD, intolerable toxicity, mortality, or voluntary withdrawal for any cause. Physician and patient participation is important in decision-making about post-progression therapy.

Salvage liver resection was determined if the criteria for a hepatectomy were satisfied. Tumor resectability following TTP therapy requires that both the technical requirements and the assessment of tumor response be met, as described previously.[13] Following salvage surgery, adjuvant therapy—entailing extending some of the initial TTP therapy for longer than 6 months—was recommended, as we previously described.[22]

Follow-Up

After the initial course of treatment, the first follow-up was observed 4–6 weeks later and, subsequently, every 2 months until October 15, 2023. Patients were assessed for treatment response and blood indicators, including routine blood, liver function, and tumor markers, among others, at each follow-up visit. In our center, two radiologists (D.X. and X.H) blinded to the treatment options and the patient's prognosis independently evaluated the tumor response using contrast-enhanced computed tomography (CE-CT) by mRECIST and RECIST1.1. Adverse events that transpired during TTP therapy were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Antiviral treatment was routinely administered for patients with hepatitis B.

Patients who underwent salvage liver resection were routinely monitored during the post-operative follow-up period. Serum alpha-fetoprotein (AFP) measurement, ultrasonography, and CE-CT were performed every 1–2 months in the first year and then every 3 months in the subsequent years.

Definitions

Salvage surgery, classified as early surgery, occurred within 9 months of initial treatment, and salvage surgery was classified as late surgery occurring after 9 months. From the commencement of TTP therapy to death or the last follow-up, overall survival (OS) was measured. PPS was calculated from the date of PD to death or last follow-up. The progression patterns were categorized into the following four based on the results of previous studies: intrahepatic or extrahepatic growth, new intrahepatic lesion, or new extrahepatic lesion.[17,23] A good tumor response was referred to as patients achieving complete or partial response at the first follow-up (4–6 weeks) after initial treatment according to mRECIST.[13]

Statistical Analysis

Statistical analysis was performed using Statistical Package for Social Sciences version 24 and R version 4.1.1. Continuous variables were expressed as the mean (± standard deviation) or medians (interquartile ranges [IQR]), and categorical variables were expressed as frequencies (percentages). We used Log rank tests and Kaplan–Meier curves to perform survival analysis. Potential risk factors for PPS were determined using the Cox proportional hazard model. Binary logistic regression methods were employed to identify the potential risk factors associated with early tumor progression. All variables with $P < 0.1$ or clinically significant factors were considered using the enter method in the following multivariable model. Backward stepwise Cox regression was used to identify the appropriate stratification variables that predict OS of patients who did not receive early salvage surgery and did not have early progression. $P < 0.05$ was considered to indicate statistical significance.

Results

Patient Characteristics

In our study, 167 patients with iuHCC were assessed and 16 were excluded (Figure 1). In TTP therapy, lenvatinib (139, 92.1%) and camrelizumab (116, 76.8%) were the principal TKI and PD-1 inhibitor (Table S1). At the baseline, 135 (89.4%) had hepatitis B, 126 patients (83.4%) were of Child–Pugh grade A, and 103 patients (68.2%) had Barcelona clinical liver cancer (BCLC) stage C (Table 1).

The median follow-up length was 22.2 months for all patients and a total of 5 patients were lost to follow-up. Table S2 provides an overview of the adverse events; in general, the adverse events of TTP treatment were tolerable. Table S3 provides an overview of the tumor response assessment. During follow-up, 35 (23.2%) patients met resectability criteria and subsequently underwent salvage surgery. Thirty-two cases (21.2%) of early salvage surgery and three cases (2.0%) of late surgery were included in the group, and, at the baseline, none of them showed extrahepatic metastases (EHM). From the start of TTP therapy until the salvage surgery, the median interval was 3.8 (3.2–5.1) months. During the follow-up, 88 patients had tumor progression, of which 10 patients (11.4%) had postoperative recurrence. These patients had a higher percentage of liver function Child–Pugh class B/C at progression when compared to that at the baseline; however, the percentage of patients whose AFP level was > 400 ng/mL had decreased (Table S4).

The Timing and Patterns of Tumor Progression

Of the total patients in the group, 55 (36.4%) patients had early tumor progression, while 96 (63.6%) did not. Thirty-three cases (21.9%) of late progression and 63 cases (41.7%) of non-progression were detected among the patients who did not experience early tumor progression. Patients with early tumor progression had more Child–Pugh grade B (25.5% vs 11.5%, $P = 0.026$), more EHM (23.6% vs 9.4%, $P = 0.017$), less BCLC stage A (5.5% vs 14.6%, $P = 0.023$), and larger target tumor diameter (10.9 vs 10.1, $P = 0.048$) in comparison to patients with non-early progression (Table 1). Table S5 displays the progression patterns of patients who received TTP.
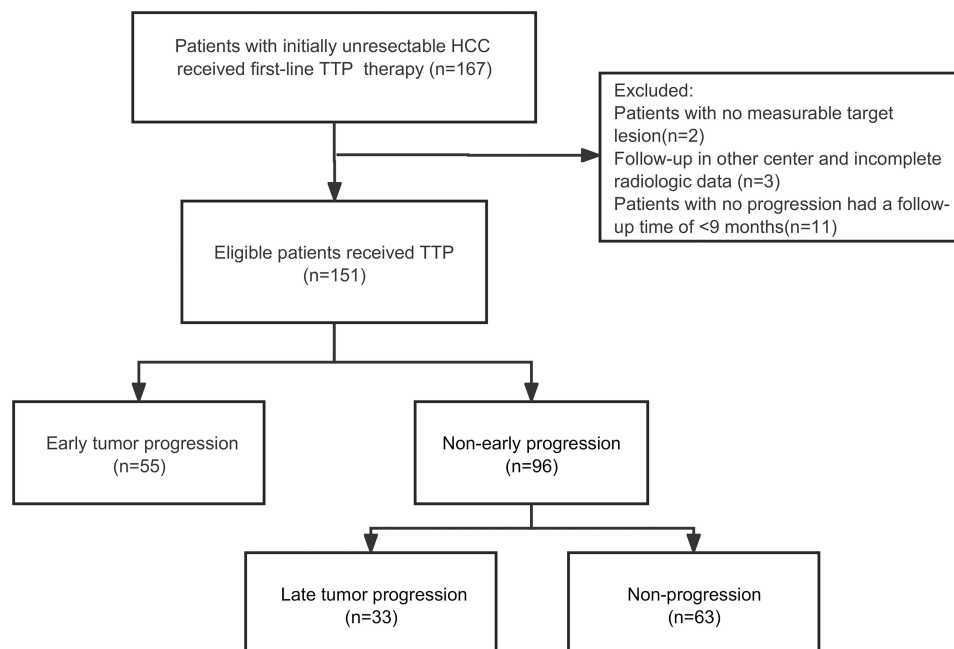

Figure 1 Study flowchart.
Abbreviations: HCC, hepatocellular carcinoma; TTP, TACE combined with TKIs plus PD-1 inhibitors.

Table 1 Baseline Characteristics of Patients

Variable	Entire Cohort (n=151)	Early Tumor Progression (n=55)	Non-early Progression (n=96)	P value
Age (year)				0.417
>60	27 (17.9%)	10 (18.2%)	17 (17.7%)	
≤60	124 (82.1%)	45 (81.8%)	79 (82.3%)	
Gender				0.417
Male	133 (88.1%)	50 (90.9%)	83 (86.5%)	
Female	18 (11.9%)	5 (9.1%)	13 (13.5%)	
BCLC stage				0.023
A	17 (11.3%)	3 (5.5%)	14 (14.6%)	
B	31 (20.5%)	7 (12.7%)	24 (25.0%)	
C	103 (68.2%)	45 (81.8%)	58 (60.4%)	
Target tumor diameter (cm)				
Median (Q1-Q3)	10.8 (8.5–14.5)	10.9 (9.3–15.5)	10.1 (8.1–13.7)	0.048
Tumor number				
Median (Q1-Q3)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.250
Large vascular invasion				0.060
Yes	98 (64.9%)	41 (74.5%)	57 (59.4%)	
No	53 (35.1%)	14 (25.5%)	39 (40.6%)	
PVTT				0.209
Yes	86 (57.0%)	35 (63.6%)	51 (53.1%)	
No	65 (43.0%)	20 (36.4%)	45 (46.9%)	
Extrahepatic metastases				0.017
Yes	22 (14.6%)	13 (23.6%)	9 (9.4%)	
No	129 (85.4%)	42 (76.4%)	87 (90.6%)	
AFP (ng/mL)				0.375
> 400	89 (58.9%)	35 (63.6%)	54 (56.2%)	
≤ 400	62 (41.1%)	20 (36.4%)	42 (43.8%)	
Etiology				0.649
Hepatitis B	135 (89.4%)	50 (90.9%)	85 (88.5%)	
Non–Hepatitis B	16 (10.6%)	5 (9.1%)	11 (11.5%)	
Antiviral therapy				0.649
Yes	135 (89.4%)	50 (90.9%)	85 (88.5%)	
No	16 (10.6%)	5 (9.1%)	11 (11.5%)	
ECOG PS				0.723
0	85 (56.3%)	32 (58.2%)	53 (55.2%)	
1	66 (43.7%)	23 (41.8%)	43 (44.8%)	
Cirrhosis				0.104
Yes	112 (74.2%)	45 (81.8%)	67 (69.8%)	
No	39 (25.8%)	10 (18.2%)	29 (30.2%)	
Child-Pugh grade				0.026
A	126 (83.4%)	41 (74.5%)	85 (88.5%)	
B	25 (16.6%)	14 (25.5%)	11 (11.5%)	
ALBI grade				0.928
1	15 (9.9%)	6 (10.9%)	9 (9.4%)	
2	130 (86.1%)	47 (85.5%)	83 (86.5%)	
3	6 (4.0%)	2 (3.6%)	4 (4.2%)	
PT (sec)	12.7 ±1.7	12.9 ±1.6	12.6 ±1.7	0.290
ALT (U/L)	43.0 (29.5–64.5)	47.0 (29.5–64.5)	42.0 (29.8–60.2)	0.975
AST (U/L)	64.0 (45.0–96.0)	70.0 (48.5–98.0)	59.0 (44.8–91.5)	0.243

(*Continued*)

Table 1 (Continued).

Variable	Entire Cohort (n=151)	Early Tumor Progression (n=55)	Non-early Progression (n=96)	P value
Salvage surgery				<0.001
Yes	35 (23.2%)	4 (7.3%)	31 (32.3%)	
No	116 (76.8%)	51 (92.7%)	65 (67.7%)	
Early salvage surgery				0.002
Yes	32 (21.2%)	4 (7.3%)	28 (29.2%)	
No	119 (78.8%)	51 (92.7%)	68 (70.8%)	

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ALT, alanine aminotransferase; PT, Prothrombin time; BCLC, Barcelona Clinic Liver Cancer; ALBI, albumin–bilirubin; AFP, α-fetoprotein; PVTT, portal vein tumor thrombosis; AST, aspartate aminotransferase.

Effect of Early Tumor Progression and Patterns of Progression on PPS

The patients who experienced early tumor progression had a median PPS of 5.2 months, while those with late tumor progression had a median PPS of 16.8 months ($P < 0.001$; Figure 2A). Only early tumor progression showed an independent correlation with PPS in multivariable analysis (HR = 3.279, 95% CI: 1.591–6.756; $P = 0.001$) (Table 2). In addition, sensitivity analysis in 78 patients who did not receive salvage surgery with tumor progression confirmed that early tumor progression impacted PPS (HR = 3.970, 95% CI: 1.778–8.862; $P = 0.001$) (Figure 2B and Table S6). Tables 2 and S6, however, showed no significant association between PPS and any of the four tumor progression patterns.

Effect of Post-Progression Therapy on PPS

Post-progression therapy was administered to 29 (52.7%) patients who experienced early progression and 32 (97.0%) patients who experienced late progression (Table S7). Patients who received post-progression therapy had significantly longer PPS than those who did not receive it (8.4 months vs 4.8 months, $P = 0.002$, Figure 3A). These findings were confirmed in 78 patients who did not receive salvage surgery (Figure 3B). Multivariable analyses, however, did not reveal potential correlation between post-progression therapy and PPS (Tables 2 and S6).
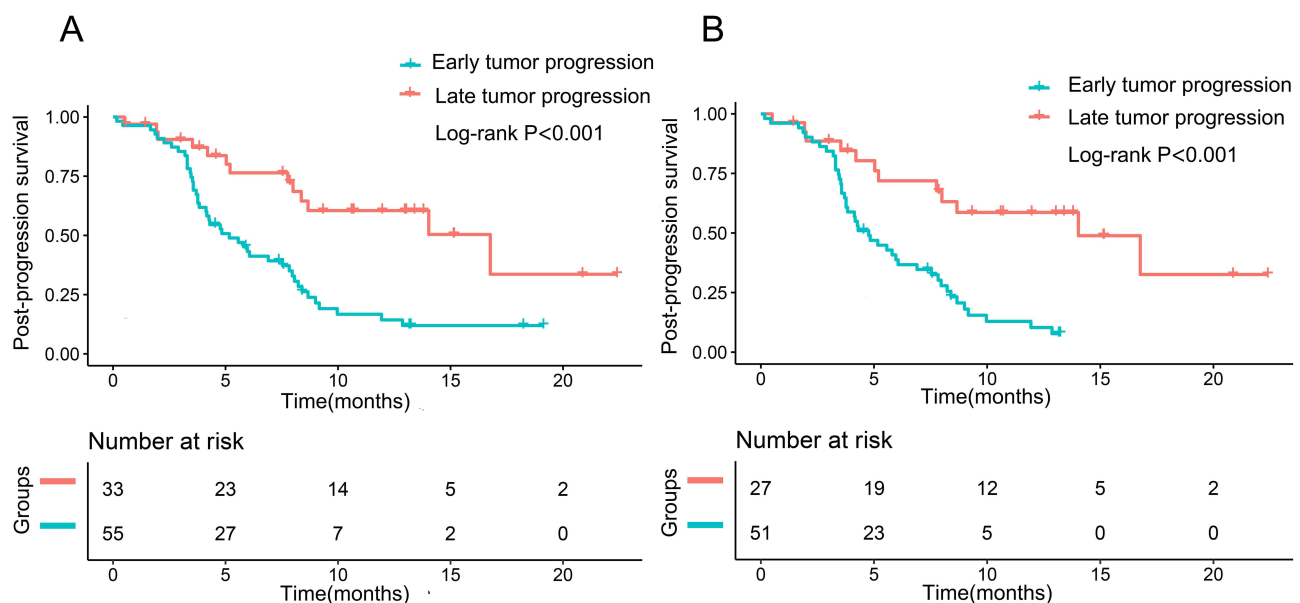

Figure 2 Kaplan-Meier analysis on post-progression survival in the early and late tumor progression groups (**A**); Kaplan-Meier analysis on post-progression survival in the early tumor progression group and the late tumor progression group in 78 patients without salvage surgery (**B**).

Table 2 Factors Related with Post-Progression Survival in 88 Patients with Tumor Progression

		Univariable			Multivariable		
		HR	95% CI	P	HR	95% CI	P
Age, y	> 60 vs ≦ 60	1.228	0.636–2.371	0.542			
Sex	Male vs Female	1.471	0.630–3.434	0.372			
Intrahepatic lesion growth	Yes vs No	1.269	0.746–2.161	0.380	1.076	0.588–1.969	0.812
Extrahepatic lesion growth	Yes vs No	1.475	0.668–3.257	0.336	2.147	0.843–5.466	0.109
New intrahepatic lesion	Yes vs No	0.693	0.397–1.209	0.196	0.847	0.442–1.625	0.617
New extrahepatic lesion	Yes vs No	1.123	0.647–1.948	0.680	0.894	0.492–1.624	0.713
Post-progression therapy	Yes vs No	0.450	0.265–0.765	0.003	0.911	0.445–1.867	0.800
Early tumor progression	Yes vs No	3.093	1.654–5.786	<0.001	**3.279**	**1.591–6.756**	**0.001**
ECOG PS	≥1 vs 0	1.318	0.781–2.224	0.301	1.222	0.677–2.207	0.505
ALBI grade	Grade1 vs 2/3	1.872	0.584–5.997	0.291			
Child-Pugh class	Class A vs B/C	0.735	0.438–1.233	0.243	0.708	0.401–1.249	0.233
AFP, ng/mL	> 400 vs ≦ 400	1.343	0.796–2.264	0.269	1.457	0.824–2.577	0.195
ALT, U/L	> 40 vs ≦ 40	0.784	0.463–1.330	0.367			
AST, U/L	> 40 vs ≦ 40	1.349	0.746–2.439	0.322			

Note: Bold values indicate statistically significant results of the multivariable analysis.
Abbreviations: HR, hazard ratio; AFP, alpha fetoprotein; ALT, alanine aminotransferase; CI, confidence interval; AST, aspartate aminotransferase; ALBI grade, albumin-bilirubin grade; ECOG PS, Eastern Cooperative Oncology Group performance status.

We also examined the impact of several post-progression treatments on PPS. The PPS of various post-progression treatments varied significantly, as seen by survival curves (*P* = 0.002, Figure S1). The immune-combination group had a higher median PPS than the other three groups.

Relationship Between Early Salvage Surgery and Early Tumor Progression

Patients who received early salvage surgery (4/32, 12.5%) showed a considerably lower early tumor progression rate than patients who did not receive early salvage surgery (51/119, 42.9%) (*P* = 0.002, Table 1). We carried out further multivariable analyses. Instead of using the BCLC stage, the first multivariable model included tumor diameter, large vascular invasion, and EHM. The exclusive independent factor influencing early tumor progression was early salvage
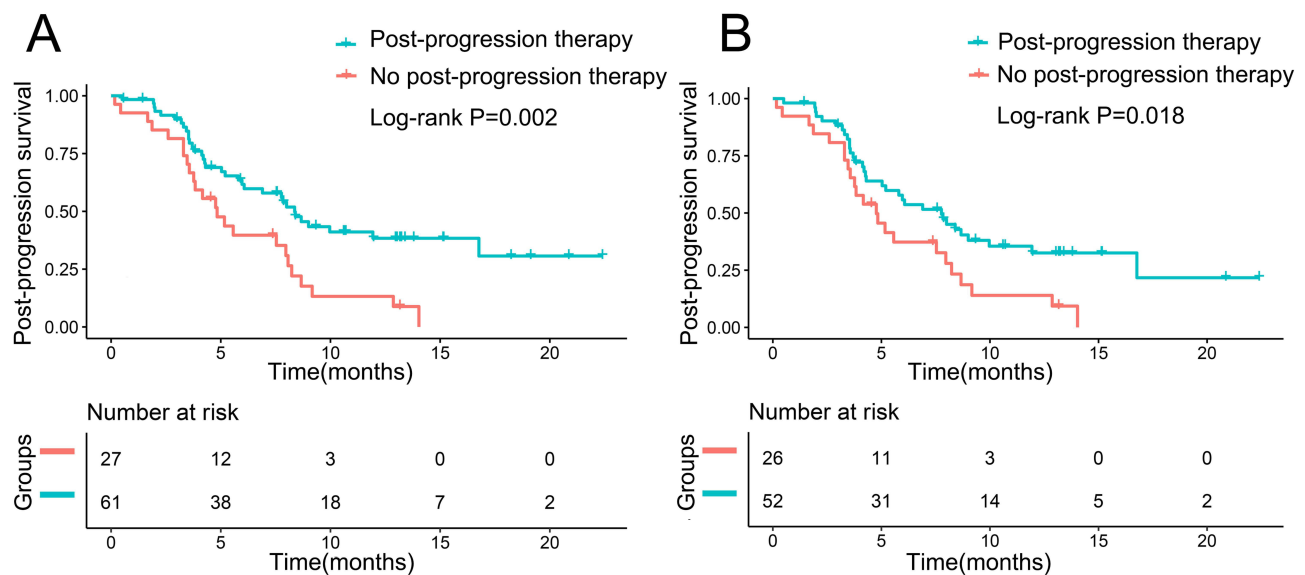

Figure 3 Kaplan–Meier curves for post-progression survival based on post-progression therapy in 88 patients with tumor progression (**A**); Kaplan–Meier curves for post-progression survival based on the post-progression therapy in 78 patients with tumor progression without salvage surgery (**B**).

Table 3 Factors Associated with Early Tumor Progression in 151 Patients with Initially Unresectable HCC Received TTP Therapy

		Univariable			Multivariable (Model 1)#			Multivariable (Model 2)#		
		OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Age, y	> 60 vs ≦ 60	0.942	0.436–2.447	0.942						
Sex	Male vs Female	1.566	0.527–4.656	0.563						
HBsAg-positive	Yes vs No	1.294	0.425–3.940	0.650						
Tumor diameter, cm	> 10 vs ≦ 10	1.972	0.981–3.965	0.057	1.668	0.776–3.582	0.190	–	–	–
Tumor number	Multiple vs single	1.412	0.710–2.809	0.325						
PVTT	Yes vs No	1.544	0.782–3.048	0.211						
Large vascular invasion	Yes vs No	2.004	0.965–4.161	0.062	1.857	0.851–4.055	0.120	–	–	–
EHM	Yes vs No	2.992	1.185–7.555	0.020	1.865	0.694–5.013	0.217	–	–	–
BCLC stage	Stage C vs A/B	2.948	1.327–6.549	0.008	–	–	–	**2.618**	**1.139–6.019**	**0.023**
AFP, ng/mL	> 400 vs ≦ 400	1.361	0.689–2.691	0.375						
NLR	> 2.76 vs ≦ 2.76	2.082	1.058–4.097	0.034	1.789	0.859–3.725	0.120	1.860	0.907–3.815	0.091
PLR	> 131.9 vs ≦ 131.9	1.644	0.842–3.212	0.145						
HBV DNA, IU/mL	≥20 vs<20	0.943	0.421–2.114	0.887						
Liver cirrhosis	Yes vs No	1.948	0.865–4.387	0.108						
ALT, U/L	> 40 vs ≦ 40	1.280	0.656–2.499	0.469						
AST, U/L	> 40 vs ≦ 40	2.149	0.806–5.729	0.126						
ALBI grade	Grade1 vs 2/3	1.184	0.398–3.523	0.762						
ECOG PS	0 vs 1	1.129	0.578–2.206	0.723						
Child-Pugh class	A vs B	0.379	0.158–0.908	0.029	0.538	0.212–1.367	0.193	0.587	0.232–1.482	0.259
CD8/CD4	> 0.57 vs ≦ 0.57	0.860	0.443–1.670	0.656						
IgG/IgM	> 13.23 vs ≦ 13.23	1.715	0.878–3.351	0.115						
Early salvage surgery	Yes vs No	0.190	0.063–0.577	0.003	**0.278**	**0.087–0.887**	**0.031**	**0.246**	**0.078–0.773**	**0.016**

Notes: #Model 1 did not contain BCLC stage into multivariable model to avoid collinearity. #Model 2 did not contain tumor diameter, large vascular invasion, and EHM into multivariable model to avoid collinearity. Bold values indicate statistically significant results of the multivariable analysis.
Abbreviations: HCC, hepatocellular carcinoma; CI, confidence interval; ALBI grade, albumin-bilirubin grade; ECOG PS, Eastern Cooperative Oncology Group performance status; TTP, TACE combined with TKIs plus PD-1 inhibitors; ALT, alanine aminotransferase; EHM, extrahepatic metastases; AST, aspartate aminotransferase; PLR, platelet to lymphocyte ratio; AFP, alpha fetoprotein; BCLC, Barcelona-Clinic liver cancer; OR, odds ratio; PVTT, portal vein tumor thrombosis; NLR, neutrophil to lymphocyte ratio; HBV, hepatitis B virus.

surgery (OR = 0.278; 95% CI: 0.087–0.887; P = 0.031) (Table 3). Included in the second multivariable model was the BCLC stage. The results showed that the independent factors impacting early tumor progression were BCLC stage (OR = 2.618; 95% CI: 1.139–6.019; P = 0.023) and early salvage surgery (OR = 0.246; 95% CI: 0.078–0.773; P = 0.016) (Table 3). In addition, the role of early salvage surgery on early tumor progression was validated in patients with good tumor response (OR = 0.221; 95% CI: 0.058–0.844; P = 0.027) (Table S8).

Risk Stratification for OS

Both early salvage surgery and early tumor progression were significantly associated with patient PFS and OS (Figure S2; Table S9). Compared to patients without early surgery and without early tumor progression, those who received early salvage surgery had also a significantly improved OS (P = 0.039, Figure S3). Due to the high heterogeneity, we conducted predictor analyses in 68 patients who did not receive early salvage surgery and did not have early progression. The findings of the multivariable analysis revealed that PVTT (HR = 3.242, 95% CI: 1.082–9.715; P = 0.036) and AFP >400 ng/mL (HR = 5.479, 95% CI: 1.230–24.398; P = 0.026) were independently linked with OS (Table S10). We could corroborate this result by conducting predictor analyses on 65 patients who did not receive salvage surgery and did not exhibit early progression (Table S11). Patients with both PVTT and AFP >400 ng/mL had a significantly worse prognosis than those with only one component or neither of the two (19.8 months vs NS, P = 0.004, Figure S4A) in patients without early surgery and without early tumor progression. Remarkably, none of the three patients who underwent late salvage surgery possessed both factors. The OS of early and late salvage surgery were also examined, although no discernable difference was detected (P = 0.480, Figure S4B).
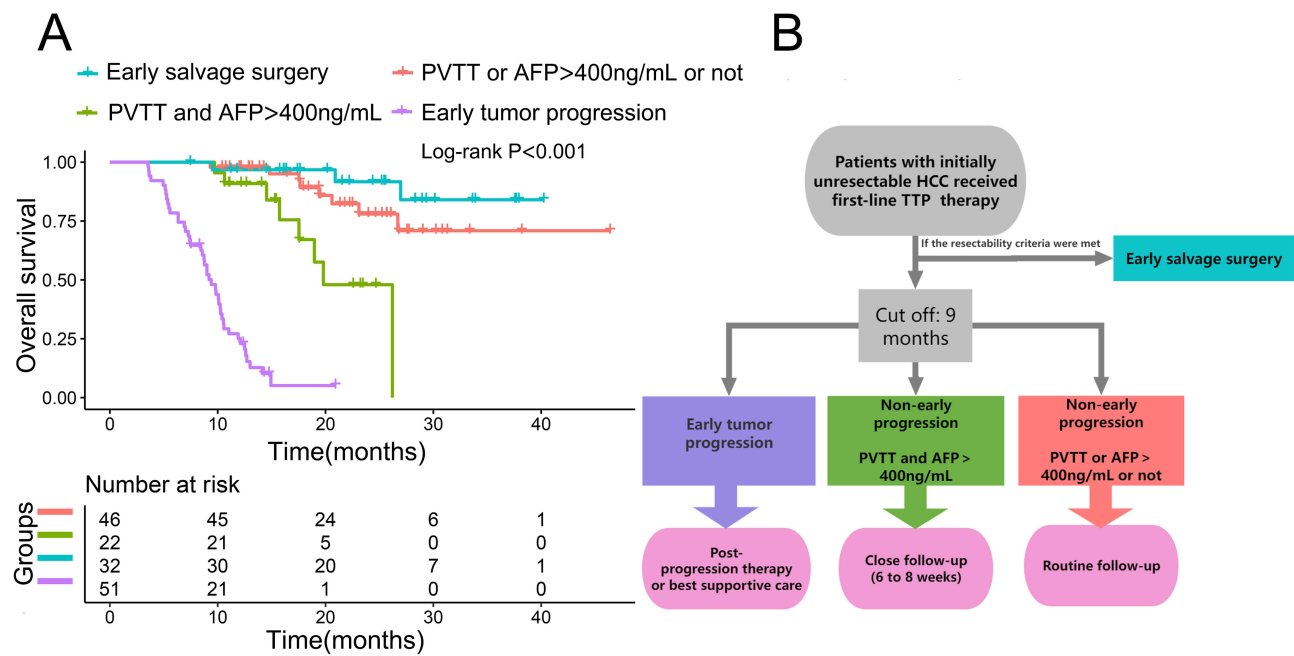
Figure 4 Kaplan–Meier curves for overall survival based on a prognostic stratification approach in the entire cohort (**A**); schematic diagram of the clinical application of the prognostic stratification approach (**B**).

Thus, based on these prognostic factors, PVTT, AFP, early tumor progression, and early salvage surgery, we further separated the 151 patients into four stratifications (Figure 4A). Risk stratification may help treatment and monitor iuHCC during TTP therapy (Figure 4B).

Discussion

Regarding combination therapy for patients with iuHCC, TTP therapy is a commonly used method.[24] In this study, we found that the timing of tumor progression rather than the patterns of progression was closely related to PPS in patients with iuHCC receiving TTP therapy. Early salvage surgery can further improve the patient's prognosis based on TTP therapy by lowering the early progression rate.

Currently, the tumor progression patterns are receiving more attention. It has been proposed that new extrahepatic lesions in patients with advanced HCC treated with sorafenib might be used to assess PPS.[16] The development of new intrahepatic lesions or EHM was associated with a worse PPS in the cohort of patients with HCC receiving selective internal radiotherapy.[15] For patients with HCC using immunotherapy, neovascular invasion was associated with poor prognosis.[17] However, our study did not associate four tumor progression patterns with PPS. According to our results, PPS is more closely related to early tumor progression than the patterns of progression. This could be explained by the fact that patients with early progression have a different tumor ecosystem, similar to that for early-relapse HCC after liver resection.[19] Additional research is required to investigate the potential molecular mechanisms. Meanwhile, the timing of tumor progression may need to be considered when designing second-line trials following TTP.

An important factor affecting PPS is post-progression therapy. The patients in our study with late progression were more likely to be treated with post-progression therapy. Immuno-combination therapy appears to be more effective in the interim among different post-progression therapies. This result is consistent with those of a previous study that employed immunotherapy in HCC patients.[17] However, the multivariable analysis revealed no significant correlation between post-progression therapy and PPS, potentially representing the present dilemma in selecting a post-progression therapy following TTP therapy. The advancement of different immune-combination therapies has extended the survival of patients with intermediate and advanced HCC and increased the number of patients eligible for post-progression therapy. Nonetheless, patients who have progressed on solafenib have participated in most clinical trials on post-progression

therapy for HCC.[25,26] This cannot meet the current clinical practice demand for post-progression therapy of HCC. Therefore, more evidence is warranted to precisely select the post-progression therapy.

Salvage liver resection may be the only curative treatment for patients with iuHCC.[6,27] Patients who underwent salvage surgery showed a significantly better prognosis than those who did not undergo surgery and those who received initial surgery.[13,22,28] The authors of a multicenter retrospective study from China concluded that, after successful downstaging, salvage surgery could increase OS more than when continuing with local-plus-systemic therapy.[29] These results suggest that salvage surgery is of great value in patients with iuHCC and that hepatectomy can be used to further improve prognosis after meeting the resectable criteria. In our study, 36.4% of patients had early tumor progression and poor PPS. Remarkably, early salvage surgery could lower the rate of early tumor progression, and this effect persisted in patients with good tumor response. Its suggests that early salvage surgery could improve certain patients' prognosis by preventing early tumor progression. Therefore, early salvage surgery is required for iuHCC during TTP therapy when the resectability criteria are met.

In patients without early salvage surgery and without early tumor progression, AFP and PVTT are indicators of OS. We created a prognostic classification method based on early salvage surgery, early tumor progression, PVTT, and baseline levels of AFP to maximize the application of our findings in clinical settings. Using this method, we divided the patients into four groups. According to the Chinese guidelines, patients with HCC undergoing immuno-combination therapy should be assessed every 6–8 weeks for a year from the start of the treatment, followed by an assessment conducted every 12–24 weeks until detection of PD.[30] In our study, patients with both PVTT and AFP >400 ng/mL had a significantly worse prognosis when compared to those with only one component or neither of the two in patients without early surgery and without early tumor progression. To detect tumor progression as soon as feasible, we propose that patients who do not have early surgery and early tumor progression, but have PVTT and AFP levels >400 ng/mL should continue to receive close follow-up (6–8 weeks) beyond 9 months.

To the best of our knowledge, this study is the first to report the potential relationship between PPS and the timing of tumor progression during TTP therapy. Nonetheless, this study has several limitations. First, selection bias was inevitable because of the retrospective nature of the study. A further validation of the findings by a prospective study is therefore necessary. Second, we used several PD-1 inhibitors and TKIs. Additional research is required to examine the effects of various combination therapies, although there is no evidence that different drug combinations have different prognoses. Third, prospective large-sample studies are required to confirm the threshold for early and late progressions. Last, as nearly 90% of the patients in our study had hepatitis B, the findings require validation in those without hepatitis B background.

Conclusions
The timing of tumor progression, rather than the patterns of progression, is associated with PPS in patients with iuHCC receiving TTP therapy. Early salvage surgery can further improve patient outcomes by lowering the early progression rate.

Data Sharing Statement
For further enquiry on all relevant data, please contact the corresponding author.

Ethical Statement
The study protocol was scrutinized and approved by the ethics committee at Guangxi Medical University Cancer Hospital (approval number: LW2023185), and complied with the Declaration of Helsinki. Written informed consent was obtained from every patient.

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Disclosure

The authors report no conflicts of interest in this work.

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