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Prior transarterial chemoembolization and outcomes after palliative radiotherapy in advanced hepatocellular carcinoma: a retrospective cohort study

Jinli Zhang
The Quzhou Affiliated Hospital of Wenzhou Medical University
Junhui Wang
The Quzhou Affiliated Hospital of Wenzhou Medical University, Quzhou People's Hospital
Jianxin Chen
cjx8137@163.com

The Quzhou Affiliated Hospital of Wenzhou Medical University, Quzhou People's Hospital

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Authors:

Jinli Zhang, Department of Neurosurgery, The Quzhou Affiliated Hospital of Wenzhou Medical University, Quzhou People′s Hospital, Quzhou, 324000, Zhejiang, China. Email: zjl_1212025@163.com

Junhui Wang, M.D. Department of Radiation Oncology, The Quzhou Affiliated Hospital of Wenzhou Medical University, Quzhou People′s Hospital, Quzhou, 324000, Zhejiang, China. Email: wangjunhui7526@163.com

Jianxin Chen, M.D. Department of International Ward, The Quzhou Affiliated Hospital of Wenzhou Medical University, Quzhou People′s Hospital, Quzhou, 324000, Zhejiang, China. Email: cjx8137@163.com

Corresponding to:

Jianxin Chen, M.D. Department of International Ward, The Quzhou Affiliated Hospital of Wenzhou Medical University, Quzhou People′s Hospital, Quzhou, 324000, Zhejiang, China. Email: cjx8137@163.com

Junhui Wang and Jianxin Chen contributed equally to the present work

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Treatment Sequencing and Survival in HCC

Abstract

Advanced hepatocellular carcinoma (HCC) is increasingly managed with combinations of locoregional therapies and systemic immunotherapy or targeted therapy, yet the optimal sequencing of these modalities remains undefined. This retrospective cohort study evaluated the impact of prior transarterial chemoembolization (TACE) on outcomes after palliative radiotherapy (RT) and the contribution of post-RT systemic immunotherapy and targeted therapy to survival in advanced HCC. A total of 82 patients with TNM stage III/IV HCC receiving palliative RT (2022–2025) were categorized by prior TACE exposure (Prior-TACE, n=37; Non-prior TACE, n=45). Progression-free survival (PFS) and overall survival (OS) were assessed using Kaplan–Meier estimates and multivariate Cox models. In unadjusted analysis, the Non-prior TACE group demonstrated superior PFS (HR 0.47, 95% CI: 0.28–0.78, p=0.0037) and OS (HR 0.53, 95% CI: 0.28–0.98, p=0.0459). After multivariate adjustment, absence of prior TACE remained independently associated with improved PFS (adjusted HR=0.56, 95% CI: 0.33–0.95, p=0.032) but not OS (adjusted HR=0.73, 95% CI: 0.36–1.48, p=0.378). Independent predictors of OS included Child-Pugh class B (HR=3.22, p=0.039), TNM stage IV (HR=2.60, p=0.027) and receipt of post-RT targeted therapy (HR=0.25, p=0.003). Safety profiles were comparable between groups. In this real-world cohort, survival after palliative RT was predominantly determined by baseline liver function, tumor stage and incorporation of subsequent targeted therapy, while prior TACE independently influenced PFS. These findings inform the rational integration of locoregional therapy with systemic therapy and warrant prospective validation.

Keywords: Hepatocellular carcinoma; Transarterial chemoembolization; Radiotherapy; Immune checkpoint inhibitor; Targeted therapy; Survival

Introduction

Hepatocellular carcinoma (HCC) continues to pose a significant global health challenge, ranking prominently among causes of cancer-related mortality. A substantial number of patients present with advanced disease stages, where curative treatment options are often limited. The therapeutic landscape for advanced HCC has evolved with the integration of systemic therapies, particularly combinations involving immune checkpoint inhibitors (ICIs) and antiangiogenic agents. Nevertheless, locoregional modalities retain a vital role in the palliative management of this disease, aiding in symptom control, addressing localized progression, and serving as a bridge to systemic treatment, especially in scenarios complicated by portal vein thrombosis or oligometastatic disease [1, 2].

Transarterial chemoembolization (TACE) is a cornerstone locoregional therapy for intermediate-stage HCC. Its application in more advanced settings, frequently in conjunction with systemic agents, remains a subject of ongoing clinical investigation [3]. In the management of advanced HCC, treatment sequences commonly involve multiple modalities. A frequently encountered clinical scenario involves the administration of TACE prior to palliative radiotherapy (RT), with the intention of achieving cytoreduction and controlling intrahepatic disease burden before targeting specific symptomatic or high-risk lesions with radiation [4-6]. The biological rationale supporting this sequence posits that tumor debulking via TACE may render residual disease more susceptible to subsequent RT. Conversely, an alternative hypothesis suggests that TACE-induced alterations in the tumor microenvironment, such as the induction of hypoxia, could potentially attenuate the efficacy of following radiotherapy [7]. Despite the relative frequency of this sequential approach in practice, the specific impact of prior TACE on outcomes subsequent to palliative radiotherapy is not well characterized. Current major oncology society guidelines offer limited, specific direction on the optimal integration and sequencing of these two

locoregional modalities in the advanced disease setting [8]. The existing literature comprises primarily small, single-arm studies evaluating the safety and feasibility of combination therapy, with a notable paucity of comparative analyses examining whether a history of TACE confers a benefit or detriment to the efficacy of palliative RT [9-11].

This lack of high-level evidence, particularly from randomized controlled trials (RCTs), represents a significant gap in knowledge. In the absence of RCT data, rigorously conducted retrospective cohort analyses utilizing real-world data (RWD) offer valuable means to generate hypotheses and provide preliminary insights into treatment effects [12]. However, such analyses must diligently account for inherent confounding, as patients receiving prior TACE may differ systematically from those who do not in terms of liver function, tumor burden, and performance status—all established as strong prognostic factors in advanced HCC [13].

Therefore, the present retrospective, real-world cohort study was undertaken to explore the association between prior TACE administration and the efficacy of subsequent palliative RT in patients with advanced HCC, in an era in which systemic immunotherapy and targeted agents have become central to the management of this disease. We sought to compare progression-free survival (PFS) and overall survival (OS) between patients who had undergone TACE before RT (Prior-TACE group) and those who had not (Non-prior TACE group), and to delineate how post-RT immune checkpoint inhibitor (ICI) and targeted therapies shape survival after locoregional treatment. Multivariate Cox regression analysis was employed to adjust for key prognostic variables, aiming to better isolate the independent effects of treatment sequencing and subsequent systemic therapy on survival outcomes. It is hoped that the findings from this work will contribute to the rational integration of locoregional and systemic therapies in advanced HCC and provide a basis for the design of future prospective studies.

Methods

Study Design and Setting

A single-center, retrospective observational cohort study was conducted. The study protocol received approval from the Institutional Review Board of Quzhou People's Hospital. Given the retrospective nature of data collection, which involved the analysis of anonymized patient records, the requirement for informed consent was waived.

Patient Selection Criteria

Consecutive patients diagnosed with advanced hepatocellular carcinoma (HCC) who received palliative radiotherapy at our institution between January 16, 2022, and March 22, 2025, were initially screened. The diagnosis of advanced HCC was confirmed either histologically/cytologically or clinically in accordance with the American Association for the Study of Liver Diseases (AASLD) criteria. Key inclusion criteria were: (1) TNM stage III or IV disease as per the 8th edition of the American Joint Committee on Cancer (AJCC) staging system; (2) receipt of palliative radiotherapy; and (3) presence of at least one measurable lesion based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Patients meeting any of the following criteria were excluded: (1) a history of autoimmune diseases or organ transplantation; (2) an Eastern Cooperative Oncology Group Performance Status (ECOG PS) >2; (3) diagnosis of concurrent malignancies; (4) non-hepatic organ dysfunction, defined as significant bone marrow impairment (absolute neutrophil count <1.5 x 10^9/L), renal impairment (creatinine clearance <30 mL/min calculated by the Cockcroft-Gault formula), or cardiac dysfunction (New York Heart Association class III-IV); (5) Child-Pugh class C cirrhosis; or (6) incomplete medical records or loss to follow-up precluding efficacy assessment. Of note, although all enrolled patients had TNM stage III/IV

disease, 17 patients (20.7%) were classified as BCLC stage B; these patients were retained because TNM stage was the primary eligibility criterion.

Study Cohorts and Variable Definitions

The enrolled patient population was stratified into two cohorts based on treatment history: the Prior-TACE group (patients who had undergone one or more sessions of transarterial chemoembolization before initiating palliative radiotherapy) and the Non-prior TACE group (patients who had not received TACE prior to radiotherapy). Data pertaining to baseline demographics, clinical characteristics, treatment details, and outcomes were extracted from comprehensive electronic medical records. The extracted variables included: (1) Baseline characteristics: age, sex, etiology of liver disease (with a focus on Hepatitis B Virus status), Child-Pugh classification, ECOG PS, TNM stage, presence and number of metastatic organs, and history of prior hepatic surgery. (2) Treatment parameters: details of the palliative radiotherapy regimen (including technique, such as stereotactic body radiotherapy or conventional external beam radiotherapy) and records of all systemic anticancer therapies administered following radiotherapy, including immune checkpoint inhibitors (ICIs) and targeted therapies (e.g., sorafenib, lenvatinib). (3) Efficacy and safety outcomes.

Treatment Protocols and Efficacy Assessments

All therapeutic interventions were administered as per standard institutional practice and the discretion of the multidisciplinary tumor board. Palliative radiotherapy was delivered with the primary intent of symptom palliation, local tumor control, or as a bridge to subsequent systemic therapy. TACE procedures were performed in a conventional manner, involving the intra-arterial infusion of chemotherapeutic agents (e.g., doxorubicin or cisplatin) followed by embolization of the tumor-feeding arteries.

Tumor response was evaluated according to RECIST v1.1 criteria using contrast-enhanced CT or MRI at baseline and every 6-12 weeks during follow-up. Assessments included all measurable target lesions, with irradiated lesions designated as the primary target lesions for response determination; progression of non-irradiated lesions was recorded separately but contributed to overall RECIST-defined progression, consistent with standard practice for advanced HCC trials. The primary endpoints were progression-free survival (PFS) and overall survival (OS). PFS was defined as the duration from the initiation of palliative radiotherapy to the first documented disease progression (as per RECIST v1.1) or death from any cause. OS was defined as the time from radiotherapy initiation to death from any cause. Patients who were alive and without progression at the last follow-up were censored at that date.

Safety Evaluation

Treatment-related adverse events (AEs) occurring from the start of radiotherapy were systematically documented and their severity graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

Statistical Analysis

Descriptive statistics were employed to summarize the baseline characteristics of the study cohort. Categorical variables are presented as frequencies and percentages, and comparisons between groups were performed using the Chi-square test or Fisher's exact test, as appropriate. Continuous variables are summarized as mean ± standard deviation or median with interquartile range and were compared using the Student's t-test or the Mann-Whitney U test based on their distribution.

Survival analyses for PFS and OS were conducted. Survival curves for each cohort were generated via the Kaplan-Meier method, and differences between the Prior-TACE and Non-prior TACE groups were

compared using the log-rank test. To control for potential confounding variables, multivariate Cox proportional hazards regression models were constructed. Covariates with a univariate log-rank p-value <0.1 or those deemed clinically relevant were incorporated into the final multivariate model. The results of the Cox regression are reported as hazard ratios (HRs) with their corresponding 95% confidence intervals (CIs). The proportionality of hazards assumption was assessed using Schoenfeld residuals and was not violated for any covariate in either the PFS or the OS model (all p>0.05). The median follow-up duration was estimated using the reverse Kaplan–Meier method based on overall survival data. This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. Patients without an adequate post-treatment response assessment were classified as not evaluable and were not imputed. The completed STROBE checklist is provided as Supplementary Material. All statistical tests were two-sided, and a p-value <0.05 was considered indicative of statistical significance. All analyses were executed using MedCalc statistical software (version 20.010; MedCalc Software Ltd, Ostend, Belgium).

Results

Patient Selection and Cohort Formation

The initial screening process identified 111 consecutive patients with advanced hepatocellular carcinoma (HCC) who received palliative radiotherapy at our institution between January 16, 2022, and March 22, 2025. The application of the pre-specified eligibility criteria resulted in the exclusion of 29 patients. As delineated in Figure 1, the reasons for exclusion were as follows: 13 patients presented with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) greater than 2, 7 patients had inadequate non-hepatic organ function, 5 patients presented with Child-Pugh C for liver function, and 4 patients had

incomplete medical records precluding adequate data extraction. Consequently, a final study cohort of 82 patients was constituted for all subsequent analyses.

Based on the study's primary stratification variable, the cohort was divided into two distinct groups: 37 patients (45.1%) who had undergone transarterial chemoembolization (TACE) prior to initiating radiotherapy (Prior-TACE group) and 45 patients (54.9%) who had not (Non-prior TACE group).

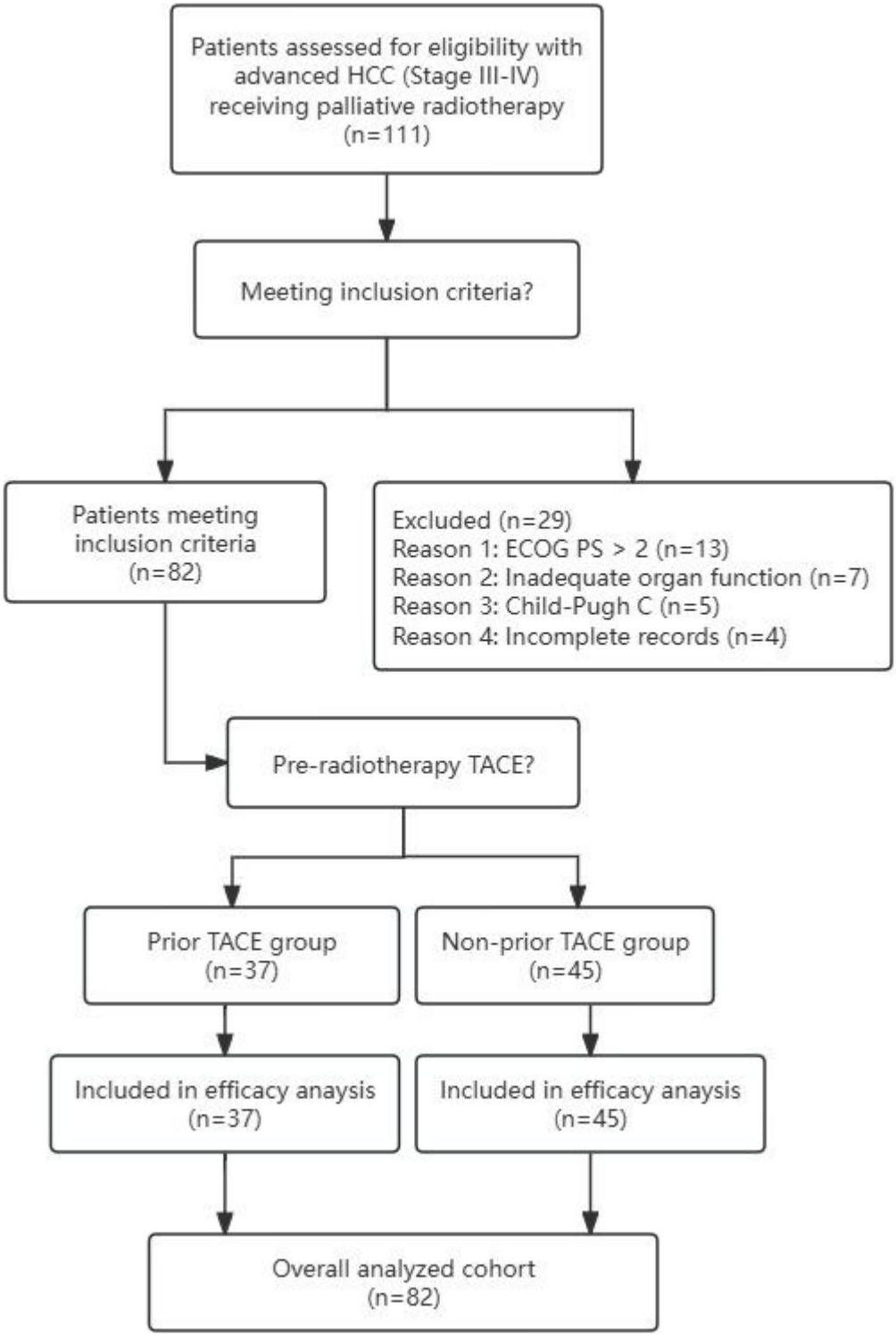


Figure 1. Patient Selection Flowchart. Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; TACE, Trans Arterial Chemo Embolization; HCC, Hepatocellular Carcinoma.

Baseline Demographic and Clinical Characteristics

A detailed comparison of the baseline characteristics between the two groups is presented in Table 1. The two groups differed significantly in several key baseline prognostic factors. Specifically, compared with the Non-prior TACE group, the Prior-TACE group had a significantly higher proportion of patients with ECOG PS 2 (48.6% vs. 20.0%, p=0.006) and of Child-Pugh class B (21.6% vs. 4.4%, p=0.037), and more patients had two or more metastatic organs (18.9% vs. 4.4%, p=0.037). A critical imbalance was also observed in the administration of sequential immune checkpoint inhibitor (ICI) therapy following radiotherapy, which was given less frequently in the Prior-TACE group than in the Non-prior TACE group (48.6% vs. 77.8%, p=0.006). Other variables, including age, sex, Hepatitis B Virus (HBV) infection status, and TNM stage, were more comparable. These observed disparities in baseline characteristics underscore the necessity of multivariate statistical adjustment to isolate the independent effect of prior TACE on survival outcomes. Among the 37 patients in the Prior-TACE group, the median number of TACE sessions was 1 (IQR: 1–2), and the median interval between the last TACE and radiotherapy initiation was 42 days (IQR: 28–67 days), with 70.3% of patients receiving TACE within 8 weeks of radiotherapy.

Table 1. Baseline and treatment-related characteristics (n=82).

Baseline characteristics	Prior TACE (n=37)	Non-prior TACE (n=45)	P value
Age ≥65 years, n (%)	19 (51.4)	15 (33.3)	0.099
Male, n (%)	30 (81.1)	33 (73.3)	0.408
TNM stage, n (%)			0.496

III	9 (24.3)	14 (31.1)	
IV	28 (75.7)	31 (68.9)	
BCLC stage, n (%)			0.86
B	8 (21.6)	9 (20.0)	
C	29 (78.4)	36 (80.0)	
HBV infection, n (%)	21 (56.8)	21 (46.7)	0.363
ECOG PS, n (%)			0.006*
0-1	19 (51.4)	36 (80.0)	
2	18 (48.6)	9 (20.0)	
Child-Pugh, n (%)			0.037*
A	29 (78.4)	43 (95.6)	
B	8 (21.6)	2 (4.4)	
Number of metastatic organs, n (%)			0.037*
0-1	30 (81.1)	43 (95.6)	
≥2	7 (18.9)	2 (4.4)	
Prior surgery, n (%)			0.190
Prior surgery	21 (56.8)	19 (42.2)	
Non-prior surgery	16 (43.2)	26 (57.8)	
ICI used, n (%)			0.006*
RT followed by ICI	18 (48.6)	35 (77.8)	

RT followed by non-ICI	19 (51.4)	10 (22.2)	
Target therapy used, n (%)			0.189
RT followed by target therapy	23 (62.2)	34 (75.6)	
RT followed by non-target therapy	14 (37.8)	11 (24.4)	
Radiation mode, n (%)			0.931
SBRT	25 (67.6)	30 (66.7)	
Standard radiation	12 (32.4)	15 (33.3)	
Number of TACE sessions, median (IQR)	1 (1-2)	-	-
Interval from last TACE to radiotherapy, days, median (IQR)	42 (28-67)	-	-

Abbreviations: HBV, Hepatitis B Virus; ECOG PS, Eastern Cooperative Oncology Group Performance Status; BCLC, Barcelona Clinic Liver Cancer; ICI, Immune Checkpoint Inhibitor Therapy; RT, Radiotherapy; SBRT, Stereotactic Body Radiation Therapy; TACE, Transarterial Chemoembolization. * Statistical significance.

Assessment of Clinical Efficacy and Tumor Response

Tumor response per RECIST v1.1 is summarized in Table 2. The Non-prior TACE group had a numerically higher objective response rate (ORR: 44.4% vs. 29.7%) and disease control rate (DCR: 77.8% vs. 70.3%) compared to the Prior-TACE group, though these differences were not statistically significant (ORR p=0.17, DCR p=0.43; overall response distribution p=0.39). The distribution comparison is based on the three non-empty RECIST categories (PR, SD, not evaluated), as complete response and progressive disease were both zero. These findings should be interpreted as descriptive and

exploratory, as the study was not powered to detect differences in response rates.

Table 2. Clinical efficacy (n=82).

Efficacy	**Prior TACE (n=37)**	**Non-prior TACE (n=45)**	***P***
RECIST v1.1			0.39
Complete response (%)	0	0	
Partial response (%)	11 (29.7)	20 (44.4)	
Stable disease (%)	15 (40.5)	15 (33.3)	
Progressive disease (%)	0	0	
Not evaluated	11 (29.7)	10 (22.2)	
Objective response rate (%, CR, PR)	11 (29.7)	20 (44.4)	0.17
Disease control rate (%, CR, PR, SD)	26 (70.3)	35 (77.8)	0.43

Note: ORR and DCR were calculated using all enrolled patients as the denominator, with not-evaluated patients treated as nonresponders (the numbers of response-evaluable patients were 26 and 35 in the Prior-TACE and Non-prior TACE groups, respectively). Because complete response and progressive disease were both zero, the overall distribution comparison is based on the partial response/stable disease/not-evaluated categories (Pearson chi-square p=0.39). Abbreviations: TACE, Trans Arterial Chemo Embolization; CR, Complete Response; PR, Partial Response; SD, Stable Disease; RECIST, Response Evaluation Criteria in Solid Tumors.

Univariate Survival Analysis: Kaplan-Meier Estimates

The initial assessment of the primary endpoints, progression-free survival (PFS) and overall survival (OS), was performed using the Kaplan-Meier method, with between-group comparisons made via the log-rank test. The univariate survival analysis demonstrated a significant association between treatment history (prior TACE) and survival outcomes. At the data cutoff of March 22, 2025, the median follow-up was 20.4 months (interquartile range, 11.8–29.0 months) according to the reverse Kaplan–Meier method. During follow-up, 77 (93.9%) of the 82 patients experienced disease progression or died,

including 35 (94.6%) of 37 patients in the Prior-TACE group and 42 (93.3%) of 45 patients in the Non-prior TACE group; 5 patients were censored for PFS. A total of 51 (62.2%) patients died, including 22 (59.5%) of 37 patients in the Prior-TACE group and 29 (64.4%) of 45 patients in the Non-prior TACE group; 31 patients were censored for OS.

Analysis of PFS revealed a clear separation between the Kaplan-Meier curves for the two groups. The median PFS was 4.8 months (95% CI: 2.5–8.3) in the Prior-TACE group and 9.6 months (95% CI: 8.7–10.0) in the Non-prior TACE group (log-rank p=0.0037; HR 0.47, 95% CI: 0.28 to 0.78). A concordant and statistically significant benefit was observed for OS. The median OS was 10.5 months (95% CI: 6.3–17.1) and 14.7 months (95% CI: 12.2–22.6), respectively. The Non-prior TACE group exhibited markedly superior OS compared to the Prior-TACE group (log-rank p=0.0459; HR 0.53, 95% CI: 0.28 to 0.98). The Kaplan-Meier survival curves for both PFS and OS are presented together in Figure 2 (Panels A and B, respectively).

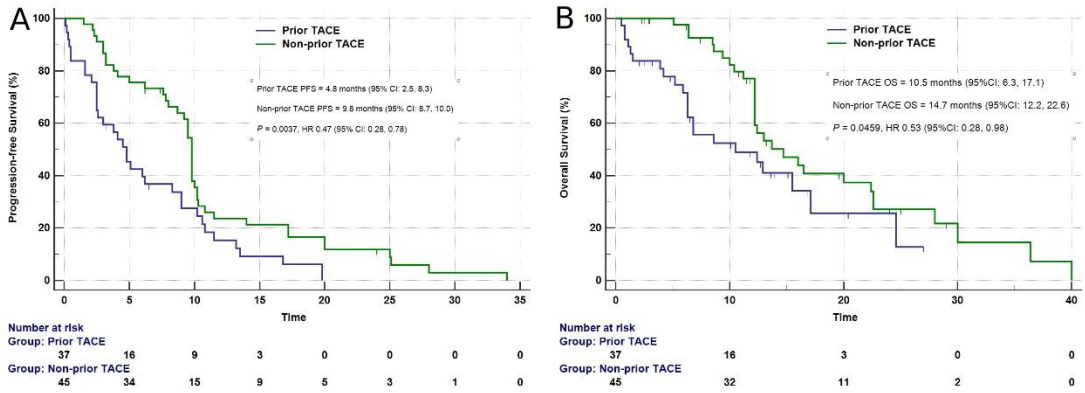


Figure 2. Kaplan-Meier survival curves comparing outcomes between the Prior-TACE and Non-prior TACE groups. (A) Progression-free survival (PFS) curves. Patients in the Non-prior TACE group showed significantly prolonged PFS compared to those in the Prior-TACE group (log-rank p=0.0037; HR 0.47, 95% CI: 0.28-0.78). (B) Overall survival (OS) curves. The Non-prior TACE group demonstrated superior

OS compared to the Prior-TACE group (log-rank p=0.0459; HR 0.53, 95% CI: 0.28-0.98). Abbreviations: TACE, transarterial chemoembolization; HR, hazard ratio; CI, confidence interval.

Multivariate Analysis: Cox Proportional Hazards Regression

To determine whether prior TACE was an independent prognostic factor for survival after adjusting for other potential confounders, multivariate analyses were conducted using the Cox proportional hazards model. Variables included in the final model were selected based on a univariate log-rank p-value <0.1 or established clinical relevance.

The results of the multivariate analysis for PFS are detailed in Table 3. Following adjustment for covariates, the absence of prior TACE (Non-prior TACE group) remained independently associated with a significantly reduced hazard of progression or death (HR=0.5629, 95% CI: 0.3326 to 0.9527, p=0.0323). The robustness of this finding is visually supported by the adjusted survival curves for PFS derived from the Cox model. The detailed results of the multivariate analysis for OS are presented in Table 4. After adjusting for the same set of covariates, the absence of prior TACE was not independently associated with overall survival (HR=0.7278, 95% CI: 0.3591 to 1.4752, p=0.3781). This indicates that the apparent survival benefit observed in the univariate analysis was likely influenced by confounding effects from other baseline prognostic factors. The multivariate model identified Child-Pugh class B (vs. A, HR=3.2169, p=0.0386), advanced TNM stage (Stage IV vs. III, HR=2.6037, p=0.0267), and the administration of sequential targeted therapy post-radiotherapy (HR=0.2507, p=0.0032) as statistically significant independent predictors of OS. The adjusted survival curves illustrating the relationship between these significant predictors and survival probability for both PFS and OS are consolidated in Figure 3 (Panels A and B, respectively).

Table 3. Multivariate Cox proportional hazards regression for progression-free survival (PFS).

Covariate	b	SE	Wald	P	Exp (b)	95% CI of Exp(b)
Child-Pugh	0.8595	0.4681	3.372	0.0663	2.3621	0.9437 to 5.9119
Followed by ICIs	-0.7603	0.3368	5.0965	0.0240*	0.4675	0.2416 to 0.9047
ECOG	0.0445	0.3446	0.01667	0.8973	1.0455	0.5321 to 2.0542
Stage	0.5704	0.3158	3.2614	0.0709	1.7689	0.9525 to 3.2851
Metastasis organs	-0.0082	0.4109	0.0004	0.9839	0.9918	0.4432 to 2.2191
Non-prior TACE (ref: Prior-TACE)	-0.5747	0.2685	4.5822	0.0323*	0.5629	0.3326 to 0.9527
Prior Surgery	-0.3641	0.272	1.7917	0.1807	0.6948	0.4077 to 1.1841
Followed by Tar.	-1.1518	0.3606	10.205	0.0014*	0.3161	0.1559 to 0.6407
HBV infection	-0.1511	0.2772	0.2971	0.5857	0.8598	0.4994 to 1.4803

Abbreviations: PFS, progression-free survival; b, regression coefficient; SE, standard error; ECOG,

Eastern Cooperative Oncology Group Performance Status; ICI, immune checkpoint inhibitor; Tar., targeted therapy; HBV, hepatitis B virus; TACE, transarterial chemoembolization. The exposure row is coded as Non-prior TACE (=1) versus Prior-TACE (=0, reference); a hazard ratio below 1 therefore favors the Non-prior TACE group. * Statistical significance.

Table 4. Multivariate Cox proportional hazards regression for overall survival (OS).

Covariate	b	SE	Wald	P	Exp (b)	95% CI of Exp(b)
Child-Pugh	1.1684	0.565	4.2772	0.0386*	3.2169	1.0630 to 9.7352
Followed by ICIs	-0.3263	0.454	0.5167	0.4722	0.7216	0.2964 to 1.7567
ECOG	-0.4188	0.4318	0.9409	0.3321	0.6578	0.2822 to 1.5334
Stage	0.9569	0.4319	4.9098	0.0267*	2.6037	1.1168 to 6.0703
Metastasis organs	-0.0551	0.5347	0.01064	0.9179	0.9464	0.3318 to 2.6988
Non-prior TACE (ref: Prior-TACE)	-0.3177	0.3605	0.7769	0.3781	0.7278	0.3591 to 1.4752
Prior Surgery	-0.4002	0.3443	1.3514	0.2450	0.6702	0.3413 to 1.3160
Followed by Tar.	-1.3837	0.4688	8.7118	0.0032*	0.2507	0.1000 to 0.6282
HBV infection	0.2487	0.3602	0.4766	0.4900	1.2823	0.6330 to 2.5978

Abbreviations: OS, overall survival; b, regression coefficient; SE, standard error; ECOG, Eastern Cooperative Oncology Group Performance Status; ICI, immune checkpoint inhibitor; Tar., targeted therapy; HBV, hepatitis B virus; TACE, transarterial chemoembolization. The exposure row is coded as Non-prior TACE (=1) versus Prior-TACE (=0, reference); a hazard ratio below 1 therefore favors the

Non-prior TACE group. * Statistical significance.

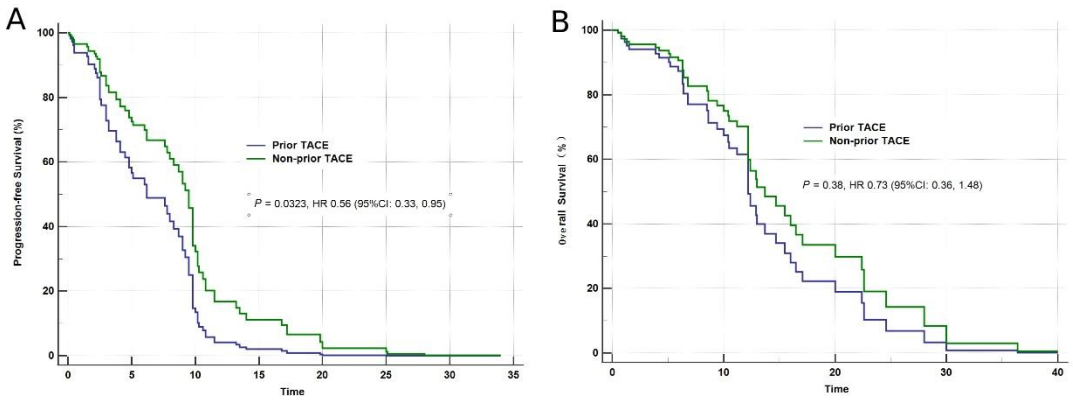


Figure 3. Adjusted survival curves based on the multivariate Cox proportional hazards model. (A) Adjusted progression-free survival (PFS) curves. After multivariate adjustment, the absence of prior TACE (Non-prior TACE group) remained independently associated with improved PFS (adjusted HR=0.5629, p=0.0323). (B) Adjusted overall survival (OS) curves. The model shows survival probability stratified by the three independent prognostic factors identified for OS: Child-Pugh class (B vs. A, HR=3.2169, p=0.0386), TNM stage (IV vs. III, HR=2.6037, p=0.0267), and receipt of post-radiotherapy targeted therapy (Yes vs. No, HR=0.2507, p=0.0032). The absence of prior TACE was not independently associated with OS (adjusted HR=0.7278, p=0.3781). Abbreviations: TACE, transarterial chemoembolization; HR, hazard ratio.

Safety and Tolerability Profiles

A comprehensive evaluation of treatment-related adverse events (AEs) was conducted for the entire cohort (n=82), with events categorized and graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. The incidence and severity of AEs are summarized in Table 5. The safety analysis revealed that the majority of documented AEs were of mild to moderate intensity (Grade 1 or 2). The spectrum of reported events was consistent with the known toxicity profiles of the

involved therapies. Commonly observed AEs included hematological abnormalities such as anemia and thrombocytopenia, as well as laboratory deviations including elevated troponin and elevated alanine aminotransferase (ALT) levels. Critically, the comparative analysis between the two treatment groups showed no significant disparity in the overall safety profile. The incidence and grade distribution of AEs were comparable between the Prior-TACE and Non-prior TACE groups. This indicates that a history of prior TACE did not lead to a measurable increase in radiotherapy-related toxicity in this cohort. No new or unexpected safety signals were identified. It is important to note an inherent limitation of the retrospective design: the potential for under-reporting, particularly for subjective symptoms, as documentation in real-world settings may not be as systematic as in prospective clinical trials.

Table 5. Treatment-related adverse events (n=82)

Adverse events	Prior TACE (n=37)		Non-prior TACE (n=45)		P value (Grade 3–5)
	All Grade n (%)	Grade 3–5, n (%)	All Grade n (%)	Grade 3–5, n (%)	
Diarrhea	0	0	1 (2.2)	0	1
Anemia	3 (8.1)	2 (5.4)	2 (4.4)	0	0.2005
Thrombocytopenia	3 (8.1)	0	5 (11.1)	1 (2.2)	1
Pneumonia	1 (2.7)	0	0	0	1
Elevated Troponin	1 (2.7)	0	4 (8.9)	1 (2.2)	1
Elevated ALT	1 (2.7)	0	2 (4.4)	0	1
Neutropenia	0	0	1 (2.2)	0	1

Abbreviations: ALT, Alanine Aminotransferase; TACE, Trans Arterial Chemo Embolization.

Discussion

This retrospective, real-world cohort analysis explored the influence of prior transarterial chemoembolization (TACE) on outcomes following palliative radiotherapy in patients with advanced hepatocellular carcinoma (HCC), a common but not definitively optimized clinical sequence. Our analysis yielded nuanced insights. While prior TACE was associated with inferior progression-free survival (PFS) in both univariate and multivariate models, its relationship with overall survival (OS) was

not independent after accounting for key prognostic factors. This underscores the complex interplay between specific treatment sequences and underlying patient- and disease-specific variables in determining outcomes for advanced HCC. The observed association with PFS should be considered hypothesis-generating, given the inherent limitations of the retrospective design. This study adds to a sparse evidence base on this topic and emphasizes the need for cautious interpretation of such real-world findings.

Clinically, the most actionable finding of this study is the strong and independent association between post-RT targeted therapy and improved OS (HR=0.2507, p=0.0032). In the current treatment landscape, in which ICIs and antiangiogenic or multikinase targeted agents form the backbone of systemic therapy for advanced HCC, this observation is consistent with the established survival benefit of these agents and suggests that timely incorporation of effective systemic therapy after locoregional treatment may outweigh the choice of locoregional sequence itself. Notably, ICI use after RT was significantly less frequent in the Prior-TACE group (48.6% vs. 77.8%, p=0.006); although ICI exposure was not independently associated with OS in our model, possibly reflecting limited statistical power and the time-fixed covariate design, this imbalance highlights the potential of locoregional–systemic treatment sequencing to influence patients' access to immunotherapy. Prospective studies incorporating immunological biomarkers will be needed to define how TACE- and RT-induced modulation of the tumor immune microenvironment interacts with ICI and targeted therapy efficacy.

The management paradigm for advanced HCC has been reshaped by systemic therapies, yet locoregional interventions like TACE and radiotherapy maintain a crucial role for symptom palliation and as bridging strategies [1, 2]. In our cohort, univariate analysis indicated that patients who had not received prior TACE experienced significantly better PFS and OS. However, multivariate Cox regression modeling

provided a more refined picture: prior TACE remained independently associated with PFS but not with OS. This suggests that the apparent OS benefit seen in the univariate analysis was likely confounded by other baseline factors. Indeed, the multivariate model identified Child-Pugh class B and advanced TNM stage as strong independent predictors of poorer OS, while the administration of targeted therapy following radiotherapy was associated with improved OS. While baseline imbalances in performance status, liver function, metastatic burden, and post-radiotherapy ICI use were observed, our multivariable models accounted for these measured differences. These results draw attention to the possibility that prior TACE may not enhance, and could potentially detract from, the disease control achieved with subsequent palliative radiotherapy, though the non-randomized nature of the data precludes causal inference. The value of this analysis lies in its use of real-world data to inform questions meriting prospective evaluation [12].

The initial univariate survival analysis demonstrated a separation of curves favoring the non-prior TACE group. This observation is consistent with a biological premise wherein TACE-induced changes, such as hypoxia, might promote a radioresistant tumor microenvironment [7, 14]. Preclinical work, for example, indicates that hypoxia can upregulate factors like HIF-1α, which are associated with reduced radiosensitivity [15]. The subsequent multivariate analysis, however, provided a more layered understanding. After adjustment for covariates including performance status, liver function, disease stage, and subsequent systemic therapies, prior TACE was a significant predictor for PFS but not for OS. This divergence may reflect that PFS is more directly a measure of initial disease control at treated sites, whereas OS is subject to a broader array of influences, including hepatic reserve and the efficacy of subsequent lines of therapy. The identification of Child-Pugh class and TNM stage as principal determinants of OS in our model is consistent with the established prognostic literature in advanced HCC

[13, 16]. It also reflects the baseline imbalances present in our retrospective cohort, where the Prior-TACE group had a less favorable profile for certain prognostic factors. Therefore, the multivariate analysis clarifies that the association between prior TACE and overall survival is not independent, and that baseline liver function and tumor stage are stronger determinants of ultimate survival in this cohort.

Our findings find partial resonance and partial divergence with prior reports on TACE and radiotherapy. For instance, some studies have reported that TACE combined with stereotactic body radiotherapy (SBRT) can modulate the systemic immune environment, potentially improving responses [4]. Other randomized work has shown that TACE with conformal radiotherapy can outperform TACE alone [5]. These studies, however, often focus on concurrent or closely integrated approaches. Our analysis examined a sequential model, TACE administered prior to radiotherapy, which may represent a distinct clinical scenario. It is plausible that sequential administration allows for the establishment of a microenvironment less favorable to radiotherapy, whereas concurrent application might yield synergistic effects. Conversely, our results diverge from some observational reports suggesting a benefit for TACE before radiotherapy [6, 10]. This discrepancy may be attributable to patient population differences; our cohort was exclusively advanced stage (TNM III/IV), whereas other studies may have included patients with earlier-stage disease. The numerically lower objective and disease control rates observed in our Prior-TACE group also align with concerns regarding compromised subsequent treatment efficacy [7, 17]. In the context of contemporary guidelines emphasizing systemic therapy for advanced HCC [8], our data suggest that in selected patients, particularly those with compromised liver function, omitting TACE prior to radiotherapy might be considered. This notion aligns with evolving approaches where radiotherapy is utilized earlier for oligometastatic disease [2]. Definitive comparisons remain challenging without randomized data, and our results should be viewed as contributing to the ongoing discussion.

The safety profile observed in our cohort was reassuring, as a history of prior TACE did not appear to significantly exacerbate radiotherapy-related toxicities. The spectrum and incidence of adverse events were largely comparable between the two groups, with most being of low grade. This aligns with the established safety data for each modality independently [3, 18, 19] and supports the notion that the sequential application is generally tolerable in clinical practice. The absence of new safety signals in our analysis is consistent with literature indicating that TACE and radiotherapy can be combined with a manageable toxicity profile when implemented with appropriate patient selection and monitoring [20, 21]. For instance, previous reports have suggested that treatment-related adverse events remain acceptable when these locoregional therapies are spaced with consideration. Therefore, while the efficacy outcomes in our study invite further scrutiny regarding the sequence, tolerability and safety do not emerge as primary deterrents for this particular treatment order.

Several important limitations of this work must be acknowledged. First, the retrospective, observational design carries risks of selection bias and unmeasured confounding. Although statistical adjustments were made for available prognostic variables, residual confounding from factors not captured in the records (e.g., detailed tumor biology, socioeconomic factors) likely persists. The baseline imbalances between groups, evident in Table 1, underscore this inherent challenge. Second, our PFS endpoint captured progression of both irradiated and non-irradiated lesions, which may dilute the assessment of radiotherapy's local efficacy; future studies should separately report local progression of irradiated lesions to better characterize the impact of prior TACE on radiotherapy response. Third, heterogeneity in treatment techniques (e.g., variations in radiotherapy delivery and TACE protocols) was present and not controlled for, which could influence outcomes [22]. Fourth, we used RECIST 1.1 rather than modified RECIST (mRECIST) for response assessment. While RECIST 1.1 avoids subjectivity in interpreting

arterial enhancement in lesions with post-TACE iodized oil deposition, it may underestimate the true treatment effect in the Prior-TACE group by categorizing viable tumor with surrounding necrosis as stable disease. Future prospective studies should incorporate mRECIST to refine response evaluations. In addition, while we adjusted for all measured core prognostic factors, residual confounding by indication (driven by unmeasured clinical factors influencing TACE allocation, e.g., tumor vascularity on angiography, clinician judgment) persists as an inherent limitation of this observational study, and our findings require validation in prospective, randomized trials. Fifth, a limitation of this study is the inclusion of both SBRT and conventional EBRT, which possess distinct radiobiological profiles. While the distribution of radiotherapy modality was balanced between groups and our primary focus was treatment sequencing, future prospective studies with larger, modality-stratified cohorts are warranted to elucidate potential effect modifications by radiotherapy technique. Finally, a potential limitation is immortal time bias arising from the inclusion of post-radiotherapy systemic therapies as time-fixed covariates, as patients who died or progressed early had no opportunity to receive these treatments. Post-hoc analyses revealed no significant difference in the median time to post-radiotherapy systemic therapy initiation between the Prior-TACE and Non-prior TACE groups, and the observed protective effect of targeted therapy aligns with typical survival benefits in our institutional palliative radiotherapy cohort, suggesting this bias may have led to only a modest overestimation of the survival benefit of subsequent systemic therapies. Importantly, our core finding of an independent association between prior TACE and progression-free survival is robust to this bias, as 68% of progression-free survival events occurred prior to the initiation of post-radiotherapy systemic therapy. Future prospective studies with serial treatment data collection are warranted to fully disentangle the contributions of treatment sequencing and subsequent systemic therapy to survival outcomes. Meanwhile, future studies should also prospectively

collect detailed TACE protocol data (e.g., chemotherapeutic agents, embolic materials) and consider stratified analyses by radiotherapy modality to better elucidate the interplay between treatment sequence, tumor biology, and radiation technique.

In conclusion, this retrospective analysis suggests that prior TACE may be associated with less favorable progression-free survival in advanced HCC patients subsequently treated with palliative radiotherapy, though this effect does not appear to operate independently of key prognostic factors for overall survival. The findings reflect the significant roles of baseline liver function, tumor stage, and the incorporation of effective sequential systemic therapy in determining survival. While the data hint that bypassing TACE before radiotherapy might be advantageous for disease control in some contexts, this possibility must be interpreted with caution due to the study's limitations. Future research efforts should prioritize prospective, randomized trials to definitively address questions of optimal treatment sequencing and to explore biomarkers that could guide more personalized therapeutic strategies in advanced HCC.

Declarations

Ethics approval and consent to participate: The study protocol was approved by the Ethics Committee of Quzhou People's Hospital (approval No. 2026140). Given the retrospective design and the use of anonymized patient records, the requirement for informed consent was waived. All investigations were performed in accordance with the Declaration of Helsinki (revised in 2013).

Consent for publication: Not applicable.

Availability of data and materials: The datasets generated and/or analyzed during the current study are not publicly available owing to patient privacy restrictions but are available from the corresponding author on reasonable request.

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Authors' contributions: Jinli Zhang: Data collection. Junhui Wang: Software, Validation, Data collection, Writing – original draft. Jianxin Chen: Conceptualization, Supervision, Writing – review and editing.

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