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Original Article

Transarterial chemoembolization combined with PD-1 inhibitors for unresectable hepatocellular carcinoma: efficacy and hepatic safety at 4-week versus 6-week treatment intervals

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Abstract: Objective: To compare the effect of 4-week and 6-week transarterial chemoembolization (TACE) intervals on tumor response and liver function in patients with unresectable hepatocellular carcinoma (HCC) receiving TACE plus programmed death-1 (PD-1) inhibitor combination therapy. Methods: A total of 186 patients with unresectable HCC who underwent TACE combined with PD-1 inhibitor therapy were enrolled in this retrospective study. All patients were categorized into two groups according to TACE treatment intervals: the 4-week interval group (n=92) and the 6-week interval group (n=94). Baseline demographic and clinical data were collected for all participants. Hepatic and renal function indicators, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), albumin (ALB), creatinine (Cr), and blood urea nitrogen (BUN), as well as serum tumor markers consisting of alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9) and carbohydrate antigen 125 (CA125), were detected at baseline and one month after treatment initiation. Tumor response was evaluated at three months post-treatment based on the RECIST 1.1, and the objective response rate (ORR) and disease control rate (DCR) were calculated accordingly. Treatment-related adverse events (AEs) were documented and graded in accordance with the CTCAE v5.0. Overall survival (OS) and progression-free survival (PFS) were calculated from the initiation of treatment to death or disease progression, with continuous follow-up until the study endpoint. Results: The 186 enrolled patients were well-balanced in baseline clinicopathologic characteristics between the two groups. Compared to the 6-week group, the 4-week group achieved significantly higher ORR (35.87% vs. 22.34%, P=0.042) and DCR (81.52% vs. 67.02%, P=0.024), a more substantial reduction in AFP level, and markedly prolonged median OS and PFS (all P<0.001). Nevertheless, the 4-week group presented significantly elevated ALT levels (P=0.001) and decreased ALB levels (P=0.012) at one month post-treatment. Multivariate Cox regression analysis identified the 4-week interval as an independent favorable prognostic factor for OS (HR=0.692, 95% CI 0.498-0.961, P=0.029). The overall incidence of AEs was comparable between the two groups. Conclusion: For patients with unresectable HCC treated with TACE combined with PD-1 inhibitors, a 4-week TACE interval yielded superior tumor response and survival benefits with acceptable hepatic safety compared to a 6-week interval, which supports the 4-week interval as an optimal clinical treatment schedule.

Keywords: Hepatocellular carcinoma, transarterial chemoembolization, PD-1 inhibitor, treatment interval, tumor response, liver function

Introduction

Hepatocellular carcinoma (HCC) accounts for approximately 75% to 85% of all primary liver malignancies worldwide and ranks third among the leading causes of cancer-related mortality globally [1, 2]. Despite advances in early screening and curative treatments including surgical resection, thermal ablation and liver transplantation, a large proportion of patients are diagnosed with intermediate or advanced HCC and thus lose the opportunity for curative therapy [3]. For these patients, treatment relies mainly on combined locoregional and sys-

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temic therapeutic strategies. Transarterial chemoembolization (TACE) is the standard first-line treatment for Barcelona Clinic Liver Cancer (BCLC) stage B HCC and is increasingly combined with systemic agents for advanced HCC [4, 5]. However, TACE-induced tumor hypoxia and compensatory angiogenesis can impair long-term therapeutic efficacy and create a pro-tumorigenic microenvironment [6-8].

The emergence of immune checkpoint inhibitors, particularly programmed death-1 (PD-1) inhibitors, has revolutionized the systemic treatment of advanced HCC [9]. By restoring T-cell-mediated anti-tumor immune responses, PD-1 inhibitors induce durable tumor regression and improve long-term survival in both first-line and second-line treatment settings [9]. Preclinical and clinical evidence has confirmed the synergistic anti-tumor effect of TACE combined with PD-1 blockade [10-12]. TACE-induced tumor ischemia and necrosis releases tumor neoantigens, which trigger tumor-specific immune activation [13], while PD-1 inhibitors reverse the immunosuppressive microenvironment induced by TACE embolization [14]. Consequently, TACE combined with PD-1 inhibitor has been widely applied in clinical practice, with superior objective response rate (ORR) and survival outcomes compared to TACE or immunotherapy monotherapy [11, 15].

Nevertheless, substantial heterogeneity exists in the clinical implementation of combined TACE and PD-1 inhibitor therapy, especially regarding the optimal interval between sequential TACE sessions [16, 17]. In routine clinical practice, TACE is conventionally performed at fixed intervals of 4 to 8 weeks, depending on institutional protocols, physician experience and individual patient tolerance [18]. However, the biological mechanisms and clinical outcomes associated with different TACE intervals in the context of concurrent immunotherapy remain poorly elucidated. A shorter TACE interval may accelerate and intensify tumor devascularization, thereby promoting neoantigen release and amplifying the synergistic effect with PD-1 inhibitors. Conversely, frequent TACE administration may cause cumulative hepatic reserve damage, aggravate systemic inflammatory responses, and increase the risk of AEs, ultimately compromising treatment tolerance and long-term prognosis [18].

Current guidelines offer no definitive recommendations regarding optimal TACE intervals for combination with systemic immunotherapy. Given the inherent synergistic potential between TACE and PD-1 blockade, optimizing the TACE treatment schedule is clinically critical. A shorter interval may sustain persistent immune activation and intratumoral hypoxia but may also aggravate hepatic injury, a key determinant of treatment tolerability and long-term prognosis. Conversely, a prolonged interval allows hepatic functional recovery yet may attenuate synergistic therapeutic efficacy. Therefore, this study compared tumor response and hepatic function changes between 4-week and 6-week TACE intervals in patients receiving TACE plus PD-1 inhibitors, aiming to identify the optimal treatment cadence that balances efficacy and safety.

Patients and methods

Study design and case selection

This retrospective cohort study was conducted at Beijing Friendship Hospital, Capital Medical University. A total of 186 patients diagnosed with unresectable HCC who received combined TACE and PD-1 inhibitor therapy between June 2020 and December 2024 were enrolled, with follow-up data collected until December 2025. This study aimed to compare tumor response, hepatic function changes, and survival outcomes between 4-week and 6-week interval regimens. All clinical data were retrieved from electronic medical records.

Inclusion criteria: (1) age ≥18 years; (2) HCC diagnosis confirmed by histopathology, cytology, or clinical imaging consistent with the guidelines from the American Association for the Study of Liver Diseases (AASLD) or the imaging criteria outlined by the European Association for the Study of the Liver (EASL) [19]; (3) BCLC stage B or C disease unsuitable for curative resection or ablation, or patients who declined radical surgery; (4) presence of at least one measurable intrahepatic target lesion per modified Response Evaluation Criteria in Solid Tumors (mRECIST); (5) Child-Pugh class A or B (score ≤7); (6) Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-2; (7) no prior exposure to immunotherapy or anti-angiogenic agents.

Exclusion criteria: (1) extrahepatic primary metastasis, main portal vein tumor thrombus extending to contralateral branches, or inferior vena cava tumor thrombus; (2) central nervous system metastasis or concurrent malignant tumors of other systems; (3) contraindications to any study medication; (4) severe uncontrolled comorbidities involving the cardiac, cerebral, renal, or pulmonary systems; (5) gastrointestinal bleeding within three months before treatment initiation; (6) prior local or systemic anti-tumor therapy, including radiofrequency ablation, iodine-125 seed implantation, or systemic chemotherapy; (7) pregnancy or lactation; (8) incomplete clinical or follow-up data.

Grouping criteria and treatment methods

Grouping according to TACE interval: TACE interval scheduling was determined by a multidisciplinary team according to individual tumor burden, hepatic reserve, and treatment tolerance. Patients were stratified into two groups based on the predefined intended TACE interval in treatment plans: the 4-week interval group (n=92) and the 6-week interval group (n=94). Treatment adherence was verified from medical records. The median (interquartile range, IQR) number of TACE sessions was 4 (3-5) in the 4-week group and 3 (2-4) in the 6-week group.

TACE procedure: All TACE procedures were performed by experienced interventional radiologists with over ten years of clinical experience. Following local anesthesia with 2% lidocaine (AstraZeneca, UK), the right femoral artery was punctured using the Seldinger technique, and a 5F vascular sheath was inserted. A 5F-RH catheter (Terumo, Japan) was deployed for celiac and superior mesenteric arteriography under digital subtraction angiography (DSA) to evaluate tumor size, location, feeding arteries, and vascular anatomy. A 2.7F microcatheter (Progreat, Terumo, Japan) was advanced superselectively into the tumor-feeding artery.

Chemoembolization was performed using an iodized oil emulsion (Lipiodol; Guerbet, France) combined with chemotherapeutic agents, including oxaliplatin 50-100 mg (Huaxia Shengsheng Pharmaceutical, Approval No. H20255933), raltitrexed 2-4 mg (Nanjing Zhengda Tianqing Pharmaceutical, Approval No. H20090325), or epirubicin 30-50 mg (Shandong New Era Pharmaceutical, Approval No. H20213436), at the operator's discretion. Subsequent embolization with gelatin sponge particles (Jiangxi Fuchuang Medical Technology, Approval No. 20263130088) was performed until stasis of tumor-feeding arterial blood flow was achieved. After procedure completion, the catheter and sheath were removed, and hemostasis was achieved by manual compression and pressure dressing. All patients remained supine for 24 hours to prevent puncture-site complications.

PD-1 inhibitor treatment: All patients received concurrent PD-1 inhibitor therapy combined with TACE. PD-1 inhibitors were administered intravenously every 3 weeks, with the first dose given 2-3 days after the initial TACE procedure. Subsequent PD-1 inhibitor administration followed a fixed 3-week schedule independent of repeat TACE timing. Combination treatment was continued until disease progression, intolerable toxicity, or completion of a minimum 6-month treatment course.

The selection and dosage of PD-1 inhibitors were based on clinical availability and approved regimens, including pembrolizumab 200 mg (MSD Ireland, SJ20180019), sintilimab 200 mg (Innovent Biologics, S20180016), toripalimab 240 mg (Zhonghe Biomedical Technology, S20180015), camrelizumab 200 mg (Shengdi Biopharmaceutical, S20190027), and tislelizumab 200 mg (BeiGene Pharmaceutical, S20190045). All intravenous infusions were completed within 30 minutes. Dose delay or permanent discontinuation was implemented for grade ≥3 immune-related adverse events (irAEs) in accordance with drug-specific prescribing guidelines. Re-treatment at standard or reduced doses was permitted after recovery to grade ≤1 irAEs at the investigator's discretion.

Data collection

Baseline demographic and clinical characteristics: Standardized case report forms were used to collect baseline demographic and clinical data from inpatient and outpatient electronic medical records. Collected variables included age, gender, body mass index, alcohol consumption history, smoking history, ECOG PS, BCLC stage, Child-Pugh grade, tumor size,

tumor number, vascular invasion, extrahepatic metastasis, etiology of HCC, and total number of TACE sessions during treatment.

Laboratory parameters: Peripheral blood samples were collected at baseline and post-treatment follow-up. Hepatic and renal function indicators, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), albumin (ALB), creatinine (Cr), and blood urea nitrogen (BUN), were detected using enzymatic and colorimetric assays on a Roche Cobas® 8000 automatic biochemical analyzer (Roche Diagnostics, Switzerland). Calibrators and quality control reagents provided by the manufacturer were used to ensure detection accuracy.

Serum tumor markers, including alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), and carbohydrate antigen 125 (CA125), were measured by electrochemiluminescence immunoassay on the Roche Cobas® 8000 platform, with reference ranges defined according to the manufacturer's instructions.

Evaluation of tumor response: Tumor response was evaluated at three months after treatment initiation by contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI). Imaging examinations were performed using a 64-slice CT scanner (Somatom Definition AS, Siemens, Germany) and a 3.0-T MRI system (Magnetom Skyra, Siemens, Germany) with liver-specific gadoxetic acid contrast (Primovist, Bayer, Germany). Treatment response was assessed per the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) criteria [20]. Complete response (CR) was defined as the disappearance of all target lesions; partial response (PR) as a ≥30% reduction in the sum of target lesion diameters; stable disease (SD) as insufficient shrinkage for PR or insufficient enlargement for progressive disease (PD); and PD as a ≥20% increase in lesion sum diameter or the emergence of new lesions. Objective response rate (ORR) was defined as the proportion of patients achieving CR or PR, and disease control rate (DCR) as the proportion achieving CR, PR, or SD.

Documentation of adverse events: All AEs occurring during combination treatment and within 30 days after the final study drug administration were recorded and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [21]. Common AEs associated with TACE and PD-1 inhibitor therapy, including hand-foot syndrome, diarrhea, abdominal pain, decreased appetite, nausea, rash, hypothyroidism, hyperbilirubinemia, and proteinuria, were systematically collected. The maximum AE grade per patient was recorded, and the incidence of any-grade AEs was calculated for intergroup comparison.

Survival outcomes: Overall survival (OS) was defined as the interval from the initiation of combined TACE and PD-1 inhibitor therapy to all-cause death, with surviving patients censored at the last follow-up. Progression-free survival (PFS) was defined as the time from treatment initiation to the first RECIST 1.1-defined disease progression or all-cause death, whichever occurred first.

Follow-up

Follow-up assessments were initiated 4-10 weeks after treatment completion and repeated every 1-3 months thereafter. All patients were followed up until December 2025, ensuring a minimum 12-month follow-up duration for all enrolled cases. Follow-up data were obtained through outpatient visits, inpatient reexaminations, and external medical record verification to monitor disease progression and survival status.

Ethics statement

This study was conducted in accordance with the Declaration of Helsinki and relevant domestic clinical research regulations. The study protocol was approved by the Institutional Ethics Committee of Beijing Friendship Hospital, Capital Medical University. Given the retrospective study design and full anonymization of all patient data, the requirement for written informed consent was waived. All patient information was strictly de-identified to ensure clinical data confidentiality throughout the study.

Data analysis

All statistical analyses were performed using SPSS 22.0 (IBM, USA) and R 4.3.1 (R Foundation, Austria). The normality of continu-

ous variables was verified by the Shapiro-Wilk test and Q-Q plots. Normally distributed data were presented as mean ± standard deviation (SD) and compared using independent t-tests; non-normal data were expressed as median (IQR) and compared using the Mann-Whitney U test. Categorical variables were described as frequencies and percentages and analyzed using the Pearson χ^2 test or Fisher's exact test as appropriate.

Kaplan-Meier survival curves and the log-rank test were used to analyze OS and PFS differences between groups. Univariate and multivariate Cox proportional hazards regression models were applied to screen independent prognostic factors for OS. Variables with P< 0.10 in univariate analysis were included in the multivariate forward stepwise regression model. The total number of TACE sessions was forcibly incorporated into the multivariate model to adjust for potential confounding effects. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated for all prognostic factors. All tests were two-tailed, and P<0.05 was defined as significant.

A *post-hoc* power analysis was performed based on the primary endpoint of ORR. With observed ORRs of 35.87% (4-week group, n=92) and 22.34% (6-week group, n=94), the two-sided χ^2 test achieved a statistical power of approximately 82% at α=0.05, indicating sufficient statistical power to detect intergroup differences. Of note, *post-hoc* power analysis relies on observed effect sizes and should be interpreted cautiously; prospective sample size calculation is recommended for future validation studies.

Results

Comparison of baseline demographic and clinical characteristics

Baseline demographic and clinicopathologic characteristics of the two groups are summarized in **Table 1**. There were no significant intergroup differences in age, sex, BMI, ECOG PS score, BCLC stage, Child-Pugh grade, tumor burden, disease etiology, or number of TACE sessions (all P>0.05), indicating well-balanced baseline prognostic factors and good comparability between the two cohorts.

Changes in hepatic and renal function one month post-treatment

Baseline hepatic and renal function indicators were comparable between the two groups (all P>0.05, **Table 2**). One month after treatment, the 4-week group showed significantly higher ALT elevation (57.36 ± 16.41 vs. 49.83 ± 14.27 U/L, P=0.001) and more obvious ALB reduction (34.27 ± 4.11 vs. 35.83 ± 4.26 g/L, P=0.012) than the 6-week group. AST and TBIL levels showed marginal inter-group differences without statistical significance (P=0.099, P= 0.062, respectively). No significant differences were observed in Cr or BUN levels between the two groups (all P>0.05). These findings suggest that a shorter TACE interval induces mild early hepatic impairment, including aggravated hepatocellular injury and decreased hepatic synthetic function, without affecting renal function.

Changes in serum tumor markers one month post-treatment

Baseline serum levels of AFP, CEA, CA19-9 and CA125 were similar between the two groups (all P>0.05). All tumor markers decreased in both groups one month after treatment. Notably, the 4-week group had a significantly lower residual AFP level than the 6-week group (412.58 ± 201.34 vs. 558.62 ± 276.19 ng/mL, P<0.001). No significant differences were found in post-treatment CEA, CA19-9, or CA125 levels between the two groups (all P>0.05, **Figure 1**). These findings indicate that a 4-week TACE interval achieves more robust early tumor regression, as reflected by a greater AFP decline.

Comparison of 3-month short-term tumor response

As shown in **Table 3**, the 4-week group exhibited superior short-term tumor control at 3 months post-treatment. Compared to the 6-week group, the 4-week group had significantly higher ORR (35.87% vs. 22.34%, P=0.042) and DCR (81.52% vs. 67.02%, P=0.024). The CR rate was slightly higher in the 4-week group (5.43% vs. 3.19%), while the PD rate was markedly lower (19.57% vs. 32.98%). These data confirm that shorter TACE intervals enhance the short-term anti-tumor efficacy of TACE-PD-1 inhibitor combination therapy.

Table 1. Comparison of baseline demographic and clinical characteristics

Item		4-week interval group (n=92)	6-week interval group (n=94)	t/χ^2	*P* value
Gender [n (%)]	Male	66 (71.74%)	69 (73.40%)	0.065	0.799
	Female	26 (28.26%)	25 (26.60%)		
Age (years)		63.89 ± 7.74	64.58 ± 7.92	0.602	0.548
BMI (kg/m^2)		22.46 ± 2.97	22.62 ± 3.05	0.347	0.729
Employment Status [n (%)]	Employed	45 (48.91%)	51 (54.26%)	0.531	0.466
	Unemployed	47 (51.09%)	43 (45.74%)		
Marital Status [n (%)]	Married	75 (81.52%)	80 (85.11%)	0.431	0.806
	Single	11 (11.96%)	9 (9.57%)		
	Divorced	6 (6.52%)	5 (5.32%)		
Current Residence [n (%)]	Urban	58 (63.04%)	55 (58.51%)	0.401	0.527
	Rural	34 (36.96%)	39 (41.49%)		
History of Alcohol [n (%)]	Yes	50 (54.35%)	54 (57.45%)	0.181	0.670
	No	42 (45.65%)	40 (42.55%)		
History of Smoking [n (%)]	Yes	55 (59.78%)	59 (62.77%)	0.174	0.676
	No	37 (40.22%)	35 (37.23%)		
ECOG PS Score [n (%)]	0 points	40 (43.48%)	47 (50.00%)	0.933	0.627
	1 point	44 (47.83%)	41 (43.62%)		
	2 points	8 (8.69%)	6 (6.38%)		
BCLC Staging [n (%)]	B	36 (39.13%)	43 (45.74%)	0.832	0.362
	C	56 (60.87%)	51 (54.26%)		
Child-Pugh grade [n (%)]	Class A	70 (76.09%)	77 (81.91%)	0.953	0.329
	Class B	22 (23.91%)	17 (18.09%)		
Tumor Size [n (%)]	≤3 cm	15 (16.30%)	18 (19.15%)	0.258	0.612
	>3 cm	77 (83.70%)	76 (80.85%)		
Tumor Number [n (%)]	≤3	58 (63.04%)	56 (59.57%)	0.236	0.627
	>3	34 (36.96%)	38 (40.43%)		
Vascular Invasion [n (%)]	Present	25 (27.17%)	29 (30.85%)	0.305	0.581
	Absent	67 (72.83%)	65 (69.15%)		
Extrahepatic Metastasis [n (%)]	Present	20 (21.74%)	21 (22.34%)	0.01	0.921
	Absent	72 (78.26%)	73 (77.66%)		
TACE Sessions [n (%)]	≤3	55 (59.78%)	64 (68.09%)	1.391	0.238
	>3	37 (40.22%)	30 (31.91%)		
Etiology [n (%)]	Hepatitis B	60 (65.22%)	57 (60.64%)	0.499	0.919
	Hepatitis C	14 (15.22%)	16 (17.02%)		
	Alcohol	13 (14.13%)	16 (17.02%)		
	Others	5 (5.43%)	5 (5.32%)		

Note: TACE, transarterial chemoembolization; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; BCLC, Barcelona Clinic Liver Cancer.

Safety analysis of treatment-related AEs

The spectrum and incidence of AEs are shown in **Figure 2**. The overall incidence of any-grade AEs was similar between the 4-week group and the 6-week group (85.87% vs. 80.85%, P=0.359). The most common AEs in both groups were decreased appetite, abdominal pain and nausea. These findings indicate that shortening the TACE interval from 6 weeks to 4 weeks did not increase the overall risk of treatment-related AEs, with favorable clinical tolerability.

Survival outcome analysis

The median follow-up duration of the entire cohort was 17.5 months (range: 1.2-24.0 mon-

Table 2. Changes in hepatic and renal function one month post-treatment

Indicator	Time	4-week interval group (n=92)	6-week interval group (n=94)	t	*P* value
ALT (U/L)	Before	39.72 ± 11.24	40.13 ± 11.58	0.25	0.803
	After	57.36 ± 16.41	49.83 ± 14.27	3.343	0.001
AST (U/L)	Before	46.83 ± 13.27	47.21 ± 13.62	0.196	0.845
	After	62.94 ± 19.56	58.47 ± 17.11	1.658	0.099
TBIL (μmol/L)	Before	16.38 ± 4.52	16.14 ± 4.39	0.369	0.713
	After	21.67 ± 6.81	19.93 ± 5.74	1.88	0.062
ALB (g/L)	Before	38.14 ± 3.89	38.52 ± 3.97	0.666	0.506
	After	34.27 ± 4.11	35.83 ± 4.26	2.539	0.012
Cr (μmol/L)	Before	71.26 ± 10.53	70.89 ± 10.31	0.248	0.805
	After	74.83 ± 12.17	73.41 ± 11.86	0.806	0.421
BUN (mmol/L)	Before	5.27 ± 1.14	5.21 ± 1.09	0.38	0.704
	After	5.89 ± 1.36	5.68 ± 1.28	1.089	0.278

Note: ALT, alanine transaminase; AST, aspartate transaminase; TBIL, total bilirubin; ALB, albumin; Cr, creatinine; BUN, blood urea nitrogen.

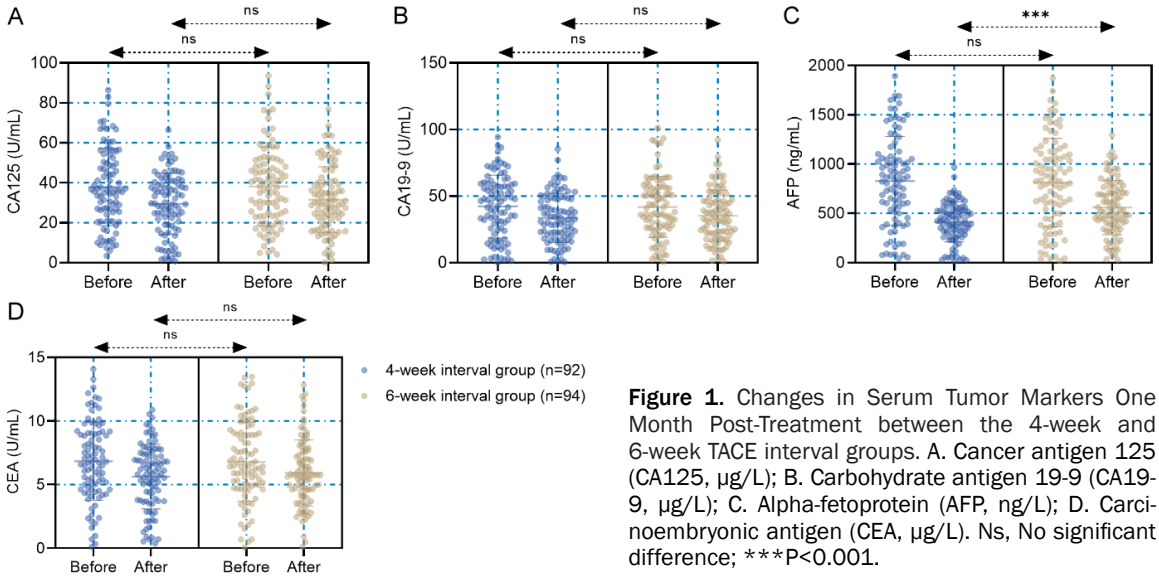

Figure 1. Changes in Serum Tumor Markers One Month Post-Treatment between the 4-week and 6-week TACE interval groups. A. Cancer antigen 125 (CA125, μg/L); B. Carbohydrate antigen 19-9 (CA19-9, μg/L); C. Alpha-fetoprotein (AFP, ng/L); D. Carcinoembryonic antigen (CEA, μg/L). Ns, No significant difference; ***P<0.001.

ths). During follow-up, 98 patients (52.7%) died (OS events), and 112 patients (60.2%) experienced disease progression or death (PFS events). In the 4-week group, 46 patients (50.0%) had censored OS data and 38 patients (41.3%) had censored PFS data; in the 6-week group, 42 patients (44.7%) had censored OS data and 36 patients (38.3%) had censored PFS data. Kaplan-Meier survival analysis showed that the 4-week group had significantly longer median OS (18.42 ± 4.28 vs. 15.71 ± 4.13 months, P<0.001) and median PFS (8.71 ± 2.69 vs. 7.24 ± 2.58 months, P< 0.001) than the 6-week group (**Figure 3**).

Univariate and multivariate Cox regression analysis of independent prognostic factors for OS

Multivariate Cox regression analysis incorporating ALBI grade, baseline NLR, post-progression systemic therapy and actual TACE session count confirmed that 4-week TACE interval was an independent protective prognostic factor for OS (HR=0.692, 95% CI: 0.498-0.961, P=0.029). Other independent risk factors for poor OS included BCLC stage C (HR=1.758, P=0.002), Child-Pugh grade B (HR=2.091, 95% CI: 1.478-2.958, P<0.001), elevated baseline

Table 3. Changes in serum tumor markers one month post-treatment [n (%)]

Marker	4-week interval group (n=92)	6-week interval group (n=94)	χ^2	*P* value
ORR	33 (35.87%)	21 (22.34%)	4.13	0.042
DCR	75 (81.52%)	63 (67.02%)	5.106	0.024
CR	5 (5.43%)	3 (3.19%)		
PR	28 (30.43%)	18 (19.15%)		
SD	42 (45.65%)	42 (44.68%)		
PD	17 (19.57%)	31 (32.98%)		

Note: ORR, Overall Response Rate; DCR, Disease Control Rate; CR, Complete Remission; PR, Partial Remission; SD, Stable Disease; PD, Progression Disease.

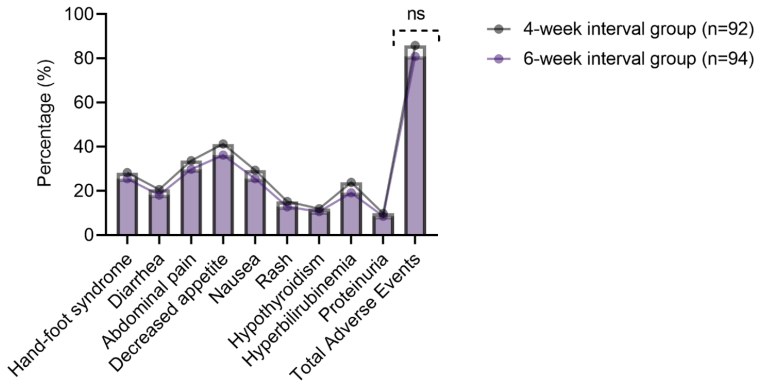

Figure 2. Distribution and Incidence of treatment-induced toxicities by the 4-week and 6-week TACE interval groups [n (%)]. Note: The adverse reaction was classified using CTCAEv5. 0; The sum indicates those who experienced one or more adverse events of all grades. ns, No significant difference; TACE, transarterial chemoembolization.

AFP (HR=1.281, P=0.003), tumor diameter >3 cm (HR=1.439, P=0.047), vascular invasion (HR=1.671, 95% CI: 1.179-2.365, P=0.004). ALBI grade 2/3 (HR=1.854, P<0.001) and baseline NLR ≥3.0 (HR=1.412, P=0.029). Post-progression systemic therapy was an independent protective factor for OS (HR=0.731, P=0.033). The actual number of TACE sessions showed no significant correlation with OS by the multivariate model (HR=1.124, P=0.342). See **Table 4**.

Discussion

This study compared the clinical efficacy and safety of two TACE intervals (4 weeks versus 6 weeks) in patients with unresectable HCC receiving combined PD-1 inhibitor therapy. The results demonstrated that a shorter 4-week TACE interval contributed to more prominent early declines in tumor markers, superior short-term tumor responses, and prolonged progression-free and OS, accompanied by mild early hepatic dysfunction without a corresponding increase in the overall burden of adverse events. These preliminary findings suggest that TACE frequency can modulate both therapeutic efficacy and hepatic functional reserve during concurrent immunotherapy. After adjustment for multiple prognostic factors, including ALBI grade, baseline NLR, post-progression treatment, and the actual number of TACE sessions, the 4-week interval remained independently associated with improved OS, further validating the reliability of our core findings.

In terms of hepatic function, patients receiving TACE at 4-week intervals exhibited significantly elevated alanine aminotransferase levels and marked reductions in serum albumin one month after treatment, compared to those treated at 6-week intervals. Aspartate aminotransferase and total bilirubin levels showed consistent changing trends. These observations indicate that more frequent transarterial embolization may aggravate acute hepatocellular injury and transiently impair hepatic synthetic function [22, 23]. Consistent with our results, Liu et al. [24] reported cumulative hepatic damage in patients receiving intensive TACE regimens, and Miksad et al. [22] confirmed that shorter inter-procedural TACE intervals delay albumin recovery. The underlying mechanism is presumably attributed to repeated ischemic injury to non-tumorous liver parenchyma, especially in patients with underlying liver cirrhosis [25, 26]. Notably, no intergroup differences in renal function were observed, indicating that the hepatic changes were procedure-specific rather than a manifestation of systemic deterioration.

In contrast, the 4-week interval group achieved a substantially greater reduction in serum AFP

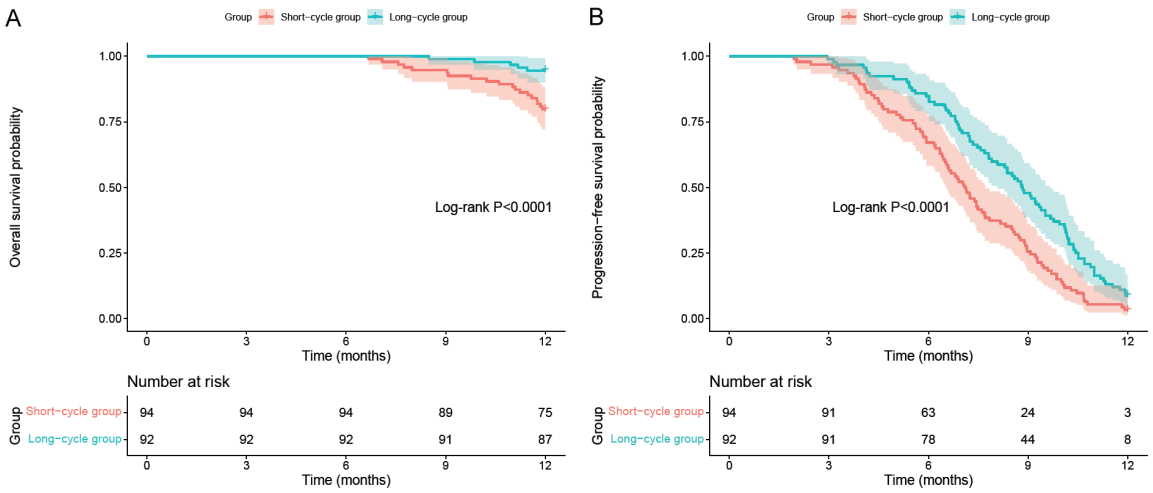

Figure 3. Kaplan-Meier curves of overall survival (A) and progression-free survival (B) stratified by TACE interval groups. Note: OS, Overall survival; PFS, Progression-free survival; TACE, transarterial chemoembolization.

Table 4. Univariate and multivariate Cox regression analysis of factors affecting overall survival in patients receiving TACE combined with PD-1 inhibitors

Variable	Univariate COX analysis		Multivariate COX analysis	
	HR (95% CI)	P	HR (95% CI)	P
TACE interval (short-cycle vs. long-cycle)	0.726 (0.538-0.986)	0.036	0.692 (0.498-0.961)	0.029
Age (per 1 year increase)	1.024 (1.006-1.042)	0.045	1.014 (0.995-1.033)	0.162
Sex (male vs. female)	1.187 (0.794-1.774)	0.427	-	-
BCLC stage (C vs. B)	1.891 (1.346-2.671)	<0.001	1.758 (1.231-2.509)	0.002
Child-Pugh grade (B vs. A)	2.214 (1.580-3.092)	<0.001	2.091 (1.478-2.958)	<0.001
ALBI grade (2/3 vs. 1)	2.103 (1.512-2.924)	<0.001	1.854 (1.312-2.618)	<0.001
AFP (per log unit)	1.315 (1.120-1.535)	0.001	1.281 (1.087-1.503)	0.003
Tumor size (>3 cm vs. ≤3 cm)	1.539 (1.087-2.170)	0.017	1.439 (1.005-2.058)	0.047
Vascular invasion (present vs. absent)	1.764 (1.261-2.464)	0.001	1.671 (1.179-2.365)	0.004
Baseline NLR (≥3.0 vs. <3.0)	1.538 (1.148-2.061)	0.004	1.412 (1.036-1.924)	0.029
Post-progression systemic therapy (yes vs. no)	0.702 (0.531-0.928)	0.013	0.731 (0.549-0.974)	0.033
Actual TACE sessions (>3 vs. ≤3)	1.209 (0.963-1.518)	0.102	1.124 (0.884-1.429)	0.342

Note: HR, hazard ratio; CI, confidence interval; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; NLR, neutrophil-to-lymphocyte ratio; TACE, trans-arterial chemoembolization. Variables with P<0.10 in univariate analysis were entered into the multivariate Cox model. The number of TACE sessions was forced into the model to assess confounding.

at the one-month follow-up. Although postoperative levels of CA125, CA19-9, and CEA were comparable between the two groups, the distinct AFP reduction in the short-interval group indicated enhanced early tumor cytoreduction with condensed TACE cycles. AFP serves not only as a biomarker for HCC diagnosis and therapeutic monitoring but also as an indicator of aggressive tumor biological behavior. Xia et al. [27] verified that a rapid AFP response after locoregional therapy correlated with favorable survival outcomes in HCC patients, and Rizzo et al. [28] found that a more profound AFP decline augmented the therapeutic benefit of subsequent immunotherapy. The pronounced AFP reduction observed in this study may result from frequent cycles of ischemia-induced tumor necrosis, which promotes extensive tumor antigen release and potentially initiates systemic anti-tumor immune responses. This interpretation is supported by preclinical models, in which sequential embolization enhances dendritic cell activation and T-cell priming when combined with immune checkpoint blockade [29].

The superior short-term tumor response in the 4-week group, characterized by higher objective response rate and disease control rate, validates the hypothesis that intensified temporal coordination of TACE and PD-1 blockade optimizes their synergistic anti-tumor efficacy, with a particularly notable difference in progressive disease rates between groups. Our findings are consistent with previous research by Wang et al. [12], who demonstrated superior tumor responses with 4-week rather than 8-week intervals in combination with lenvatinib and PD-1 inhibitors. Similarly, Zou et al. [30] reported that patients receiving TACE every 4-5 weeks achieved better radiologic responses than those with prolonged treatment intervals, despite their cohort not uniformly receiving concurrent immunotherapy. The biological rationale for this synergistic effect is twofold: first, repeated TACE procedures sustain the release of tumor-associated antigens and damage-associated molecular patterns, which act as endogenous immune adjuvants [31]; second, PD-1 blockade exerts optimal therapeutic effects during the peak period of T-cell infiltration after embolization [31]. Accordingly, a shorter TACE interval enables precise temporal matching of these two immunotherapeutic events.

Notably, survival analysis revealed that the 4-week interval was associated with prolonged overall and PFS. Multivariate Cox regression analysis further confirmed TACE interval as an independent prognostic factor for OS, even after adjustment for established confounding variables, including BCLC stage, Child-Pugh classification, baseline AFP level, tumor size, and vascular invasion status. The prognostic value of TACE interval was comparable to that of other well-recognized survival predictors in HCC. Our results align with the findings of Lee et al. [32], who identified TACE frequency as an independent survival indicator in a mixed HCC cohort, and Wang et al. [12], who confirmed improved clinical outcomes with shortened TACE intervals in the context of combined immunotherapy. Collectively, these data indicate that the early radiologic and biomarker advantages conferred by 4-week TACE intervals translate into substantial survival benefits for patients.

Encouragingly, the overall incidence and spectrum of adverse events were comparable between the two groups. The most common treatment-related toxicities, including decreased appetite, abdominal pain, and nausea, are typical adverse reactions of both TACE and PD-1 inhibitor therapy, and their consistent incidence across groups confirmed that shortening the TACE interval does not compromise treatment tolerability. This finding has important clinical implications, as concerns about cumulative treatment toxicity frequently hinder clinicians from adopting intensive TACE regimens. It should be noted that this study analyzed only selected adverse events and did not systematically evaluate patient quality of life or patient-reported outcomes. Nevertheless, the safety profile observed in our study was consistent with previous reports [33, 34], which demonstrated no increase in grade ≥3 adverse events when TACE intervals were shortened in combination with sorafenib, despite the distinct therapeutic regimen from the PD-1 inhibitor combination adopted in our research. Additionally, this study incorporated multiple PD-1 inhibitors with varying pharmacokinetic and pharmacodynamic properties. Although all included agents are approved for HCC treatment [35, 36], subtle differences in their synergistic effects with TACE cannot be excluded from a mechanistic perspective. PD-1 inhibitors differ significantly in Fc region function: for example, camrelizumab has a canonical IgG4 backbone, while toripalimab is an IgG4κ monoclonal antibody with a modified Fc region that reduces FcγR binding affinity [37, 38]. Such structural variations may alter antibody-dependent cell-mediated cytotoxicity and Fc receptor binding, thereby reshaping the tumor immune microenvironment [39, 40]. Furthermore, differences in receptor occupancy rate, half-life, and off-target effects may theoretically modulate the degree of T-cell reactivation following TACE-induced tumor antigen release [41, 42]. However, head-to-head comparative studies of different PD-1 inhibitors combined with locoregional therapy remain scarce. Given the limited sample size of this study, subgroup analyses comparing the efficacy and safety of individual PD-1 inhibitors were not performed. Large-scale prospective studies are warranted to explore drug-specific effects and the underlying immunological mechanisms.

These findings carry important clinical significance. If validated in prospective trials, the

4-week TACE interval will serve as a simple and clinically feasible strategy to enhance the efficacy of PD-1 inhibitor combination therapy without inducing unacceptable hepatic toxicity. For patients with preserved hepatic reserve and good performance status, this intensified interval regimen can be prioritized. In contrast, a 6-week TACE interval may be preferable for patients with marginal hepatic function or a history of hepatic decompensation, to preserve residual liver function while achieving effective disease control. Our results do not support a one-size-fits-all TACE interval, but highlight the necessity of individualized treatment scheduling based on baseline hepatic function, tumor burden, and therapeutic goals. Furthermore, this study underscores the urgent need for prospective trials to optimize TACE frequency specifically for the immunotherapy era, rather than relying on empirical evidence from single-agent TACE treatment.

Several limitations of this study should be acknowledged. First, this is a single-center retrospective study. Despite rigorous statistical adjustment, unmeasured residual confounding factors could not be completely excluded. Second, patient allocation to the two interval groups was non-randomized, with treatment schedules determined by multidisciplinary clinical assessment, which may have introduced subtle selection bias, although baseline characteristics were well balanced between groups. Propensity score matching was not adopted here to avoid further reduction in sample size and statistical power; multivariate Cox regression was used instead to adjust for major established prognostic confounders. Third, the follow-up period was restricted to one year, leaving long-term survival outcomes and late-onset treatment toxicities unassessed. Fourth, group allocation was based on predefined intended TACE intervals rather than verified cycle-to-cycle interval adherence; although the total number of TACE sessions was adjusted for by multivariate analysis, minor scheduling variability could not be fully accounted for. Fifth, biomarker evaluation was limited to AFP alone, without comprehensive immune profiling or circulating tumor DNA detection, which constrains in-depth exploration of the underlying immunological mechanisms. Lastly, the sample size was adequate for hypothesis-generating analysis but insufficient to support robust stratified subgroup comparisons.

Future research should prioritize prospective randomized controlled trials to validate our findings and compare fixed TACE intervals with response-guided or individualized on-demand TACE strategies. Integrating translational endpoints, including dynamic circulating tumor cell changes, T-cell receptor repertoire shifts, and tumor mutational burden dynamics, will help further clarify the immune-dependent mechanisms linking TACE interval frequency to therapeutic efficacy. Additionally, incorporating patient-reported outcomes and cost-effectiveness analyses can provide comprehensive evidence for the clinical applicability of intensified 4-week TACE regimens. Pending further prospective validation, this study establishes TACE interval as a modifiable prognostic factor for clinical outcomes in patients with unresectable HCC receiving TACE plus PD-1 inhibitor combination immunotherapy.

Conclusion

A 4-week TACE interval confers superior short-term tumor responses, greater AFP reduction, and prolonged survival compared to a 6-week interval in unresectable HCC patients treated with TACE combined with PD-1 inhibitors. The intensified schedule induces only mild, transient early hepatic impairment without increasing overall adverse event burden, and TACE interval was validated as an independent prognostic factor for overall survival. These findings support that shortened TACE cycles optimize synergistic anti-tumor efficacy with concurrent immunotherapy, reinforcing the value of individualized interval scheduling tailored to patients' baseline hepatic reserve, tumor burden, and treatment goals. Further prospective randomized controlled trials are warranted to define the optimal TACE frequency for modern immunotherapy-combined HCC treatment regimens.

Disclosure of conflict of interest

None.

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References

[1] Yang XA, Jin R, Zhang LM and Ying DJ. Global trends of targeted therapy for hepatocellular carcinoma: a bibliometric and visualized study from 2008 to 2022. Medicine (Baltimore) 2023; 102: e34932.

[2] Kim DY. Changing etiology and epidemiology of hepatocellular carcinoma: Asia and worldwide. J Liver Cancer 2024; 24: 62-70.

[3] Hucke F, Emmer H, Emmer R, Hucke M, Bota S, Fürstner M, Hausegger K, Mittermair R and Peck-Radosavljevic M. Changes in the epidemiology of hepatocellular carcinoma in Carinthia, Austria, 2012-2023. Cancers (Basel) 2023; 15: 5215.

[4] van Doorn DJ, Hendriks P, Burgmans MC, Rietbergen DDD, Coenraad MJ, van Delden OM, Bennink RJ, Labeur TA, Klümpen HJ, Eskens FALM, Moelker A, Vegt E, Sprengers D, Mostafavi N, Ijzermans J and Takkenberg RB. Liver decompensation as late complication in HCC patients with long-term response following selective internal radiation therapy. Cancers (Basel) 2021; 13: 5427.

[5] Gan C, Yuan Y, Shen H, Gao J, Kong X, Che Z, Guo Y, Wang H, Dong E and Xiao J. Liver diseases: epidemiology, causes, trends and predictions. Signal Transduct Target Ther 2025; 10: 33.

[6] Zong S, Huang G, Pan B, Zhao S, Ling C and Cheng B. A hypoxia-related miRNA-mRNA signature for predicting the response and prognosis of transcatheter arterial chemoembolization in hepatocellular carcinoma. J Hepatocell Carcinoma 2024; 11: 525-542.

[7] Gong F, Zheng L, Xu J, Wu Y, Jin Q, Lu J, Pei Z, Zhao Z, Chen M, Tu J, Fang S, Chen W, Wei K, Yang N, Gong C, Wu F, Zhang Y, Ni C, Cheng L, Liu Z and Ji J. Magnesium microspheres for enhanced transarterial chemoembolization therapy of hepatocellular carcinoma: from animal models to a pilot clinical study. Sci Adv 2025; 11: eadv0885.

[8] Yuan G, Liu Z, Wang W, Liu M, Xu Y, Hu W, Fan Y, Zhang X, Liu Y and Si G. Multifunctional nanoplatforms application in the transcatheter chemoembolization against hepatocellular carcinoma. J Nanobiotechnology 2023; 21: 68.

[9] Liu Y, Pan J, Gao F, Xu W, Li H and Qi X. Efficacy and safety of PD-1/PD-L1 inhibitors in advanced hepatocellular carcinoma: a systematic review and meta-analysis. Adv Ther 2023; 40: 521-549.

[10] Sun W, Liu Y and Wang L. Feasibility and safety of the clinical outcomes of TACE combined with lenvatinib and PD-1 blockades in the treatment of hepatocellular carcinoma with portal vein tumor thrombus: a retrospective exploratory study. Int J Gen Med 2024; 17: 3627-3640.

[11] Zhao S, Zhou M, Wang P, Yang J, Zhang D, Yin F and Song P. Sorafenib, lenvatinib, or lenvatinib combining PD-1 inhibitors plus TACE in unresectable hepatocellular carcinoma: a retrospective analysis. Technol Cancer Res Treat 2022; 21: 15330338221133640.

[12] Wang WJ, Liu ZH, Wang K, Yu HM, Cheng YQ, Xiang YJ, Feng JK, Zhou LP, Zhou HK, Pan WW, Guo WX, Shi J and Cheng SQ. Efficacy and safety of TACE combined with lenvatinib and PD-1 inhibitors for unresectable recurrent HCC: a multicenter, retrospective study. Cancer Med 2023; 12: 11513-11524.

[13] Yu J, Wang Q, Zhang X, Guo Z and Cui X. Mechanisms of neoantigen-targeted induction of pyroptosis and ferroptosis: from basic research to clinical applications. Front Oncol 2021; 11: 685377.

[14] Davern M, Gaughan C, O' Connell F, Moran B, Mylod E, Sheppard AD, Ramjit S, Yun-Tong Kung J, Phelan JJ, Davey MG, Ryan EJ, Butler C, Quinn L, Howard C, Tone E, Phoenix E, Butt WT, Lynam-Lennon N, Maher SG, Ravi N, Donohoe CL, Reynolds JV, Lysaght J and Donlon NE. PD-1 blockade attenuates surgery-mediated immunosuppression and boosts Th1 immunity perioperatively in oesophagogastric junctional adenocarcinoma. Front Immunol 2023; 14: 1150754.

[15] Zou X, Xu Q, You R and Yin G. Efficacy and safety of TACE combined with regorafenib plus PD-1 inhibitor in the treatment of hepatocellular carcinoma after sorafenib resistance. J Hepatocell Carcinoma 2023; 10: 267-279.

[16] Kudo M. Implications of the TACTICS trial: establishing the new concept of combination/sequential systemic therapy and transarterial chemoembolization to achieve synergistic effects. Liver Cancer 2022; 11: 487-496.

[17] Kudo M, Kawamura Y, Hasegawa K, Tateishi R, Kariyama K, Shiina S, Toyoda H, Imai Y, Hiraoka A, Ikeda M, Izumi N, Moriguchi M, Ogasawara S, Minami Y, Ueshima K, Murakami T, Miyayama S, Nakashima O, Yano H, Sakamoto M, Hatano E, Shimada M, Kokudo N, Mochida S and Takehara T. Management of hepatocellular carcinoma in Japan: JSH consensus statements and recommendations 2021 update. Liver Cancer 2021; 10: 181-223.

[18] Deng G, Zhang H, Xue H, Zheng K and Zhao C. The effect of interval time of transcatheter arterial chemoembolization with drug-eluting beads on the efficacy and safety of unresectable hepatocellular carcinoma: a case-control study. Front Oncol 2025; 15: 1679167.

[19] Kim TH, Kim SY, Tang A and Lee JM. Comparison of international guidelines for noninvasive diagnosis of hepatocellular carcinoma: 2018 update. Clin Mol Hepatol 2019; 25: 245-263.
[20] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-247.
[21] Freites-Martinez A, Santana N, Arias-Santiago S and Viera A. Using the common terminology criteria for adverse events (CTCAE - Version 5.0) to evaluate the severity of adverse events of anticancer therapies. Actas Dermosifiliogr (Engl Ed) 2021; 112: 90-92.
[22] Miksad RA, Ogasawara S, Xia F, Fellous M and Piscaglia F. Liver function changes after transarterial chemoembolization in US hepatocellular carcinoma patients: the LiverT study. BMC Cancer 2019; 19: 795.
[23] Schindler P, Kaldewey D, Rennebaum F, Trebicka J, Pascher A, Wildgruber M, Köhler M and Masthoff M. Safety, efficacy, and survival of different transarterial chemoembolization techniques in the management of unresectable hepatocellular carcinoma: a comparative single-center analysis. J Cancer Res Clin Oncol 2024; 150: 235.
[24] Liu H, Wang C, Wang R, Cao H, Cao Y, Huang T, Lu Z, Xiao H, Hu M, Wang H and Zhao J. New insights into mechanisms and interventions of locoregional therapies for hepatocellular carcinoma. Chin J Cancer Res 2024; 36: 167-194.
[25] Liu H and Man K. New insights in mechanisms and therapeutics for short- and long-term impacts of hepatic ischemia reperfusion injury post liver transplantation. Int J Mol Sci 2021; 22: 8210.
[26] Rampes S and Ma D. Hepatic ischemia-reperfusion injury in liver transplant setting: mechanisms and protective strategies. J Biomed Res 2019; 33: 221-234.
[27] Xia D, Bai W, Wang Q, Chung JW, Adhoute X, Kloeckner R, Zhang H, Zeng Y, Sripongpun P, Nie C, Kim SU, Huang M, Hu W, Ding X, Yin G, Li H, Zhao H, Bronowicki JP, Li J, Li J, Zhu X, Wu J, Zhang C, Gong W, Li Z, Lin Z, Xu T, Yin T, Anty R, Song J, Shi H, Shao G, Ren W, Zhang Y, Yang S, Zheng Y, Xu J, Wang W, Zhu X, Fu Y, Liu C, Kaewdech A, Ding R, Zheng J, Liu S, Yu H, Zheng L, You N, Fan W, Zhang S, Feng L, Wang G, Zhang P, Li X, Chen J, Zhang F, Shao W, Zhou W, Zeng H, Cao G, Huang W, Jiang W, Zhang W, Li L, Feng A, Wang E, Wang Z, Han D, Lv Y, Sun J, Ren B, Xia L, Li X, Yuan J, Wang Z, Luo B, Li K, Guo W, Yin Z, Zhao Y, Xia J, Fan D, Wu K, Bettinger D, Vogel A and Han G; China HCC-TACE study group. Tumor burden with AFP improves survival prediction for TACE-treated patients with HCC: an international observational study(☆). JHEP Rep 2024; 7: 101216.
[28] Rizzo A, Brunetti O and Brandi G. Hepatocellular carcinoma immunotherapy: predictors of response, issues, and challenges. Int J Mol Sci 2024; 25: 11091.
[29] Jin ZC, Zhong BY, Chen JJ, Zhu HD, Sun JH, Yin GW, Ge NJ, Luo B, Ding WB, Li WH, Chen L, Wang YQ, Zhu XL, Yang WZ, Li HL and Teng GJ; CHANCE Investigators. Real-world efficacy and safety of TACE plus camrelizumab and apatinib in patients with HCC (CHANCE2211): a propensity score matching study. Eur Radiol 2023; 33: 8669-8681.
[30] Zou X, Xu Q, You R and Yin G. Correlation and efficacy of TACE combined with lenvatinib plus PD-1 inhibitor in the treatment of hepatocellular carcinoma with portal vein tumor thrombus based on immunological features. Cancer Med 2023; 12: 11315-11333.
[31] Posa A, Contegiacomo A, Ponziani FR, Punzi E, Mazza G, Scrofani A, Pompili M, Goldberg SN, Natale L, Gasbarrini A, Sala E and Iezzi R. Interventional oncology and immuno-oncology: current challenges and future trends. Int J Mol Sci 2023; 24: 7344.
[32] Lee M and Shin HP. Efficacy of transarterial chemoembolization (TACE) for early-stage hepatocellular carcinoma. Medicina (Kaunas) 2023; 59: 2174.
[33] Yu J, Yan D, Wei S, Yang L and Yi P. Efficacy and safety of TACE combined with tyrosine kinase inhibitors and camrelizumab for unresectable hepatocellular carcinoma: a systematic review and meta-analysis. Oncol Lett 2024; 28: 401.
[34] Ding Z, Fang G, Tang Y and Zeng Y. The impact of PD-1 inhibitors on prognosis in unresectable hepatocellular carcinoma treated with TACE and lenvatinib: a retrospective study. Sci Rep 2024; 14: 14334.
[35] Zhang L, Liu R, Deng T and Ba Y. Advances in medical treatment of advanced hepatobiliary and pancreatic cancer in 2022. Cancer Innov 2023; 2: 36-51.
[36] Zhang J, Hu C, Xie X, Qi L, Li C and Li S. Immune checkpoint inhibitors in HBV-caused hepatocellular carcinoma therapy. Vaccines (Basel) 2023; 11: 614.
[37] Lu D, Xu Z, Zhang D, Jiang M, Liu K, He J, Ma D, Ma X, Tan S, Gao GF and Chai Y. PD-1 N58-glycosylation-dependent binding of monoclonal antibody Cemiplimab for immune checkpoint therapy. Front Immunol 2022; 13: 826045.
[38] Jiang M, Liu M, Liu G, Ma J, Zhang L and Wang S. Advances in the structural characterization

of complexes of therapeutic antibodies with PD-1 or PD-L1. MAbs 2023; 15: 2236740.
[39] Liang X, Du L and Fan Y. The potential of FCRL genes as targets for cancer treatment: insights from bioinformatics and immunology. Aging (Albany NY) 2023; 15: 4926-4948.
[40] Knorr DA, Blanchard L, Leidner RS, Jensen SM, Meng R, Jones A, Ballesteros-Merino C, Bell RB, Baez M, Marino A, Sprott D, Bifulco CB, Piening B, Dahan R, Osorio JC, Fox BA and Ravetch JV. FcγRIIB is an immune checkpoint limiting the activity of Treg-targeting antibodies in the tumor microenvironment. Cancer Immunol Res 2024; 12: 322-333.
[41] Longuespée R, Theile D, Zörnig I, Hassel JC, Lindner JR, Haefeli WE and Fresnais M. Molecular prediction of clinical response to anti-PD-1/anti-PD-L1 immune checkpoint inhibitors: new perspectives for precision medicine and mass spectrometry-based investigations. Int J Cancer 2023; 153: 252-264.
[42] Kasichayanula S, Mandlekar S, Shivva V, Patel M and Girish S. Evolution of preclinical characterization and insights into clinical pharmacology of checkpoint inhibitors approved for cancer immunotherapy. Clin Transl Sci 2022; 15: 1818-1837.