Original Article

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Radiotherapy enhances triple therapy for conversion and survival in patients with unresectable hepatocellular carcinoma with portal vein tumor thrombus

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SUMMARY: Triple therapy (TT), consisting of transarterial chemoembolization, immune checkpoint inhibitors, and tyrosine kinase inhibitors, is recommended as a conversion therapy for patients with unresectable hepatocellular carcinoma (uHCC). However, patients with uHCC with portal vein tumor thrombosis (PVTT) have a limited response to TT alone. This study evaluated whether combining TT with radiotherapy (TTR) could increase conversion resection rates and improve the prognosis of uHCC with PVTT. A total of 123 patients treated at our institution from 2020-2024 were retrospectively analyzed, comprising 103 patients receiving TT and 20 receiving TTR. The overlap weighting (OW) method was used to minimize bias. Compared with the TT group, patients in the TTR group had a significantly greater early tumor shrinkage rate (85.0% *vs.* 59.2%, $p = 0.029$). Moreover, conversion resection rates were significantly higher in the TTR group (65.0% *vs.* 35.0%, $p = 0.012$), and the median overall survival (OS) was notably prolonged (median OS not reached *vs.* 31.9 months, $p = 0.031$). Following OW adjustment of the data, we obtained similar results. Multivariate analysis confirmed TTR as an independent protective factor for both OS (HR = 0.354, 95% CI = 0.127-0.984, $p = 0.046$) and the conversion resection rate (OR = 0.261, 95% CI = 0.081-0.838, $p = 0.024$). Treatment-related adverse events were manageable. Thus, TTR offers an improved conversion resection rate and survival outcomes compared with TT alone in patients with uHCC with PVTT and represents a promising therapeutic strategy.

Keywords: unresectable hepatocellular carcinoma, portal vein tumor thrombosis, radiotherapy, conversion resection

1. Introduction

Hepatocellular carcinoma (HCC) is a highly aggressive malignancy and the third leading cause of cancer-related mortality in patients worldwide; it is responsible for more than 800,000 deaths annually (*1*). Liver resection remains the primary curative treatment for HCC, with reported 5-year overall survival (OS) rates ranging from 50% to 70% (*2*). However, owing to its asymptomatic onset and rapid progression, over 60% of patients present with intermediate or advanced disease, precluding curative surgery (*2*). Although recent advances in both systemic and locoregional therapies have improved long-term outcomes in these patients (*3*), the OS rates remain unsatisfactory, particularly in patients with portal vein tumor thrombosis (PVTT).

Conversion therapy has emerged as a promising strategy for initially unresectable HCC (uHCC), enabling curative-intent resection and improved survival (*2*). Various conversion therapy regimens have been investigated (*4*), among which triple therapy (TT), which combines immune checkpoint inhibitors (ICIs), tyrosine kinase inhibitors (TKIs), and transarterial chemoembolization (TACE), has shown superior efficacy and is endorsed by the Chinese expert consensus (*4-7*). Compared with TACE or systemic therapy alone, TT significantly improves resection rates, OS, and progression-free survival (PFS) in patients with uHCC (*5*). However, PVTT is an independent risk factor in these patients, affecting the conversion resection rate, OS and PFS (*8,9*). PVTT progression accelerates disease progression, portal hypertension, hepatic decompensation, and related complications, with reported median growth rates of up to 0.9 mm/day (*10*). These observations highlight the urgent need for targeted PVTT management during conversion therapy. Emerging evidence suggests that stereotactic body radiotherapy (SBRT) combined with systemic therapy may improve outcomes compared with systemic therapy alone in patients with uHCC with PVTT (*11,12*).

On the basis of these observations, we hypothesized that in these patients, TT augmented with RT (TTR) may represent a more effective conversion therapy than TT. To investigate this premise, we conducted this study.

2. Materials and Methods

2.1. Study population

This study enrolled patients with uHCC with PVTT who received conversion therapy with either TT or TTR at our center between January 2020 and January 2024. The inclusion criteria for this study were as follows: 1) age ≥ 18 years; 2) liver function classified as Child–Pugh class A or B; 3) a diagnosis of HCC according to the American Association for the Study of Liver Diseases guidelines or by postoperative pathological examination; 4) Barcelona Clinic Liver Cancer (BCLC) stage C disease, with confirmed portal vein involvement as verified by imaging; 5) Eastern Cooperative Oncology Group (ECOG) performance status score of 0–1; and 6) no history of other malignancies. The exclusion criteria were as follows: patients aged <18 years, patients with recurrent HCC, individuals with extrahepatic metastases, and those presenting spontaneous tumor rupture. PVTTs was radiologically confirmed *via* pretreatment imaging and classified according to the Japan Liver Cancer Study Group criteria as follows: VP1 (third-order branch involvement), VP2 (second-order branch involvement), VP3 (first-order branch involvement), and VP4 (main trunk or contralateral branch involvement) (*13*). This study was approved by the Ethics Committee of West China Hospital of Sichuan University (No. 2025-795) and conformed to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies (*14*).

2.2. Treatment

Treatment regimens were individually tailored by a multidisciplinary team (MDT). Eligible patients received one of the following targeted therapy regimens: lenvatinib (12 mg/day for patients weighing ≥ 60 kg; 8 mg/day for patients weighing < 60 kg), apatinib (250 mg/day), sorafenib (400 mg twice daily), donafenib (200 mg twice daily), bevacizumab (15 mg/kg every 3 weeks), or regorafenib (160 mg/day). The ICIs administered included atezolizumab (1200 mg every 3 weeks), sintilimab (200 mg every 3 weeks), toripalimab (240 mg every 3 weeks), camrelizumab (200 mg every 2 weeks), and tislelizumab (200 mg every 3 weeks).

TACE procedures were performed under local anesthesia *via* right femoral artery access. Following arteriography of the celiac trunk and superior mesenteric artery to assess the liver's arterial vascularization, chemotherapy agents, including 5-fluorouracil (800–1000 mg) and epirubicin-adriamycin (30–40 mg), were administered according to the body surface area. Subsequently, lipiodol and polyvinyl alcohol foam embolization particles were selectively injected into the hepatic segmental artery corresponding to the target tumor site. The volume of embolization agents ranged from 5 to 30 mL, with the dose adjusted on the basis of the tumor's location, size, and number.

For patients who underwent radiotherapy, the target area was delineated by experienced radiation oncologists under CT guidance. The gross tumor volume (GTV) encompassed the portal vein filling defect and adjacent primary hepatic lesions. To generate the clinical target volume (CTV), the GTV was expanded by 5 mm, and an additional margin of 5 mm was subsequently added to the CTV to form the planning target volume (PTV). Decisions regarding the prescribed radiation dose and fractionation schedule were determined by tumor location and volume, as well as proximity to critical anatomical structures. The linear-quadratic (LQ) formalism along with the biologically effective dose (BED) derived from the LQ model was used to evaluate the effect of fractionated irradiation. The BED was calculated using the following equation: $BED = nd \times [1 + d/(\alpha/\beta)]$, where n represents the number of radiation fractions, d denotes the fraction size, and an α/β ratio of 10 was used to determine the BED delivered to the tumor (*15*). Ultimately, the radiotherapy regimen and dosage were individualized for each patient according to tumor dimensions and proximity to intrahepatic lesions.

2.3. Efficacy assessment and follow-up

Tumor response and PVTT response was assessed according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) version 1.1 (*16*) at 3-month intervals, with subsequent therapeutic strategies (including surgical interventions) determined by MDT consensus. Early tumor shrinkage (ETS) was defined as a reduction of at least 10% from baseline in the sum of the longest diameters of target lesions at the first tumor assessment (*17*). A major pathological response (MPR) was defined as 10% or fewer residual viable tumor cells (indicating ≥90% necrosis), whereas a pathological complete response (pCR) was characterized by the absence of viable tumor cells in the resected tissue. For patients exhibiting either disease progression to treatment or grade ≥ 3 treatment-related adverse events (trAEs), the current regimen was discontinued and second-line alternatives were evaluated. OS was calculated from treatment initiation to death from any cause or last follow-up (1 March 2025). PFS was defined as the time from first treatment to progressive disease (PD) or death or recurrence from any reason

(*18*). Recurrence-free survival (RFS) was defined as the time interval from conversion resection to the occurrence of recurrence.

2.4. Definitions

The albumin-bilirubin (ALBI) grade was computed using the following established formula: ALBI score = (log10 bilirubin [μmol/L] × 0.66) + (albumin [g/L] × -0.085) (*19*). ALBI values were divided into 3 grades as follows: grade 1 (ALBI score < -2.60), grade 2 (-2.60 ≤ ALBI score ≤ -1.39), and grade 3 (ALBI score > -1.39) (*19*). Thrombocytopenia was defined as a platelet count <100×10⁹/L (*20*). Perioperative complications were assessed according to the Clavien-Dindo grading system (*21*), with grade ≥3 complications considered severe complications (*20*).

2.5. Statistical analysis

Categorical variables are presented as frequency counts and percentages, with between-group comparisons performed using Pearson's chi-square test or Fisher's exact test. Continuous variables are expressed as the means ± standard deviations, and group comparisons were conducted using independent Student's *t* tests or Mann-Whitney *U* tests. Survival outcomes were analyzed using the Kaplan-Meier method. Factors with a *p* value of less than 0.1 in the univariate analysis were subsequently entered into the multivariate analysis. A *p* value of less than 0.05 was considered statistically significant. To further address potential confounding, we applied overlap weighting (OW). All the statistical analyses were conducted using R software (version 4.4.2) or SPSS (version 23.0) for Windows.

3. Results

3.1. Patient characteristics

This study initially identified 159 uHCC patients with PVTT. After applying the predefined inclusion/exclusion criteria (Figure 1), 36 patients were excluded, yielding a final cohort of 123 patients: 103 who received TT and 20 who received TTR. The baseline characteristics were well balanced between the groups (Table 1). The predominant etiology among the HCC patients was hepatitis B virus (HBV) infection (91.9%). The mean tumor diameter was 8.42 cm. The extent of PVTT was as follows: VP2, 7 (5.7%) patients; VP3, 72 (58.5%) patients and VP4, 44 (35.8%) patients. A total of 94.3% of the patients suffered from VP3 or VP4 PVTT. After applying OW, the TT and TTR groups each had a weighted effective sample size (ESS) of 15.38, and their baseline clinical characteristics were well balanced (Table 1).

The median total prescribed dose in the TTR group was 40 Gy (range: 24-50 Gy), delivered in a median of 5 fractions (range: 3-25). The BED_{10} ranged from 59.5- 85.5Gy. As listed in Supplemental Table S1 (*https://www.biosciencetrends.com/action/getSupplementalData.php?ID=266*), lenvatinib was the predominant TKI in both cohorts (TT: 85.4%; TTR: 85.0%). Similarly, camrelizumab was the most frequently administered ICI in the two groups (TT: 81.6%; TTR: 75.0%)

3.2. Comparison of the tumor response between the two groups

As shown in Supplemental Figure S1 (*https://www.biosciencetrends.com/action/getSupplementalData.php?ID=266*), according to mRECIST, the TT group exhibited a complete response (CR) in 13 patients (12.6%), a partial response (PR) in 35 patients (34.0%), stable disease (SD) in 29 patients (28.2%), and progressive disease (PD) in 26 patients (25.2%). In contrast, the TTR group demonstrated CR in 4 patients (20.0%), PR in 10 patients (50.0%), SD in 4 patients (20.0%), and PD in 2 patients (10.0%). Compared

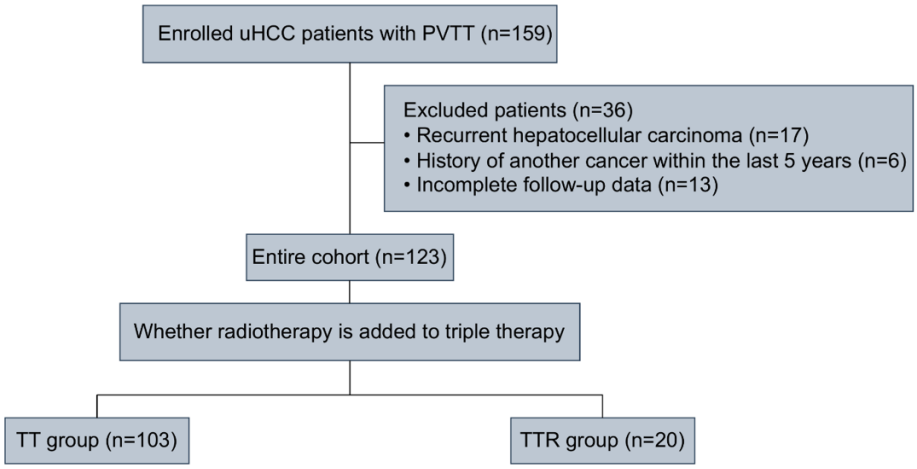

Figure 1. Flowchart of this study.

Table 1. Comparison of the baseline characteristics between the TT group and the TTR group

Variables	Primary cohort			OW cohort		
	TT group	TTR group	SMD	TT group	TTR group	SMD
n	103	20		15.38	15.38	
Age (years)	52.2 ± 10.8	49.7 ± 12.2	0.215	50.8 ± 11.1	50.8 ± 11.6	< 0.001
Gender			0.181			< 0.001
Female	10 (9.7%)	1 (5.0%)		0.9 (6.1%)	0.9 (6.1%)	
Male	93 (90.3%)	19 (95.0%)		14.4 (93.9%)	14.4 (93.9%)	
Platelet ($\times 10^9$/L)	172 ± 88.2	174 ± 84.8	0.033	176.7 ± 91.8	176.7 ± 86.3	< 0.001
ALBI, *n* (%)			0.019			< 0.001
Grade 1	66 (64.1%)	13 (65.0%)		10.1 (65.6%)	10.1 (65.6%)	
Grade 2	37 (35.9%)	7 (35.0%)		5.3 (34.4%)	5.3 (34.4%)	
History of hepatitis			0.007			< 0.001
HBV-related	94 (91.3%)	19 (95.0%)		14.7 (95.4%)	14.7 (95.4%)	
Non-HBV	1 (1.0%)	1 (5.0%)		0.7 (4.6%)	0.7 (4.6%)	
AFP (ng/mL)			0.099			< 0.001
≥ 400	62 (60.2%)	13 (65.0%)		9.9 (64.5%)	9.9 (64.5%)	
< 400	41 (39.8%)	7 (35.0%)		5.5 (35.5%)	5.5 (35.5%)	
Tumor number			0.206			< 0.001
Multiple	62 (60.2%)	10 (50.0%)		8.1 (52.7%)	8.1 (52.7%)	
Single	41 (39.8%)	10 (50.0%)		7.3 (47.3%)	7.3 (47.3%)	
Tumor diameter (cm)			0.596			< 0.001
< 5	15 (14.6%)	8 (40.0%)		4.9 (31.7%)	4.9 (31.7%)	
≥ 5	88 (85.4%)	12 (60.0%)		10.5 (68.3%)	10.5 (68.3%)	
PVTT			0.106			< 0.001
vp2	6 (5.8%)	1 (5.0%)		7.1 (5.8%)	7.2 (5.8%)	
vp3	61 (59.2%)	11 (55.0%)		71.5 (58.3%)	70.2 (56.8%)	
vp4	36 (35.0%)	8 (40.0%)		43.9 (35.8%)	46.3 (37.4%)	

OW, overlap weighting; ECOG PS, Eastern Cooperative Oncology Group Performance Status; TBil, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; AFP, alpha fetoprotein; ALBI, albumin-bilirubin; HBV, hepatitis B virus; HCV, hepatitis C virus; up to seven, up to seven criteria.

Table 2. The best tumor responses in the TT group and TTR group

mRECIST 1.1	Primary cohort			OW cohort		
	TT group (*n* = 103)	TTR group (*n* = 20)	*p*	TT group (*n* = 15.38)	TTR group (*n* = 15.38)	*p*
Overall response						
CR, *n* (%)	13 (12.6%)	4 (20.0%)	0.382	1.90 (12.3%)	2.41 (15.7%)	0.693
PR, *n* (%)	35 (34.0%)	10 (50.0%)	0.173	5.00 (32.5%)	7.81 (50.8%)	0.154
SD, *n* (%)	29 (28.2%)	4 (20.0%)	0.451	4.64 (30.2%)	3.44 (22.4%)	0.489
PD, *n* (%)	26 (25.2%)	2 (10.0%)	0.137	3.84 (24.9%)	1.72 (11.2%)	0.127
ORR, n (%)	48 (46.6%)	14 (70.0%)	0.095	6.90 (44.8%)	10.22 (66.5%)	0.085
DCR, *n* (%)	77 (74.8%)	18 (90.0%)	0.241	11.54 (75.1%)	13.66 (88.8%)	0.126
PVTT						
CR, *n* (%)	34 (33.0%)	12 (60.0%)	**0.042**	5.05 (32.9%)	9.14 (59.4%)	**0.037**
Non-CR/Non-PD, *n* (%)	57 (55.3%)	7 (35.0%)	0.155	8.58 (55.8%)	5.40 (35.1%)	0.112
PD, *n* (%)	12 (11.7%)	1 (5.0%)	0.691	1.75 (11.4%)	0.84 (5.5%)	0.461
Early tumor shrinkage	61 (59.2%)	17 (85.0%)	**0.029**	9.74 (63.3%)	13.09 (85.1%)	**0.028**

OW, overlap weight; mRECIST, modified Response Evaluation Criteria in Solid Tumors; CR, Complete response; PR, Partial response; SD, Stable disease; PD, Progressive disease; ORR, objective response rate; DCR, disease control rate; PVTT, portal vein tumor thrombosis; TT, triple therapy; TTR, triple therapy with radiotherapy.

with the TT group, the TTR group demonstrated a numerically greater objective response rate (ORR; 70.0% *vs.* 46.6%; $p = 0.095$) and disease control rate (DCR; 90.0% *vs.* 74.8%; $p = 0.241$), although these differences did not reach statistical significance (Table 2). Notably, 85.0% of TTR patients achieved ETS, compared to 59.2% of TT patients ($p = 0.029$). In contrast, as shown in Table 2, the CR rate for PVTT was significantly improved in the TTR cohort (60.0% *vs.* 33.0%; $p = 0.042$). After applying OW, the CR rate of PVTT was 32.9% in TT group and 59.4% in TTR group ($p = 0.037$). Furthermore, 8 (22.2%) patients in the TT group and 3 (23.1%) patients in the TTR group achieved a pCR ($p = 1.000$). MPR was observed in 15 (41.7%) patients in the TT group and 7 (53.8%) patients in the TTR group ($p = 0.449$).

3.3. Factors independently associated with conversion resection

Thirteen (65.0%) patients in the TTR group and 36 (35.0%) patients in the TT group successfully underwent conversion resection. The conversion resection rate was significantly greater in the TTR cohort than in the TT cohort (p = 0.012). As presented in Table 3, multivariate analysis revealed that VP4 PVTT (OR = 3.278, 95% CI = 1.291-8.322, p = 0.012), ALBI grade 2 (OR = 2.831, 95% CI = 1.068-7.509, p = 0.037) and TTR (OR = 0.261, 95% CI = 0.081-0.838, p = 0.024) were independently associated with conversion resection rate. Among these factors, the TTR was a protective factor.

3.4. Safety of conversion resection

All of the patients underwent R0 resection. Among the 49 patients who successfully underwent liver resection following conversion therapy, severe postoperative complications were observed in 7 (19.4%) patients in the TT group and in 1 (7.7%) patient in the TTR group. Of these, 2 patients in the TT group experienced two or more postoperative complications simultaneously. The incidence of severe postoperative complications was comparable between the two groups (p = 0.663). Detailed information on these severe complications is provided in Supplemental Table S2 (*https://www.biosciencetrends.com/action/getSupplementalData.php?ID=266*).

3.5. Comparison of Survival Outcomes in the TTR and TT groups

The median follow-up duration was 35.3 months for the TT group and 32.9 months for the TTR group. During follow-up, 47 patients (45.6%) in the TT group and 4 patients (20.0%) in the TTR group died. The median OS (mOS) was 31.9 months (95% CI: 23.1-40.8) in the TT group, whereas it was not reached in the TTR group (p = 0.031). After applying OW, the mOS remained significantly longer in the TTR group (not reached) compared to the TT group (31.9 month; 95% CI: 25.9-not reached, p = 0.014). The 1-, 2-, 3-, and 4-year OS rates for patients in the TTR group were 94.7%, 89.5%, 82.0%, and 70.3%, respectively, whereas those for the TT group were 81.0%, 61.7%, 47.3%, and 41.1%, respectively (Figure 2A, p = 0.031). Disease progression occurred in 65 patients (63.1%) in the TT group and 9 patients (45.0%) in the TTR group. The median PFS (mPFS) was 35.5 months for the TTR group and 18.7 months for the TT group (p = 0.074). After applying OW, the mPFS was 35.5 months in the TTR group and 21.9 months in the TT group (p = 0.071). The 1-, 2-, 3-, and 4-year PFS rates for the TTR group were 85.0%, 63.8%, 45.3%, and 45.3%, respectively, whereas those for the TT group were 58.1%, 44.0%, 29.9%, and 29.9%, respectively (Figure 2B, p = 0.074).

We further compared the survival outcomes between patients who underwent successful conversion resection and those who did not across the two groups. Among patients who successfully underwent conversion resection, RFS and OS were similar between the TT and TTR groups (Supplemental Figure S2, p = 0.830; p = 0.670, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=266*). However, among patients who failed to undergo conversion resection, the OS was significantly better in the TTR group than in the TT group (Figure 3, p = 0.034).

We applied the Benjamini-Hochberg (BH) procedure for multiple comparison correction to these primary endpoints, minimizing the risk of false positives and ensuring the robustness of the data and validity of the results (Supplemental Table S3, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=266*).

Table 3. Univariate and multivariate analyses of factors associated with successful conversion resection

Variable	UV OR (95% CI)	*p*	MV OR (95% CI)	*p*
Age (≤ 60 *vs.* > 60 years)	0.779 (0.264-2.296)	0.651		
Gender (Male *vs.* Female)	0.507 (0.126-2.033)	0.338		
ALT (≤ 40 *vs.* > 40 U/L)	1.221 (0.452-3.302)	0.694		
AST (≤ 35 *vs.* > 35 U/L)	0.358 (0.071-1.818)	0.215		
HBeAg (Positive *vs.* Negative)	2.157 (0.750-6.204)	0.154		
AFP (≥ 400 *vs.* < 400 ng/mL)	0.910 (0.387-2.135)	0.828		
Tumor number (Single *vs.* Multiple)	0.925 (0.375-2.279)	0.865		
Tumor diameter (≥ 5 *vs.*< 5 cm)	1.900 (0.645-5.592)	0.244		
PVTT (Vp4 *vs.* Vp2/VP3)	2.780 (1.234-6.267)	**0.014**	3.278 (1.291-8.322)	**0.012**
ALBI grade (Grade 2 *vs.* Grade 1)	2.349 (1.059-5.213)	**0.036**	2.831 (1.068-7.509)	**0.037**
Thrombocytopenia (Yes *vs.* No)	1.136 (0.469-2.751)	**0.778**		
Treatment group (TTR group *vs.* TT group)	0.289 (0.106-0.790)	**0.015**	0.261 (0.081-0.838)	**0.024**

PVTT, portal vein tumor thrombosis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBeAg, hepatitis B virus e antigen; AFP, alpha fetoprotein; ALBI, albumin-bilirubin; TT, triple therapy; TTR, triple therapy with radiotherapy; UV, univariate; MV, multivariate; OR, odds ratio.

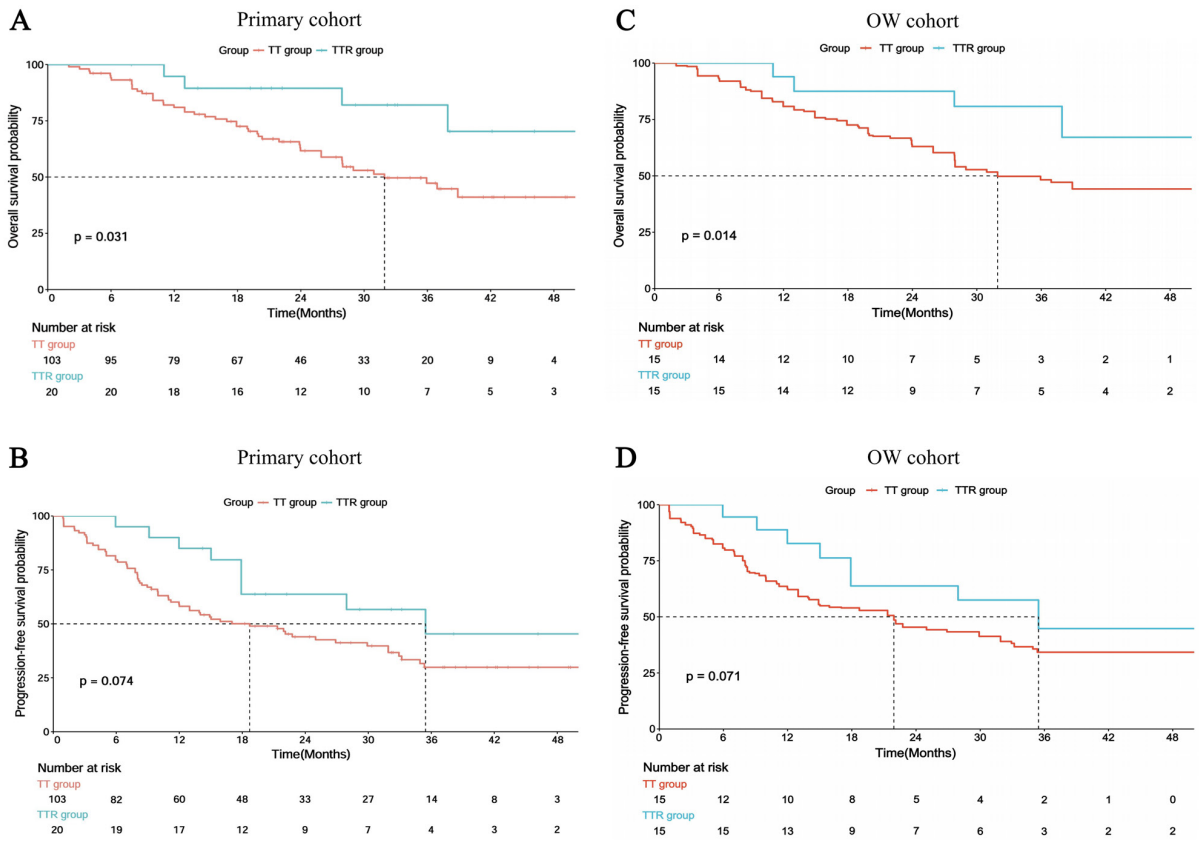

Figure 2. Overall survival and progression-free survival curves for the TT group and the TTR group.

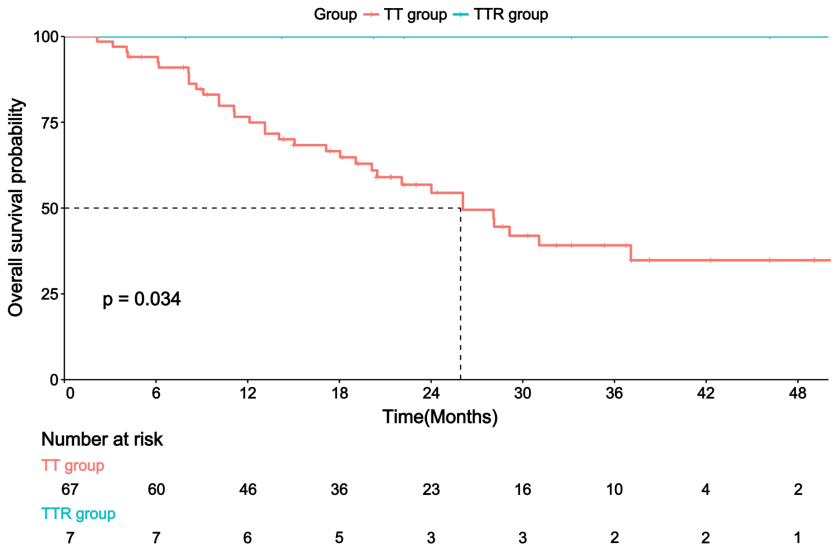

Figure 3. Overall survival curves for the TT group and the TTR group who failed to receive conversion resection.

3.6. Factors independently associated with OS and PFS

As shown in Table 4, univariate analysis suggested that male sex, thrombocytopenia, and treatment group had potential prognostic value in predicting OS. However, multivariate analysis confirmed that only thrombocytopenia (HR = 2.020, 95% CI = 1.035-3.940, $p = 0.039$) and TTR (HR = 0.354, 95% CI = 0.127-0.984, $p = 0.046$) were independently associated with OS. The TTR was identified as a protective factor for OS in this study.

Univariate analysis also revealed male sex, tumor diameter, and treatment group as potential prognostic factors for PFS (Supplemental Table S4, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=266*). However, multivariate analysis revealed

Table 4. Univariate and multivariate analyses of independent factors associated with overall survival

Variable	UV HR (95% CI)	*p*	MV HR (95% CI)	*p*
Age (≤ 60 *vs.* > 60 years)	0.972 (0.486-1.942)	0.935		
Gender (Male *vs.* Female)	0.481 (0.217-1.071)	0.073		
ALT (≤ 40 *vs.* > 40 U/L)	0.882 (0.496-1.568)	0.668		
AST (≤ 35 *vs.* > 35 U/L)	1.717 (0.721-4.087)	0.222		
HBeAg (Positive *vs.* Negative)	1.456 (0.684-3.098)	0.330		
AFP (≥ 400 *vs.* < 400 ng/mL)	1.010 (0.577-1.766)	0.972		
Tumor number (Single *vs.* Multiple)	1.190 (0.684-2.072)	0.538		
Tumor diameter (≥ 5 *vs.*< 5 cm)	1.555 (0.730-3.310)	0.252		
PVTT (Vp4 *vs.* Vp2/VP3)	0.669 (0.361-1.238)	0.200		
ALBI grade (Grade 2 *vs.* Grade 1)	1.288 (0.729-2.274)	0.383		
Thrombocytopenia (Yes *vs.* No)	2.027 (1.037-3.960)	**0.032**	2.020 (1.035-3.940)	**0.039**
Treatment group (TTR group *vs.* TT group)	0.342 (0.123-0.951)	**0.040**	0.354 (0.127-0.984)	**0.046**

PVTT, portal vein tumor thrombosis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBeAg, hepatitis B virus e antigen; AFP, alpha fetoprotein; ALBI, albumin-bilirubin; TT, triple therapy; TTR, triple therapy with radiotherapy; UV, univariate; MV, multivariate; HR, hazard ratio.

that only male sex was independently associated with poorer PFS (HR = 2.038, 95% CI = 1.000-4.138, p = 0.049).

3.7. Adverse reactions

As listed in Supplemental Table S5 (*https://www.biosciencetrends.com/action/getSupplementalData.php?ID=266*), among all 123 treated patients, the most common trAE was hypothyroidism, which was observed in 25 patients (20.3%), followed by thrombocytopenia in 24 patients (19.5%) and hand-foot skin reactions in 19 patients (15.4%). Overall, all trAEs were generally manageable in both cohorts, with no treatment-related deaths occurring.

4. Discussion

The prognosis of uHCC with PVTT remains dismal. The BRIDGE study reported an mOS of approximately 15 months for patients with BCLC stage C, whereas patients with untreated PVTT had an mOS of only 2.4-4.0 months (*22*). Tumor invasion of the portal venous system promotes aggressive intrahepatic spread and, once beyond the hepatic portal veins, induces hemodynamic instability *via* reduced portal perfusion (*23,24*), leading to rapid hepatic decompensation, portal hypertension, and associated complications that severely constrain treatment options (*25*). Most patients with PVTT are ineligible for resection at diagnosis; a national cohort study in Korea revealed that only 15.1% of these patients underwent liver resection at diagnosis (*26*). Numerous studies have suggested that the combination of TACE with ICIs and TKIs could achieve a better ORR than existing first-line systemic therapies (*27,28*). For example, Yang *et al*. demonstrated that patients with initial uHCC who received triple conversion therapy had a significantly higher rate of liver resection than did those receiving TACE alone (34.6% *vs.* 23.5%) (*27*). Additionally, Wu *et al*. reported that 54.5% of patients with uHCC could progress to resectable HCC after TT (*28*). Accordingly, the Chinese expert consensus recommended the use of TT for conversion therapy for patients with initial uHCC (*29*). Conversion therapy may offer a potential opportunity for radical liver resection and improved OS in these patients. Our study confirmed that TTR may result in a higher rate of successful conversion resection and longer OS than in patients with initial uHCC.

Systemic therapy is recommended for patients with HCC with BCLC stage C disease by both the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver (*3,30*). Recent advancements in systemic therapy have significantly improved outcomes for patients with advanced HCC (*3*). For example, the Imbrave-150 study demonstrated that the mOS for patients receiving atezolizumab plus bevacizumab was 19.2 months, which was significantly greater than that for patients treated with sorafenib (*31*). The ORR in the Imbrave-150 study, assessed by mRECIST, also increased to 35% (*31*). However, despite these advancements, both the OS and ORR for current first-line systemic therapies for patients with uHCC remain suboptimal. In the STAH trial, the median OS for patients receiving sorafenib plus TACE was 12.8 months, while the LAUNCH Phase III trial reported a median OS of 17.8 months with TACE plus Lenvatinib (*32,33*). Building on these findings, the OS in our TTR group has not yet been reached, suggesting that the combination of triple therapy with radiotherapy may offer more substantial survival benefits for patients with uHCC with PVTT.

PVTT is a well-established negative prognostic factor in conversion therapy for initial uHCC, independently limiting resection feasibility (*8,9*). Studies have consistently shown that therapies such as TACE, ICIs, and TKIs are less effective in patients

with PVTT than in those without (*34-36*). For example, Chuma *et al*. reported an ORR of 37.5% in patients with HCC with more than 50% liver occupation, compared with only 26.7% in those with VP4 PVTT (*36*). Additionally, Xiang *et al*. confirmed that TACE yielded a prognosis similar to that of best supportive care in HCC patients with VP4 PVTT (*34*). In clinical practice, PVTT growth velocity is notably rapid. Gon *et al*. indicated that the average growth rate of PVTT was as high as 0.9 mm/day (*10*). Therefore, conversion therapy for patients with uHCC with PVTT necessitates tailored treatment strategies specifically targeting the PVTT. However, previous studies on conversion therapy for these patients did not adequately address this issue. Studies have also demonstrated that, compared with systemic therapy alone, combining radiotherapy with systemic therapy improves both the ORR and OS in patients with PVTT (*12,37*). For example, Hu *et al.* (*12*) reported an ORR of 47.5% for patients with uHCC treated with camrelizumab-apatinib combined with radiotherapy, which was significantly greater than that for patients receiving camrelizumab-apatinib alone. In our study, we similarly reported that the conversion resection rate was significantly greater in the TTR group than in the TT group. These pronounced survival benefits likely result from the synergistic effects of radiotherapy, immune checkpoint inhibition, antiangiogenic therapy, and local interventions (*38-40*). As a local modality, radiotherapy not only induces lethal DNA damage in tumor cells but also triggers immunogenic cell death, which stimulates systemic antitumor immunity and enhances the infiltration of cytotoxic immune cells, thereby amplifying the effects of immunotherapy (*41-43*). Furthermore, antiangiogenic agents can enhance the efficacy of radiotherapy by normalizing the tumor vasculature and creating an immunologically favorable tumor microenvironment (*44,45*).

In this study, the ORR was greater in the TTR group (70.0%) than in the TT group (46.6%), although the difference was not statistically significant, likely due to the smaller TTR sample size. Interestingly, the conversion resection rate was significantly greater in the TTR group than in the TT group. Many patients in the TTR group exhibited meaningful tumor shrinkage, though these reductions did not meet the mRECIST criteria for PR or CR. Therefore, to better capture these effects, we refined the mRECIST standard by applying ETS and found that 59.2% of TT patients and 85.0% of TTR patients achieved ETS ($p = 0.029$). Furthermore, the evaluation of treatment efficacy indicated a higher CR rate for PVTT in the TTR group ($p = 0.042$), demonstrating the TTR regimen's capacity to elicit tumor responses. Furthermore, while OS was notably longer in the TTR group than in the TT group, the difference in PFS between the two groups was not statistically significant. Multivariate analysis indicated that conversion therapy did not independently contribute to PFS. A significant number of patients in both groups underwent conversion resection, and following liver resection, patients' PFS increased. Additionally, previous studies have highlighted that in advanced HCC, the correlation between PFS and OS may be weaker (*46*). While PFS primarily reflects tumor progression, OS captures a broader range of factors, including prolonged survival and delayed treatment effects. Notably, immunotherapy often induces delayed immune responses, which may not be immediately reflected in PFS but can significantly impact OS over time. This aligns with findings from other studies, such as the IMbrave-150 trial, where PFS improvements did not directly correlate with OS benefits; however, the combination of immune checkpoint inhibitors and targeted therapies led to substantial long-term survival gains. The delayed immune effects of TTR may account for the lack of significant short-term improvement in PFS. Radiotherapy induces immunogenic cell death, triggering systemic immune responses that enhance the effects of subsequent therapies. However, these effects may take months to fully manifest. While PFS reflects early tumor responses, it may not capture the long-term, cumulative benefits of treatment, which are more accurately represented by OS (*47*). Moreover, factors such as tumor biology, individual patient characteristics, and treatment regimens can influence PFS outcomes. These may explain the lack of a significant difference in PFS between the two groups.

Notably, the OS was significantly longer in the entire TTR group than in the TT group, particularly in patients who failed to undergo conversion resection. Previous studies have indicated that the OS of patients with uHCC with PVTT is extremely poor, especially those with VP3-4 PVTT (*48*). Some studies have even suggested that the mOS of these patients without any treatment is only 2.7 months. In the present study, however, the OS was notably greater than that reported in previous studies (*49*). These findings suggest that TTR may serve as a viable treatment option, even for patients who are not eligible for liver resection, as it may still lead to a favorable prognosis. However, given the small sample size of the TTR group, further studies are needed to confirm these results.

This study had several limitations. First, this was a single-center study with a small sample size in the TTR group. Second, as with many previous studies, we were unable to standardize the use of ICIs and TKIs in our clinical practice (*50*). This variation was due to differences in the drugs covered by medical insurance in different regions of China.

In conclusion, our results demonstrate that the addition of RT to TT significantly enhances both the conversion resection rate and OS in patients with uHCC patients with PVTT compared with TT alone. This combined modality approach offers a safe and effective therapeutic strategy for managing these patients.

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