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ORIGINAL RESEARCH

TACE Combined with Lenvatinib-PD-1 Versus TACE Monotherapy as Conversion Therapy Before Liver Resection in Unresectable Hepatocellular Carcinoma: A Retrospective, Propensity Score Matching Study

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Background: Transarterial chemoembolization (TACE) combined with Lenvatinib plus programmed death-1 inhibitor (PD-1 inhibitor) is recommended for unresectable hepatocellular carcinoma (uHCC), and it has increased the probability of successful conversion. Our aim was to compare the clinical benefits of TACE combined with Lenvatinib-PD-1 inhibitor versus TACE monotherapy as conversion therapy for patients with uHCC who subsequently underwent liver resection (LR).

Materials and Methods: This retrospective study included 213 uHCC patients who underwent LR after receiving either TACE combined with Lenvatinib plus PD-1 inhibitor (combination group, n=109) or TACE monotherapy (monotherapy group, n=104). Propensity score matching was employed to minimize baseline confounding variables between cohorts. Tumor response, disease-free survival (DFS), overall survival (OS), and adverse events (AEs) were assessed between treatment arms.

Results: Among 68 matched pairs of patients who underwent LR, only 1 patient developed small-for-size syndrome. The combination group demonstrated superior treatment responses compared with the monotherapy group, with a significantly higher objective response rate (92.65% vs 80.88%, *p=0.043*) and pathological complete response rate (36.76% vs 11.76%, *p<0.001*). Furthermore, histopathological analyses revealed a lower incidence of microvascular invasion in the combination group compared with the monotherapy group (14.71% vs 29.41%, *p=0.039*). Survival analyses demonstrated significantly improved DFS (median not reached vs 20.0 months, *p=0.002*) and OS (median not reached for both, *p=0.005*) in the combination group. Multivariate Cox proportional hazards regression identified preoperative monotherapy as an independent adverse prognostic factor for both DFS (HR, 2.46) and OS (HR, 3.05). Although combination therapy showed superior therapeutic efficacy, it was linked to a significantly higher incidence of rash and hand-foot skin reactions.

Conclusion: Compared to TACE monotherapy, TACE combined with Lenvatinib-PD-1 inhibitor as conversion therapy can improve long-term survival outcomes in patients with uHCC who undergo subsequent LR, with an acceptable safety profile.

Keywords: hepatocellular carcinoma, conversion therapy, transarterial chemoembolization, Lenvatinib, programmed death-1 inhibitor

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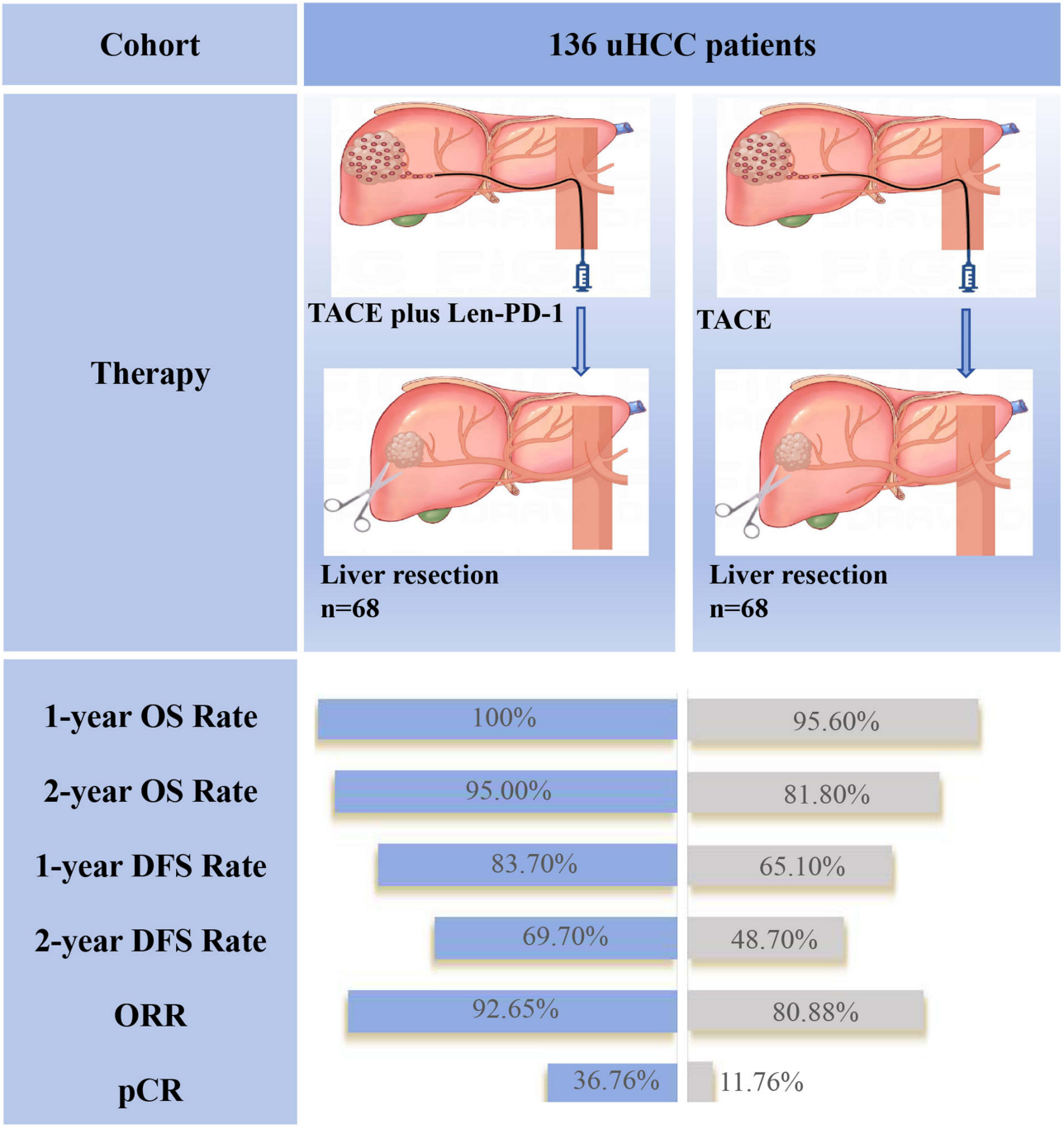
Graphical Abstract



Introduction

Hepatocellular carcinoma (HCC) is recognized as the principal histologic subtype of primary hepatic malignancies worldwide, with epidemiological studies consistently reporting its proportion at 75–85% of all cases.[1] Liver resection (LR) continues to serve as the most effective curative intervention for resectable HCC, providing optimal long-term survival outcomes and the potential for a cure.[2] Regrettably, fewer than 30% of patients meet the resection criteria, mainly because the high proportion of patients present with advanced-stage disease at initial diagnosis.[3] Among patients

with unresectable HCC (uHCC), the five-year survival rate remains dismally low at under 20%, highlighting an extremely poor overall prognosis.[4] Conversion therapy involves the use of locoregional or systemic treatments to render initially unresectable malignancies eligible for surgical resection.[5] Traditionally, transarterial chemoembolization (TACE) has been the mainstay of conversion therapy for uHCC. However, TACE monotherapy demonstrates limited efficacy in large or diffuse HCC, with conversion rates rarely exceeding 20% and significant risk of adverse events.[6,7]

Over the past decade, significant breakthroughs in treating uHCC have emerged with the widespread adoption of tyrosine kinase inhibitors (TKIs) and programmed death-1 (PD-1) inhibitors, coupled with the systematic exploration of diverse combination therapeutic strategies in clinical practice. Among various systemic regimens, single-agent systemic therapies have demonstrated limited clinical efficacy. The overall response rates (ORR) with sorafenib, cabozantinib, and regorafenib monotherapy were 3.3%, 4.0%, and 6.5%, respectively.[8–10] Lenvatinib, a multitargeted tyrosine kinase inhibitor, has demonstrated an ORR of approximately 18.8%, which is notably higher compared to the ORRs reported for sorafenib monotherapy.[11] Furthermore, the combination of Lenvatinib plus a PD-1 inhibitor has achieved remarkable ORR ranging from 36.0% to 54.2%, with conversion success rates ranging from 15.9% to 30.8%.[12] Recent evidence suggests that locoregional therapies, particularly TACE or hepatic arterial infusion chemotherapy (HAIC), may enhance the tumor microenvironment's response to immune checkpoint inhibitors (ICIs).[13] Indeed, the triple combination of TACE, Lenvatinib, and PD-1 inhibitor has demonstrated superior efficacy, with ORR reaching 76.4% and conversion rates of 25–54.5%, substantially surpassing outcomes of monotherapy approaches.[14,15] Despite these promising advances, current literature primarily focuses on the safety and efficacy profiles of combination regimens as first-line treatment for uHCC, with limited data on post-conversion surgical outcomes. This knowledge gap prompted our retrospective investigation comparing clinical outcomes between two cohorts of successfully converted uHCC patients: those who received the combination therapy (TACE-Lenvatinib-PD-1 inhibitor) versus TACE monotherapy, both followed by LR.

Materials And Methods

Study Population and Eligibility

This study received ethical approval (No. II2023-027) from the Institutional Review Board of the Third Affiliated Hospital of Sun Yat-sen University and was conducted in accordance with the Declaration of Helsinki. Patients were deemed unresectable if they presented with intermediate- or advanced-stage HCC (Barcelona Cancer Liver Clinic stages B or C) or were incapable of tolerating curative liver resection (eg, resulting from insufficient remnant liver volume after the operation). This retrospective study included clinical data from consecutive patients with uHCC who received conversion therapy (combination group: TACE combined with Lenvatinib-PD-1 inhibitor; monotherapy group: TACE monotherapy) at our institution from January 2018 to December 2022, and subsequently underwent LR after successful conversion therapy. A total of 213 patients were eligible for inclusion and were diagnosed according to the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Disease (AASLD) criteria.[16,17] The criteria for inclusion were as follows: (1) age 18–80 years; (2) Child–Pugh grade A or B; (3) initial treatment with TACE without prior or current malignancies; and (4) histologically confirmed HCC and Eastern Cooperative Oncology Group (ECOG) status score of 0 or 1. The criteria for exclusion were as follows: (1) had history of previous systemic therapy, intra-arterial chemoinfusion, or TACE; (2) had severe medical comorbidities; and (3) currently had or had previously experienced malignant tumors excluding HCC; or (4) had undergone other local regional treatments (percutaneous ethanol injection, radiofrequency ablation, or iodine 125 seed implantation) in addition to TACE during this study; and (5) lost to follow-up after the LR procedure. Among the 213 patients, 109 received TACE combined with Lenvatinib-PD-1 inhibitor followed by LR (combination group), whereas 104 received TACE monotherapy followed by LR (monotherapy group). The study flowchart is presented in Figure 1.

TACE Procedure

Using the Seldinger technique, a percutaneous femoral artery puncture was performed, and under fluoroscopic guidance, the catheter was positioned within the hepatic artery for digital subtraction angiography (DSA), which captured images from the early arterial phase to the late portal venous phase. The angiographic findings were analyzed by pretreatment enhanced CT/MRI. In cases where incomplete tumor staining or sparse visualization of hepatic vessels was observed

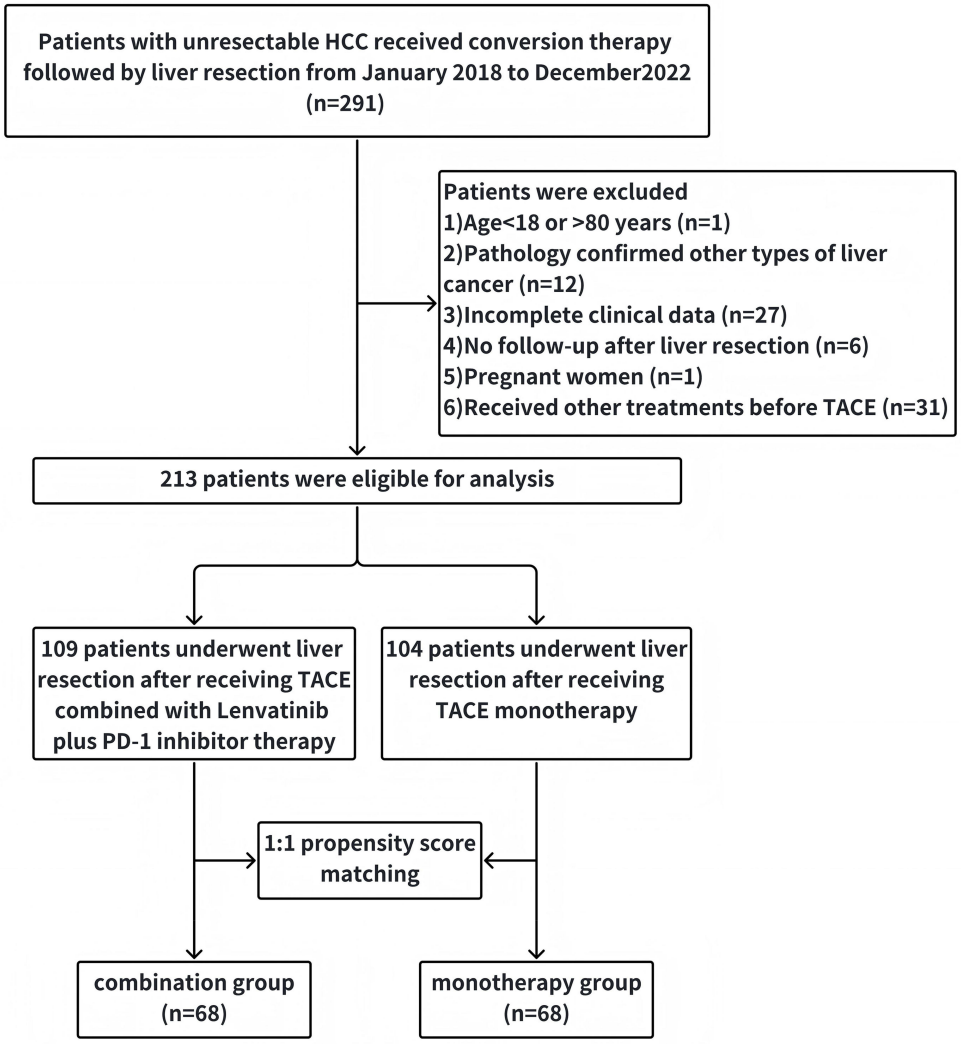


Figure 1 Flowchart of patient selection for this retrospective study.
Abbreviations: HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; PD-1, programmed death-1 inhibitor.

during hepatic artery angiography, additional angiography of the superior mesenteric artery, renal arteries, and diaphragmatic arteries was conducted to accurately identify tumor-feeding vessels. All patients enrolled in the study received conventional TACE (C-TACE) or drug-eluting bead TACE (DEB-TACE) as the initial treatment. For C-TACE, 10–20 mL of lipiodol was fully mixed with 20–40 mg of epirubicin and then injected into the tumor-nourishing artery via microcatheter superselectively. On the basis of the flow rate and diameter of the tumor-nourishing artery, Embosphere microspheres (100–300 μm or 300–500 μm, Embosphere, Merit Medical) or gelatine sponge particles (150–350 μm or 350–560 μm, Hangzhou Alicon Pharm SCI&TEC CO, LTD) were chosen for embolization until the tumor staining completely disappeared. For DEB-TACE, appropriate-diameter HepaSpheres (30–60 μm or 50–100 μm, Merck Medical) or DC Beads (70–150 μm or 150–300 μm, Boston Scientific), carrying 40–60 mg of epirubicin (Pfizer), were slowly injected into the target vessel. All TACE interventions were conducted by interventional radiologists possessing over 15 years of specialized experience in hepatic interventions.

Systemic Therapy

Lenvatinib (Lenvima, Merck, 12 mg Qd for weight ≥60 kg, 8 mg Qd for weight <60 kg) was the TKI utilized in this study. The first oral administration of this drug was performed on the third day after TACE. PD-1 inhibitors (tislelizumab, sintilimab, and camrelizumab) were administered intravenously 3–5 days after TACE at a dosage of 200 mg each time,

and injections were given every three weeks. For patients who did not meet the surgical criteria, combination therapy was continued until the occurrence of intolerable toxicity, disease progression, or the patient elected to discontinue treatment upon comprehensive evaluation.

Liver Resection Procedure

A multidisciplinary team evaluated whether the patient was eligible for LR on the basis of the following criteria: 1: Child–Pugh class A; 2: feasibility of R0 resection while ensuring sufficient remaining liver volume and function; 3: the remaining liver volume accounts for more than 40% of the standard liver volume (for those with chronic liver disease or cirrhosis) or more than 30% (without liver-related disease); and 4: no severe or persistent adverse events (AEs) observed during the administration of TACE, Lenvatinib, or PD-1 inhibitors. Patients in the combination group scheduled for LR were required to discontinue Lenvatinib for at least 1 week and PD-1 inhibitors for at least 2 weeks. The interval between the last TACE procedure and the LR was more than four weeks for both the combination group and monotherapy group.

Follow-Up

The follow-up duration encompassed two sequential periods: the conversion interval (from initial TACE to LR) and the post-resection period (from LR to the final follow-up). During the conversion therapy, patients were monitored at regular 4–6 week intervals. Tumour response before LR was evaluated via enhanced CT or MRI, and LR was considered only for complete response (CR, no enhancement was observed for the tumor), partial response (PR, reduction of the tumor enhancement range to ≥30%), or stable disease (SD: disease control lies between PR and PD; PD: increase in the tumor enhancement range to >20% or new lesions appear) according to the modified Response Evaluation Criteria in Solid Tumor criteria (mRECIST).[18] In the first six months after LR, patients were closely monitored every 2–3 months, and every 6–12 months thereafter. Throughout the follow-up period, all the patients provided a medical history, comprehensive physical examination, radiological imaging (mainly enhanced abdominal CT and MRI), and laboratory tests (including complete blood count, hepatic and renal function, hepatitis B surface antigen (HBsAg), coagulation function, serum α-fetoprotein (AFP) and HBV-DNA). All AEs were evaluated and categorized using the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCICTCAE, v5.0). The follow-up cut-off for the study was March 31, 2024. Overall survival (OS) was calculated from the date of HCC diagnosis until death due to any cause or the last follow-up assessment. Disease-free survival (DFS) was calculated from the date of LR until either radiographic confirmation of tumor recurrence or the end of follow-up. Figure 2 illustrates the therapy processes for two representative cases.

Statistical Analysis

The study utilized propensity score matching (PSM) methodology to balance baseline characteristics and mitigate selection bias between cohorts. Matching was performed at a 1:1 ratio via the nearest neighbour approach, with the calliper width set at 0.20. All the statistical analyses were performed via R software (version 4.3.0). Continuous variables were presented as medians (interquartile ranges) or means (standard deviations), while categorical variables were reported as counts (percentages), with the former analyzed using the Mann–Whitney *U*-test and the latter assessed through the chi-square test or Fisher's exact test depending on data distribution and sample size. Survival analysis of OS and DFS was performed via the Kaplan–Meier method, and the results were compared via the Log rank test. Multivariate analysis was conducted using the Cox proportional hazards model to determine independent prognostic factors. Statistical significance was assessed using a two-sided significance level of 0.05.

Results

Demographic and Clinical Characteristics

This study included 186 males and 27 females. As presented in Table 1, there was no significant difference in gender, age, ECOG PS, HBsAg positivity, Child-Pugh, portal vein tumor thrombus (PVTT) or tumor number between the two

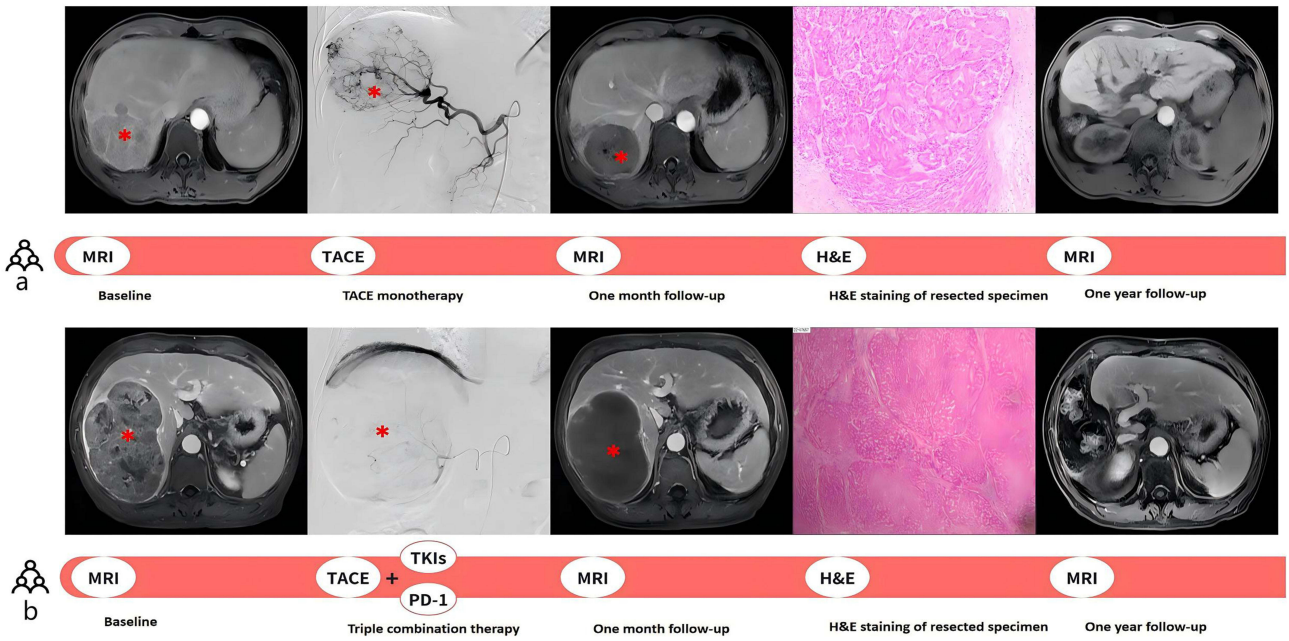


Figure 2 Treatment processes of two representative cases. (**a**) A 47-year-old man presented with a large HCC (size: 10.4×9.5 × 7.4 cm) in liver segments VI–VII. The tumor showed satellite nodules and was in contact with the right and middle hepatic veins. Post-DEB-TACE MRI at day 37 indicated tumor shrinkage (size: 8.4×7.6 × 6.3 cm) with a complete response. A right partial hepatectomy was performed, and pathology revealed less than 10% residual tumor cells. One-year follow-up MRI showed no recurrence. (**b**) A 73-year-old man had massive HCC (size: 15.2×13.7 × 16.3 cm) in segments V–VIII. Initial MRI showed the tumor to be unresectable due to vascular invasion and insufficient future liver remnant. After 2 cycles of combined therapy (DEB-TACE/Lenvatinib/sintilimab), the tumor shrank to 12.8×9.5 × 14.2 cm, with increased liver volume. The patient underwent laparoscopic right hepatectomy and cholecystectomy, with pathology showing complete tumor cell necrosis. One-year follow-up MRI revealed no recurrence. The red asterisk (✱) represents the target lesion; MRI, Magnetic Resonance Imaging; TACE, transarterial chemoembolization; TKIs, tyrosine kinase inhibitors; PD-1, programmed death-1 inhibitor.

groups ($p>0.05$). The combination group patients had a significantly higher preoperative AFP level (p=0.019), a higher frequency of DEB-TACE (p<0.001), and a larger tumor size (p<0.001) than those in the monotherapy group.

After 1:1 PSM analysis, two new cohorts were generated with 68 patients each in the combination group and the monotherapy group. There were no significant differences in preoperative AFP level, TACE type, or tumor size between the two groups.

Table 1 Demographic and Clinical Characteristics of the Study Population in Entire Cohort and PSM Cohort

	Before PSM			After PSM		
	Combination Group (N=109)	**Monotherapy Group (N=104)**	**P-value**	**Combination Group (N=68)**	**Monotherapy Group (N=68)**	**P-value**
Gender			0.454			0.805
Female	12 (11.01)	15 (14.42)		9 (13.24)	10 (14.71)	
Male	97 (88.99)	89 (85.58)		59 (86.76)	58 (85.29)	
Age, years			0.197			0.343
≥60	25 (22.94)	32 (30.77)		17 (25.00)	22 (32.35)	
<60	84 (77.06)	72 (69.23)		51 (75.00)	46 (67.65)	
ECOG PS			0.068			0.226
0	41 (37.61)	52 (50.00)		26 (38.24)	33 (48.53)	
1	68 (62.39)	52 (50.00)		43 (59.72)	41 (56.94)	
HBV infection			0.085			0.545
Negative	7 (6.42)	14 (13.46)		5 (7.35)	7 (10.29)	
Positive	102 (93.58)	90 (86.54)		63 (92.65)	61 (89.711)	

(*Continued*)

Table 1 (Continued).

	Before PSM			After PSM		
	Combination Group (N=109)	**Monotherapy Group (N=104)**	**P-value**	**Combination Group (N=68)**	**Monotherapy Group (N=68)**	**P-value**
AFP, ng/mL			0.019			0.863
≥400	55 (50.46)	36 (34.62)		30 (44.12)	29 (42.65)	
<400	54 (49.54)	68 (65.38)		38 (55.88)	39 (57.35)	
Child_Pugh			0.294			0.771
A	101 (92.66)	92 (88.46)		62 (91.18)	61 (89.71)	
B	8 (7.34)	12 (11.54)		6 (8.82)	7 (10.29)	
TACE type			<0.001			0.834
DEB-TACE	94 (86.24)	63 (60.58)		53 (77.94)	54 (79.41)	
C-TACE	15 (13.76)	41 (39.42)		15 (22.06)	14 (20.59)	
PVTT			0.101			1.000
Present	35 (32.11)	23 (22.12)		18 (26.47)	18 (26.47)	
Absent	74 (67.89)	81 (77.88)		50 (73.53)	50 (73.53)	
Tumor number			0.534			0.389
Single	56 (51.38)	49 (47.12)		40 (58.82)	35 (51.47)	
Multiple	53 (48.62)	55 (52.88)		28 (41.18)	33 (48.53)	
Tumor Size, cm			<0.001			1.000
<8	44 (40.37)	70 (67.31)		41 (60.29)	41 (60.29)	
≥8	65 (59.63)	34 (32.69)		27 (39.71)	27 (39.71)	

Abbreviations: PSM, propensity score matching; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HBV infection, Hepatitis B virus infection; AFP, alpha-fetoprotein; C-TACE, conventional transcatheter arterial chemoembolization; DEB-TACE, drug-eluting bead transcatheter arterial chemoembolization; PVTT, portal vein tumor thrombus.

AEs of Conversion Therapy and LR

Treatment-related adverse events are shown in the Supplementary Table S1. All reported mortality was unrelated to therapeutic procedures, and most AEs were manageable, with statistically similar results observed between the groups for the majority of complications. The most frequent AEs during conversion therapy in both groups included fever, nausea, constipation, vomiting, and abdominal pain. Notably, significant differences were observed between the combination therapy and monotherapy groups in specific adverse events. Rash (19.12% vs 0%, $p<0.001$) and hand-foot skin reaction (25.00% vs 0%, $p<0.001$) were exclusively observed in the combination therapy group. The hand-foot skin reaction showed a significant difference in grade 3–4 events between the groups (10.29% vs 0%, $p=0.020$). In patients experiencing grade 3–4 immune-related AEs, symptoms were relieved after dermatological treatment and suspension of ICIs. During the perioperative period of LR, both groups experienced similar rates of complications including incisional infection, abdominal infection, pneumonia, bile leakage, ionic abnormalities, and hypoproteinemia. The most common post-resection issues were ionic abnormalities (25.00% vs 29.41%, $p=0.563$) and hypoproteinemia (23.53% vs 20.59%, $p=0.676$).

The degree of intraoperative bleeding in the combination group was significantly greater than that in the monotherapy group ($p=0.032$); however, comparable outcomes were observed for surgical duration ($p=0.816$) or postoperative hospital stay ($p=0.309$) (Supplementary Table S2). Moreover, one patient in the combination group developed small-for-size syndrome due to insufficient residual liver volume. This patient recovered and was discharged on postoperative Day 24 after undergoing medical intervention.

Tumour Response and Pathological Analysis

As shown in Table 2. Before PSM, the combination group showed better radiological response (CR+PR: 93.58% vs 79.81%, $p=0.003$), higher pathological complete response (pCR) (40.37% vs 12.50%, $p<0.001$), and lower microvascular invasion (MVI) rates (13.76% vs 27.88%, $p=0.011$), while microsatellite presence remained comparable (8.26% vs

Table 2 Tumor Response According to the mRECIST Criteria and Postoperative Pathology

Tumor Response	Before PSM			After PSM		
	Combination group (N=109)	Monotherapy group (N=104)	P-value	Combination group (N=68)	Monotherapy group (N=68)	P-value
Radiological response			0.003			0.043
CR+PR	102 (93.58)	83 (79.81)		63 (92.65)	55 (80.88)	
SD	7 (6.42)	21 (20.19)		5 (7.35)	13 (19.12)	
Pathological response			<0.001			<0.001
Complete	44 (40.37)	13 (12.50)		25 (36.76)	8 (11.76)	
Incomplete	65 (59.63)	91 (87.50)		43 (63.24)	60 (88.24)	
Microvascular invasion			0.011			0.039
Present	15 (13.76)	29 (27.88)		10 (14.71)	20 (29.41)	
Absent	94 (86.24)	75 (72.12)		58 (85.29)	48 (70.59)	
Microsatellite			0.879			1.00
Present	9 (8.26)	8 (7.69)		6 (8.82)	6 (8.82)	
Absent	100 (91.74)	96 (92.31)		62 (91.18)	62 (91.18)	

Abbreviations: PSM, propensity score matching; CR, complete response; PR, partial response; SD, stable disease.

7.69%, *p=0.879*). After matching, these findings were consistently maintained. The combination group demonstrated superior radiological response (CR+PR: 92.65% vs 80.88%, *p=0.043*), significantly higher pCR (36.76% vs 11.76%, *p<0.001*), and lower MVI rates (14.71% vs 29.41%, *p=0.039*). Statistical analysis revealed no significant difference in microsatellite presence between the groups (8.82% vs 8.82%, *p=1.00*).

OS Analysis

As of April 1, 2024, the median duration of follow-up was 30.5 months (IQR 24.0–40.3) for the combination group and 34.0 months (IQR 23.8–46.0) for the monotherapy group. Neither the combination group nor the monotherapy group reached the median OS in the entire or matched cohort. In the entire cohort, 8 (8/109, 7.34%) patients in the combination group and 29 (29/104, 27.88%) patients in the monotherapy group died during the follow-up period. The 1-, 2-, and 3-year OS rates were 100%, 96.0%, and 92.0%, respectively, in the combination group and 97.1%, 82.4%, and 73.5%, respectively, in the monotherapy group. After PSM, 6 (6/68, 8.82%) patients in the combination group and 22 (22/68, 32.35%) patients in the monotherapy group died during the follow-up period. The 1-, 2-, and 3-year OS rates were 100%, 95.0%, and 90.6%, respectively, in the combination group and 95.6%, 81.8%, and 67.9%, respectively, in the monotherapy group. In both the entire cohort (Figure 3A, HR 3.51; 95% CI: 1.595–7.700; $p<0.001$) and the matched cohort (Figure 3C, HR 3.37; 95% CI: 1.362–8.324; *p=0.005*), the combination group demonstrated significantly longer OS versus monotherapy group.

DFS Analysis

In the entire cohort, the median DFS was 20.0 months in the monotherapy group but was not reached in the combination group. 30 (30/109, 27.5%) patients in the combination group and 57 (57/104, 54.8%) patients in the monotherapy group experienced recurrence during the follow-up period. The 1-, 2-, and 3-year DFS rates were 84.3%, 72.1%, and 70.5%, respectively, in the combination group and 64.7%, 46.7%, and 41.2%, respectively, in the monotherapy group. After PSM, the median DFS was 20.0 months in the monotherapy group but was not reached in combination group. 19 (19/68, 27.94%) patients in the combination group and 37 (37/68, 54.41%) patients in the monotherapy group experienced recurrence during the follow-up period. The 1-, 2-, and 3-year DFS rates were 83.7%, 69.7%, and 69.7%, respectively, in the combination group and 65.1%, 48.7%, and 39.4%, respectively, in monotherapy group. In the entire cohort (Figure 3B, HR 2.419; 95% CI: 1.553–3.766; *p<0.001*) and the matched cohort (Figure 3D, HR 2.305; 95% CI: 1.324–4.012; *p=0.002*), the monotherapy group demonstrated significantly shorter DFS compared to the combination group.

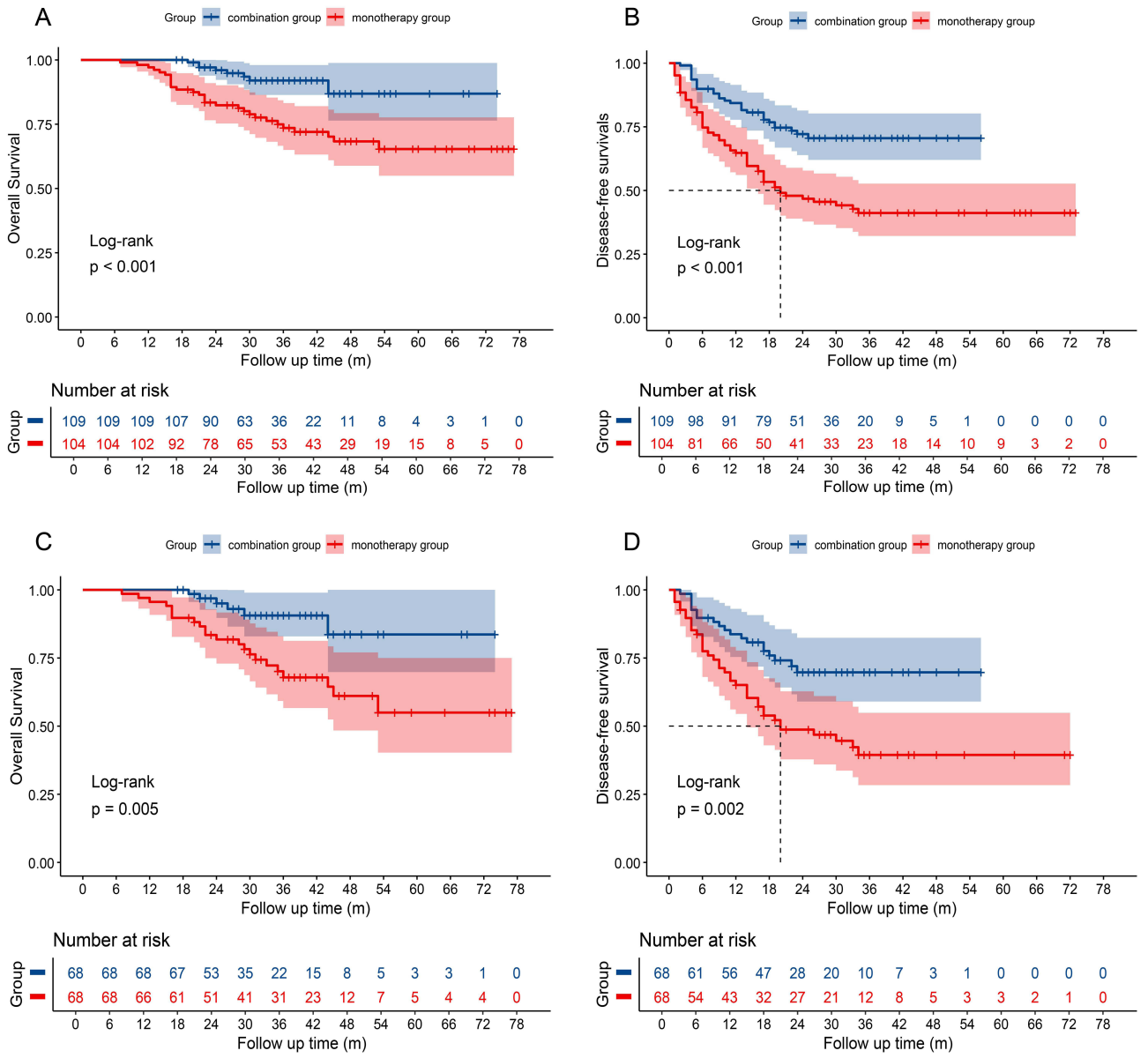


Figure 3 Kaplan-Meier survival curves comparing OS and DFS among patients who underwent different conversion regimens before (**A** and **B**) and after PSM (**C** and **D**). Combination group (TACE combined with Lenvatinib plus PD-1 inhibitor) had significantly longer OS and better DFS than monotherapy group (TACE monotherapy)(all P < 0.05).
Abbreviations: OS, overall survival; DFS, disease-free survival; PSM, propensity score matching; TACE, transcatheter arterial chemoembolization; PD-1 inhibitors, programmed death-1 inhibitors.

Univariate and Multivariate Analyses

As shown in Supplementary Table S3, univariate analysis revealed that prognostic factors (*p<0.05*), including conversion regimen, HBV infection and TACE type, were associated with OS. However, in the multivariate analysis only the conversion regimen (HR 3.05, 95% CI: 1.33–6.97; *p=0.008*) was an independent prognostic factor.

Univariate analyses revealed that the conversion regimen, TACE type, and tumour number were associated with postoperative DFS. In the multivariate analysis, the conversion regime (HR 2.46, 95% CI: 1.49–4.08, *p<0.001*) and tumour number (HR 2.06, 95% CI: 1.28–3.33, *p=0.003*) were independent prognostic factors.

Subgroup Analysis

Subgroup analyses were performed to identify populations with potentially improved 2-year disease-free survival, as early recurrence following curative HCC resection typically manifests within the initial two years. The forest plot analysis (Figure 4)

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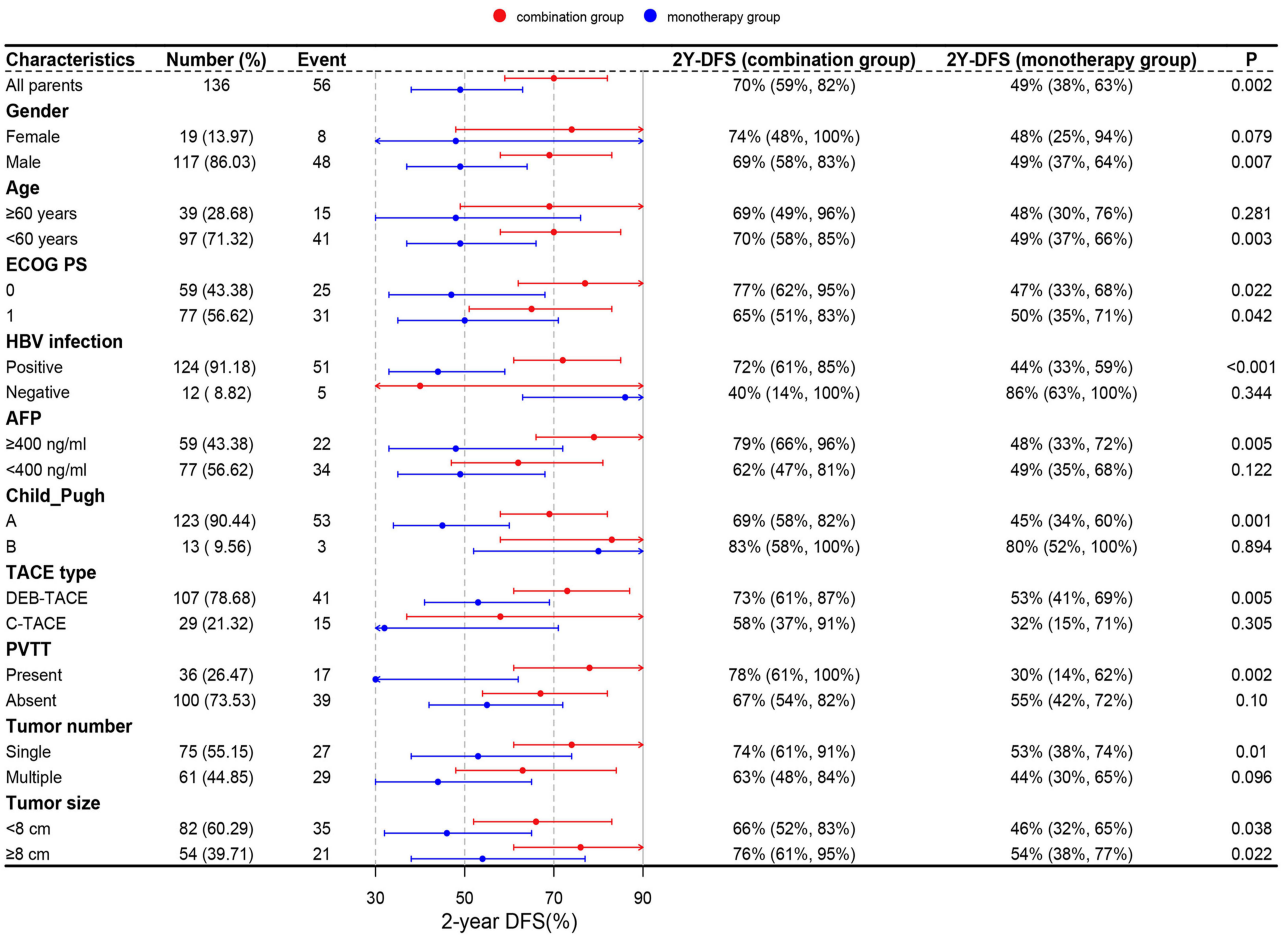

Figure 4 Forest plots for subgroup analysis.

Abbreviations: DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HBV infection, Hepatitis B virus infection; AFP, alpha-fetoprotein; C-TACE, conventional transcatheter arterial chemoembolization; DEB-TACE, drug-eluting bead transcatheter arterial chemoembolization; PVTT, portal vein tumor thrombus.

demonstrated significant survival advantages for patients with uHCC who received the combination therapy of TACE plus TKIs and PD-1 inhibitor conversion treatment across multiple subgroups. Subgroup analysis revealed significant survival advantages across multiple patient characteristics: male gender ($p=0.007$), age <60 years ($p=0.003$), ECOG performance status 0–1 ($p=0.022$, $p=0.042$), and HBV etiology ($p<0.001$). The survival benefit was also evident in patients receiving DEB-TACE ($p=0.005$), those with Child-Pugh A status ($p=0.001$), AFP ≥400 ng/mL ($p=0.005$), PVTT ($p=0.002$), solitary tumors ($p=0.01$), and regardless of tumor size (≥8 cm: $p=0.038$; <8 cm: $p=0.022$).

Discussion

Accumulating clinical evidence has demonstrated the therapeutic efficacy of combination regimens as conversion therapy for uHCC. Multiple studies have elucidated the remarkable efficacy and favorable safety profile of integrated therapeutic approaches combining TACE, TKIs, and a PD-1 inhibitor in the management of uHCC.[14,19] Nevertheless, there remains a paucity of comprehensive data regarding perioperative safety profiles, long-term outcomes, and prognostic determinants in patients who undergo LR following combination therapy, particularly when compared to those receiving TACE monotherapy in the preoperative setting. Our study demonstrated that among patients who attained resectable status following conversion therapy, the preoperative combination therapy yielded superior outcomes, characterized by significantly prolonged DFS and OS when compared to preoperative TACE monotherapy. Notably, this enhanced efficacy was achieved without an increase in the incidence of severe postoperative complications or an extended length of hospital stay. However, the combination therapy group reported a higher incidence of adverse events during the conversion period, including rash (19.12% vs 0%, $p<0.01$) and

hand-foot skin reactions (25.0% vs 0%, *p<0.01*). These adverse events were likely associated with the regimen comprising Lenvatinib and a PD-1 inhibitor. Additionally, there was an observed increase in blood loss (*p=0.032*) during LR in the combination group, which may be attributable to bone marrow suppression induced by the preoperative chemotherapy agents, as well as the antiangiogenic properties of TKIs.[20]

Even with significant advances in monitoring techniques and therapeutic interventions, HCC remains associated with poor clinical outcomes, primarily attributed to its high early recurrence rates, which persist even after successful surgical resection.[21] The study demonstrated that postoperative recurrence remains a significant challenge in achieving favorable oncologic outcomes following LR, particularly early recurrence. In the monotherapy group, 37 patients (54.1%) experienced tumor recurrence, with early recurrence accounting for 51.3% of these cases. In contrast, the combination group demonstrated a significantly lower early recurrence rate of 33.5%. This findings highlight the positive effect of preoperative combination therapy in improving patient prognosis compared to monotherapy alone. Early recurrence primarily stems from two sources: micrometastases may occur in hepatic parenchyma beyond the therapeutic margin or persist as residual tumor foci in the primary tumor bed.[22] Previous studies have shown that histopathological analyses of post-resection HCC specimens reveal MVI detection rates of approximately 20–60%, which can be detected even in early-stage HCC.[23,24] This is particularly significant as over 60% of all HCC recurrences are early recurrences closely associated with the MVI presence.[25] In our present study, the combination group demonstrated superior outcomes, evidenced by higher rates of both preoperative radiological and postoperative pCR. Notably, the MVI rate (14.71% vs 29.41, *p=0.039*) was significantly lower in the combination group. Yang et al's research identified preoperative TACE inducing tumor necrosis <60% as an independent risk factor for both MVI (HR 6.076) and early recurrence (HR 1.428), while tumor necrosis >90% was an independent protective factor against MVI (HR 0.144) and early recurrence (HR 0.742).[25] Moreover, Yang et al's multivariate analysis revealed that the degree of tumor necrosis following TACE treatment exhibited a significant correlation with the incidence of MVI, rather than the number of TACE sessions.[25] Therefore, in our study, the combination group had a lower MVI rate may due to the greater tumor necrosis (pCR, 36.76% vs 11.76, *p<0.001*) induced by the preoperative combination therapy. There may be several reasons why preoperative combination therapy showed a better tumor response. First, TACE therapy induces a hypoxic environment within the tumor tissue, leading to the upregulation of VEGF expression and increased tumor angiogenesis.[26] Lenvatinib as an antiangiogenic multikinase inhibitor, can enhance the effectiveness of TACE through combating hypoxia-induced angiogenesis by targeting VEGF 1–3, FGFR 1–4, KIT, PDGFRα, and RET;[27,28] reducing tumor microvessel density, tumor interstitial pressure, and vascular permeability; and normalizing the tumor vasculature, thereby enhancing the therapeutic effect of TACE.[29] Second, the release of large amounts of antigens from necrotic tumor cells by TACE with Lenvatinib improves the antitumour immune response, which can enhance the antitumor effects of PD-1 inhibitors.[30] Third, Lenvatinib combined with PD-1 inhibitors therapy can improve antitumor immunity by synergistically regulating the tumor immune microenvironment and promoting T-cell infiltration into the tumor.[31]

Interestingly, the two groups had significantly different 2-year DFS rates (73% vs 53%, *p=0.005*) in the DEB-TACE subgroup analysis but not in the C-TACE subgroup analysis. Drug-eluting beads combine the dual functions of embolic agent and drug carrier to accurately deliver chemotherapeutic drugs to tumor tissue in a controlled and sustained manner.[32] These microspheres extends the duration of drug release within the tumor while promoting an increase in local drug concentration, enhancing the degree of tumor ischemic necrosis compared to lipiodol.[33] Furthermore, tumors treated with C-TACE demonstrate diminished immune cell infiltration, whereas DEB-TACE can provoke moderate intratumoral and pronounced peritumoral immune cell infiltration have been confirmed by previous study.[34] Therefore, DEB-TACE promotes better tumor treatment response and may also enhance the efficacy of systemic therapy in conversion therapy. Subgroup analysis also revealed that preoperative combination therapy significantly improved 2-year DFS rates in high tumor burden patients, including those with AFP ≥400 ng/mL (79% vs 48%, *p=0.005*), PVTT (78% vs 30%, *p=0.002*), and tumor size ≥8 cm (76% vs 54%, *p=0.022*). In contrast to other subgroups, patients with multinodular HCC showed no significant improvement in 2-year DFS rates with preoperative combination therapy (63% vs 44%, *p=0.096*). Multivariate analysis further supported this observation, identifying multiple tumor nodules as an independent adverse prognostic factor for DFS (HR 2.06). This result aligned with our previous observations that patients with multifocal HCC derive limited clinical benefit from either TACE monotherapy or combination therapy with TACE

plus Lenvatinib.[35,36] The underlying mechanisms may be attributed to several factors. The conventional lipiodol-based TACE emulsion is inherently unstable and can be easily washed away, reducing the sustained delivery of the therapeutic agent to the tumor.[37] This phenomenon is particularly evident in cases of multifocal HCC.[38] In contrast, DEB-TACE has been shown to improve the stability of the chemotherapeutic drugs.[36] However, since the drug-eluting beads cannot pass through the hepatic sinusoids, a small portion of the tumor supplied by the portal vein may still remain unaffected, leading to tumor residue.[39] Therefore, as a local treatment method, TACE may not result in complete necrosis for every tumor focus in HCC patients with multifocal. Despite the application of systemic therapies, intratumoral heterogeneity remains a significant challenge, contributing to the limited efficacy of current treatments for multifocal HCC. Furthermore, only a subset of tumors appears to be effectively managed by immunosurveillance, while many others have developed various mechanisms to evade immune detection, resulting in a poorer prognosis.[40,41]

This study has several limitations that should be acknowledged. First, owing to its retrospective nature and lack of randomization, inherent selection bias was difficult to avoid, although PSM was performed to balance the baseline characteristics. Second, the analysis included only patients who underwent LR after conversion therapy, the limited sample size and insufficient follow-up duration constrained both statistical analysis and long-term conclusions. Finally, considering that nearly all patients in this study had an HBV background, these results may not be generalizable to all HCC patients. In future, multicentre prospective randomized controlled studies need to be performed to evaluate the potential benefits of combination conversion therapy in uHCC patients.

In conclusion, compared with TACE monotherapy, TACE combined with Lenvatinib-PD-1 inhibitor could improve the long-term survival outcomes of uHCC patients undergoing LR after conversion success. In addition, LR is an effective, safe and feasible treatment option after successful conversion for uHCC.

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University and complied with the Declaration of Helsinki 1975 (Ethical number: II2023-027). Informed consent was waived due to the retrospective nature of the study, with assurance that data was either anonymized or kept confidential.

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