Original Article

Real-world effectiveness and safety of TACE combined with lenvatinib plus immune checkpoint inhibitors in patients with BCLC-B stage hepatocellular carcinoma

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Background: More effective treatment strategies need to be established for patients with Barcelona Clinic Liver Cancer (BCLC)-B stage hepatocellular carcinoma (HCC). The combination of transarterial chemoembolization (TACE) with lenvatinib and immune checkpoint inhibitors (ICIs) has been shown to have potential in the treatment of unresectable HCC. However, the real-world data on the use of this combined therapy in patients with BCLC-B stage HCC are limited. Therefore, this study aimed to validate the efficacy and safety of the combination of TACE with lenvatinib plus ICIs in the treatment of patients with BCLC-B stage HCC in a real-world setting.

Methods: A total of 121 patients who were newly diagnosed with BCLC-B stage HCC were enrolled in this study. Of these patients, 52 received treatment with TACE combined with lenvatinib plus ICIs (the combination group), and 69 received TACE alone (the monotherapy group). Propensity score matching (PSM) was used to reduce potential biases. The primary endpoint of the study was overall survival (OS), while the secondary endpoints were progression-free survival (PFS), the objective response rate (ORR), and the disease control rate (DCR). Adverse events (AEs) were also recorded and evaluated.

Results: The OS of the combination group was longer than that of the monotherapy group (median OS: 30.9 *vs.* 13.0 months, P<0.001), as was the PFS (median PFS: 12.3 *vs.* 8.3 months, P=0.19). The ORR of the combination group was higher than that of the monotherapy group (61.5% *vs.* 33.3%, P=0.002), as was the DCR (92.3% *vs.* 76.8%, P=0.02). After PSM, the OS of the combination group was longer than that of the monotherapy group (median OS: not reached *vs.* 9.8 months, P<0.001), as was the PFS (median PFS: 13.4 *vs.* 7.6 months, P=0.28). The ORR of the combination group was higher than that of the monotherapy group (59.0% *vs.* 30.8%, P=0.01), as was the DCR (89.7% *vs.* 74.4%, P=0.08). In the multivariate Cox regression analysis, combination therapy was associated with a better OS (hazard ratio =0.36, 95% confidence interval: 0.20–0.64, P<0.001). In terms of the AEs, 8 of 52 patients (15.4%) in the combination group, and 4 of 69 patients (5.8%) in the monotherapy group experienced grade 3 or 4 AEs (P=0.08), but no grade 5 AEs were observed.

Conclusions: The combination of TACE with lenvatinib plus ICIs showed excellent efficacy in the treatment of patients with BCLC-B stage HCC, and the safety profile was acceptable.

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Keywords: Hepatocellular carcinoma (HCC); lenvatinib; immune checkpoint inhibitors (ICIs); transarterial chemoembolization (TACE); overall survival (OS)

Submitted Jan 09, 2025. Accepted for publication Feb 16, 2025. Published online Feb 26, 2025.
doi: 10.21037/jgo-2025-33
View this article at: https://dx.doi.org/10.21037/jgo-2025-33

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors in the world, and is also the third most common cause of cancer-related deaths globally (1). Surgery is considered the most effective treatment for HCC; however, due to the lack of obvious early symptoms and signs of the disease, most patients are diagnosed at the middle or late stage of the disease, losing the opportunity for radical surgery; thus, the overall treatment effect and prognosis of HCC patients remain poor (2,3).

Under the Barcelona Clinic Liver Cancer (BCLC) staging system, most HCC patients at stage BCLC-A are treated with surgery, while those at stage BCLC-C are treated with systemic therapy (4). For stage BCLC-B HCC patients, clinical guidelines widely recommend transarterial chemoembolization (TACE) as the standard treatment method (5-7). However, controversy continues as to whether BCLC-B stage HCC patients should undergo surgery (4,8). Some findings suggest that BCLC-B stage HCC patients have a better prognosis with surgical treatment than interventional and systemic therapies, but there is still a lack of real-world evidence on this issue (9,10).

TACE, as an effective local treatment method, delivers chemotherapeutic drugs to the blood vessels supplying the tumor, and embolizes the tumor-feeding arteries, which can lead to tumor necrosis, thereby reducing the tumor burden and controlling tumor progression. However, TACE and surgical treatment do not benefit all BCLC-B stage HCC patients, whose overall treatment effect and prognosis are not ideal, which has prompted clinicians to search for new treatment methods.

In recent years, studies have shown that the combination of TACE local treatment with systemic therapy is effective in improving the clinical outcomes of advanced HCC patients, and in increasing patient survival rates. The results of the Transcatheter Arterial Chemoembolization Therapy In Combination With Sorafenib (TACTICS) trial showed that the combination of TACE with sorafenib improved the progression-free survival (PFS) and overall survival (OS) of patients with unresectable hepatocellular carcinoma (uHCC) (11). However, not all relevant studies have reached positive conclusions. A global multicenter, randomized, placebo-controlled trial [Sorafenib or Placebo in Combination With TACE for Intermediate Stage Hepatocellular Carcinoma (SPACE)] found that combination therapy (TACE plus sorafenib) only extended the time-to-tumor progression (TTP) by 3 days compared to TACE alone, suggesting that TACE plus

Highlight box

Key findings

- In real-world settings, the combination of transarterial chemoembolization (TACE) with lenvatinib plus immune checkpoint inhibitors (ICIs) has been shown to have excellent efficacy and manageable safety in the treatment of patients with Barcelona Clinic Liver Cancer (BCLC)-B stage hepatocellular carcinoma (HCC).

What is known, and what is new?

- TACE is the standard treatment for BCLC-B stage HCC, but its efficacy is limited; combining TACE with systemic therapy can enhance the treatment outcomes for unresectable HCC.
- Patients with BCLC-B stage HCC who received the combination therapy of TACE with lenvatinib plus ICIs experienced significant clinical benefits. The median overall survival (OS) of the combination therapy group was significantly higher than that of the TACE monotherapy group (30.9 *vs.* 13.0 months). The objective response rate (ORR) and disease control rate of the combination therapy group were 61.5% and 92.3%, respectively, and the combination therapy was associated with good safety. Additionally, prealbumin <140 mg/L and alkaline phosphatase ≥90 U/L were identified as an independent risk factor related to OS.

What is the implication, and what should change now?

- The combination of TACE with lenvatinib plus ICIs improved the survival prognosis of patients with BCLC-B stage HCC, and thus could become a new standard option for the treatment of BCLC-B stage HCC.
- Combination therapy can serve as a preparation for other treatments, including surgery, as it has the ability to achieve favorable ORRs without causing severe impairment to the liver function of patients.

sorafenib does not provide clinically meaningful benefits for intermediate stage HCC (12). Despite this, there are still studies that support the positive effects of TACE combination therapy. In the multi-center phase-III TACE With Lenvatinib Versus Lenvatinib Alone in First-line Treatment of Advanced HCC (LAUNCH) study conducted in China, the median OS and PFS of patients treated with the combination of TACE and lenvatinib was longer and the objective response rate (ORR) was higher than those of patients treated with TACE alone, which indicated that the combination therapy can improve clinical prognosis (13).

A study has shown that lenvatinib and tislelizumab demonstrate good efficacy and acceptable safety in uHCC (14). Thus, research needs to be conducted on the combination of TACE with lenvatinib targeted therapy plus immunotherapy for HCC. A single-arm clinical trial showed that the combination of lenvatinib with sintilimab plus TACE significantly improved the survival prognosis of patients with advanced HCC (15). Recently, some retrospective studies have also provided clinical evidence that the combination of TACE with lenvatinib and immune checkpoint inhibitors (ICIs) is more effective in treating uHCC than the combination of TACE with lenvatinib alone (16-19). However, currently, there are limited data on this treatment regimen for BCLC-B stage HCC patients, and there is a lack of targeted research in this area. Therefore, this study aimed to evaluate the efficacy and safety of the combination of TACE with lenvatinib plus ICIs in BCLC-B stage HCC patients. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-2025-33/rc).

Methods

Study population

This study reviewed the data of patients who were newly diagnosed with BCLC-B stage HCC and received either TACE combined with lenvatinib plus ICIs treatment or TACE alone at the Guangxi Medical University Cancer Hospital from January 2019 to April 2023. The diagnosis of HCC was primarily based on the analysis of images from contrast-enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI); a tumor ≥2 cm with one typical radiological feature of HCC was sufficient for the clinical diagnosis, regardless of whether alpha-fetoprotein (AFP) levels were elevated. The staging of HCC was based on the BCLC staging system (4,7).

To be eligible for inclusion in this study, the patients had to meet the following inclusion criteria: (I) have been newly diagnosed with BCLC-B stage HCC; (II) be aged 18 years or older; (III) liver function Child-Pugh score A or B; (IV) have an Eastern Cooperative Oncology Group performance status of 0–1; and (V) have received either TACE combined with lenvatinib plus ICIs treatment or TACE alone (the combined treatment was defined as TACE followed by the first lenvatinib treatment within no more than 3 days, and within no more than 1 week for ICIs treatment, and lenvatinib for more than 1 month); (VI) have at least one measurable lesion according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria (20); and (VII) have undergone enhanced CT/MRI assessments within 1 month before the first treatment, and every 2–3 months after the treatment. Patients were excluded from the study if they met any of the following exclusion criteria: (I) had a history of other malignant tumors; (II) had incomplete clinical or follow-up data; and/or (III) had recurrent HCC. *Figure 1* illustrates the flowchart of the patient enrollment strategy.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by board of Ethics Committee of Guangxi Medical University Cancer Hospital (No. LW2024119) and informed consent was taken from all the patients.

Procedures

The TACE treatment was implemented before the administration of the systemic therapy. The TACE procedure was performed under local anesthesia with the right femoral artery selected as the puncture site. The Seldinger technique was used to puncture and insert a 5F arterial sheath, after which a catheter was inserted into the celiac trunk or superior mesenteric artery for arteriography. A microcatheter was then selectively advanced into the arterial branches supplying the tumor, where chemotherapeutic agents, such as raltitrexed, oxaliplatin, or pirarubicin, were infused. Subsequently, a mixture of iodized oil emulsion and polyvinyl alcohol embolic microspheres was injected to embolize the tumor-supplying vessels. The specific dosages of the chemotherapeutic agents and embolic materials were determined based on a comprehensive analysis of the patient's liver function, body surface area, and tumor size. Postoperatively, routine follow-up was conducted, and if residual tumor activity was detected or new lesions appeared, TACE was repeated as needed. The success of

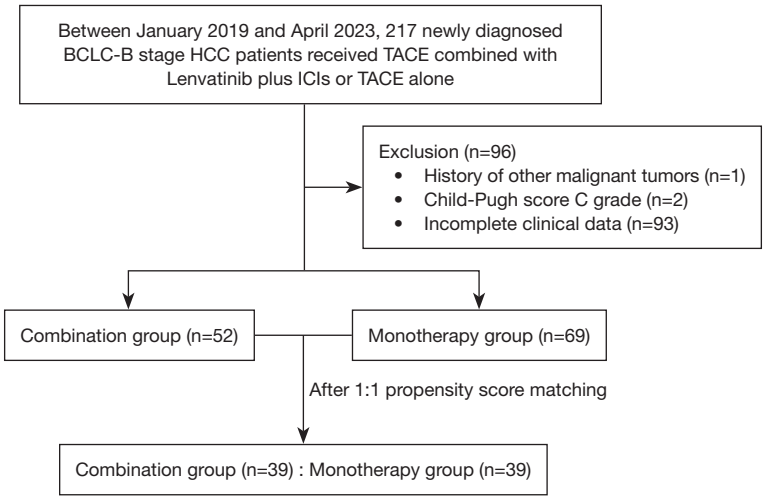

Figure 1 Patient selection flowchart. BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; ICIs, immune checkpoint inhibitors; TACE, transarterial chemoembolization.

TACE was defined as a reduction in or the cessation of blood flow in the tumor-supplying arteries.

Patient received lenvatinib treatment within 3 days after the TACE. the drug dosage was determined based on body weight. Each patient took lenvatinib orally once a day, at a dose of 8 mg (body weight <60 kg) or 12 mg (body weight ≥60 kg). The ICIs used in the study included tislelizumab or camrelizumab, which were administered intravenously once every 3 weeks at a dose of 200 mg each time. Each patient received only one type of ICIs drug at a time. Treatment interruptions, dose adjustments, or changes in medication were based on tumor progression, the occurrence of intolerable adverse reactions, or the patient's own choice.

Outcomes and assessment of adverse events

The primary endpoint of the study was OS, and the secondary endpoints were PFS, the ORR, and the disease control rate (DCR). OS was defined as the time from the start of initial treatment to death from any cause. Tumor response was assessed according to the mRECIST criteria, and was classified into progressive disease (PD), stable disease (SD), partial response (PR), and complete response (CR). PFS was defined as the time from the start of initial treatment to the first occurrence of PD or death, whichever occurred first. The ORR was defined as the proportion of patients who achieved a CR or PR. The DCR was defined as the proportion of patients who achieve a CR, PR, or SD.

Data on adverse events (AEs) related to treatment were extracted from outpatient visit records or electronic medical records, and were documented and evaluated according to the Common Terminology Criteria for Adverse Events (version 5.0), established by the National Cancer Institute.

Statistical analysis

The tools used for the data analysis were SPSS (version 27.0, IBM) and R statistical software (version 4.4.0, R Foundation for Statistical Computing). A P value of less than 0.05 was considered statistically significant.

To reduce potential bias, a propensity score matching (PSM) analysis was performed, using the nearest neighbor matching method to match the two groups of patients at a ratio of 1:1. The preplanned matching variables included gender, age, cirrhosis, Child-Pugh score, hepatitis B surface antigen, hepatitis C virus antibody, long-term alcohol consumption, largest tumor diameter, tumor number, confined to hemihepatic lobe, AFP, total bilirubin (TBIL), alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), albumin (ALB), prealbumin (PALB), prothrombin time (PT), platelet (PLT) count, number of TACEs, and TACE technique.

The continuous variables were converted into categorical variables. The categorical variables were expressed as the count and percentage, and the distribution of the categorical variables was compared using Pearson's Chi-squared test or Fisher's exact test. The Kaplan-Meier method was used to evaluate the OS and PFS of the two groups of patients, and the log-rank test was used to

calculate the differences between the survival curves. A Cox proportional hazards regression model was used for the univariate and multivariate analyses to assess the factors related to OS in BCLC-B stage HCC patients. Variables with a P value <0.05 in the univariate analysis were selected for inclusion in the stepwise forward multivariate analysis. Subgroup analyses were conducted for predefined relevant clinical variables to compare OS between the two groups of patients.

Results

Patient demographic and baseline clinical characteristics

During the study period from January 2019 to April 2023, a total of 121 patients were enrolled in the study according to the inclusion and exclusion criteria. Among the 121 patients, 52 received TACE combined with lenvatinib plus ICIs [camrelizumab (n=35) and tislelizumab (n=17)] treatment, and 69 received TACE alone. The median number of TACE treatments in both the combination group and the monotherapy group was 2. The median age of the study population was 58 years. The majority of patients in the study were male, with 47 (90.4%) male patients in the combination group and 60 (87.0%) in the monotherapy treatment group. Almost all patients had hepatitis B, while patients with hepatitis C antibody positivity and long-term alcohol consumption were few. Every hepatitis B patient received entecavir or tenofovir treatment. A total of 105 (86.8%) patients in both groups beyond the up-to-7 criteria, and 91 (75.2%) patients had tumors not confined to hemihepatic lobe, indicating a heavy tumor burden and a scattered distribution of tumors in the study population. After PSM, 39 patients were successfully matched in the combination group and the monotherapy group, respectively. There were no significant differences in the baseline characteristics between the two groups before and after PSM (*Table 1*).

Treatment efficacy

The study follow-up ended on May 10, 2024, and the patients had a median follow-up time of 25.7 months. A total of 66 patients died during the study period, of whom 15 were from the combination group and 51 were from the monotherapy group. The median OS of the entire cohort was 21.5 months [95% confidence interval (CI): 15.7–34.1]. The OS of the patients in the combination group was significantly longer than that in the monotherapy group [median OS: 30.9 months (95% CI: 24.6–not reached) *vs.* 13.0 months (95% CI: 8.7–21.5), P<0.001; *Figure 2A*]. For the combination group, the 1-year OS rate was 81.7%, the 2-year OS rate was 70.0%, and the 3-year OS rate was 48.4%. For the monotherapy group, the 1-year OS rate was 51.6%, the 2-year OS rate was 36.2%, and the 3-year OS rate was 25.4%. Based on the mRECIST, the PFS for the entire cohort was 11.1 months (95% CI: 7.3–15.6). The PFS of the combination group was longer than that of the monotherapy group [median PFS: 12.3 months (95% CI: 10.0–25.3) *vs.* 8.3 months (95% CI: 4.1–21.3), P=0.19; *Figure 2B*].

After PSM, a total of 39 patients died during the study period, of whom 11 were from the combination group and 28 were from the monotherapy group. The OS and PFS of the entire cohort were 21.5 months (95% CI: 14.7–not reached) and 11.5 months (95% CI: 5.6–21.8), respectively. Similar to the other results, the OS of the combination group was significantly better than that of the monotherapy group [median OS: not reached (95% CI: 24.6–not reached) *vs.* 9.8 months (95% CI: 8.7–27.0), P<0.001; *Figure 3A*]. For the combination group, the 1-year OS rate was 80.8%, the 2-year OS rate was 66.4%, and the 3-year OS rate was 59.8%. For the monotherapy group, the 1-year OS rate was 48.7%, the 2-year OS rate was 32.2%, and the 3-year OS rate was 19.3%. For the combination group, the median PFS was 13.4 months (95% CI: 7.3–not reached), while for the monotherapy group, the median PFS was 7.6 months (95% CI: 3.4–not reached). The PFS of the combination group was longer than that of the monotherapy group, but the difference was not statistically significant (P=0.28; *Figure 3B*).

Additionally, the ORR and DCR of the combination group were both higher than those of the monotherapy group (61.5% *vs.* 33.3%, P=0.002; 92.3% *vs.* 76.8%, P=0.02). After PSM, the ORR and DCR of the combination group were also increased compared to those of the monotherapy group (59.0% *vs.* 30.8%, P=0.01; 89.7% *vs.* 74.4%, P=0.08). The best tumor response based on the mRECIST is shown in *Table 2*.

A Cox regression analysis was performed on the two groups of patients (*Table 3*). The multivariate analysis showed that TACE combined with lenvatinib plus ICIs treatment was an independent protective factor for OS [hazard ratio (HR) =0.36, 95% CI: 0.20–0.64, P<0.001], while PALB <140 mg/L (HR =2.85, 95% CI: 1.52–5.35, P=0.001) and ALP ≥90 U/L (HR =1.97, 95% CI: 1.02–3.83,

Table 1 Baseline demographic and clinical characteristics of the patients

Characteristics	Before PSM			After PSM		
	Monotherapy group (N=69)	Combination group (N=52)	P	Monotherapy group (N=39)	Combination group (N=39)	P
Gender			0.56			0.71
Female	9 (13.0)	5 (9.6)		5 (12.8)	3 (7.7)	
Male	60 (87.0)	47 (90.4)		34 (87.2)	36 (92.3)	
Age, years			0.06			>0.99
<55	23 (33.3)	26 (50.0)		17 (43.6)	17 (43.6)	
≥55	46 (66.7)	26 (50.0)		22 (56.4)	22 (56.4)	
Cirrhosis			0.46			0.77
No	11 (15.9)	11 (21.2)		7 (17.9)	8 (20.5)	
Yes	58 (84.1)	41 (78.8)		32 (82.1)	31 (79.5)	
Child-Pugh score			0.08			>0.99
A	54 (78.3)	47 (90.4)		34 (87.2)	34 (87.2)	
B	15 (21.7)	5 (9.6)		5 (12.8)	5 (12.8)	
Hepatitis B surface antigen			0.76			>0.99
Negative	8 (11.6)	7 (13.5)		5 (12.8)	5 (12.8)	
Positive	61 (88.4)	45 (86.5)		34 (87.2)	34 (87.2)	
Hepatitis C virus antibody			>0.99			>0.99
Negative	67 (97.1)	50 (96.2)		37 (94.9)	38 (97.4)	
Positive	2 (2.9)	2 (3.8)		2 (5.1)	1 (2.6)	
Long-term alcohol consumption			0.99			0.53
No	57 (82.6)	43 (82.7)		34 (87.2)	32 (82.1)	
Yes	12 (17.4)	9 (17.3)		5 (12.8)	7 (17.9)	
Largest tumor diameter, cm			0.65			0.59
<5	17 (24.6)	11 (21.2)		8 (20.5)	10 (25.6)	
≥5	52 (75.4)	41 (78.8)		31 (79.5)	29 (74.4)	
Tumor number			0.66			0.65
<4	32 (46.4)	22 (42.3)		18 (46.2)	16 (41.0)	
≥4	37 (53.6)	30 (57.7)		21 (53.8)	23 (59.0)	
Confined to hemihepatic lobe			0.22			0.76
No	49 (71.0)	42 (80.8)		32 (82.1)	33 (84.6)	
Yes	20 (29.0)	10 (19.2)		7 (17.9)	6 (15.4)	
Beyond up-to-7 criteria			0.31			>0.99
No	11 (15.9)	5 (9.6)		5 (12.8)	4 (10.3)	
Yes	58 (84.1)	47 (90.4)		34 (87.2)	35 (89.7)	
AFP, ng/mL			0.73			0.48
<400	39 (56.5)	31 (59.6)		26 (66.7)	23 (59.0)	
≥400	30 (43.5)	21 (40.4)		13 (33.3)	16 (41.0)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Before PSM			After PSM		
	Monotherapy group (N=69)	Combination group (N=52)	P	Monotherapy group (N=39)	Combination group (N=39)	P
TBIL, μmol/L			0.40			>0.99
<17.1	45 (65.2)	30 (57.7)		23 (59.0)	23 (59.0)	
≥17.1	24 (34.8)	22 (42.3)		16 (41.0)	16 (41.0)	
ALT, U/L			0.94			0.65
<40	31 (44.9)	23 (44.2)		17 (43.6)	15 (38.5)	
≥40	38 (55.1)	29 (55.8)		22 (56.4)	24 (61.5)	
AST, U/L			0.86			>0.99
<40	15 (21.7)	12 (23.1)		10 (25.6)	10 (25.6)	
≥40	54 (78.3)	40 (76.9)		29 (74.4)	29 (74.4)	
ALP, U/L			0.25			>0.99
<90	21(30.4)	11 (21.2)		9 (23.1)	9 (23.1)	
≥90	48(69.6)	41 (78.8)		30 (76.9)	30 (76.9)	
ALB, g/L			0.08			0.33
<30	15 (21.7)	5 (9.6)		7 (17.9)	4 (10.3)	
≥30	54 (78.3)	47 (90.4)		32 (82.1)	35 (89.7)	
PALB, mg/L			0.28			0.34
<140	25 (36.2)	14 (26.9)		15 (38.5)	11 (28.2)	
≥140	44 (63.8)	38 (73.1)		24 (61.5)	28 (71.8)	
PT, s			0.48			0.82
≤13	38 (55.1)	32 (61.5)		22 (56.4)	23 (59.0)	
>13	31 (44.9)	20 (38.5)		17 (43.6)	16 (41.0)	
PLT, 10^9/L			0.67			0.26
<100	10 (14.5)	9 (17.3)		10 (25.6)	6 (15.4)	
≥100	59 (85.5)	43 (82.7)		29 (74.4)	33 (84.6)	
Number of TACEs			0.51			>0.99
≤3	60 (87.0)	43 (82.7)		36 (92.3)	35 (89.7)	
>3	9 (13.0)	9 (17.3)		3 (7.7)	4 (10.3)	
TACE technique			0.18			>0.99
c-TACE	54 (78.3)	35 (67.3)		29 (74.4)	29 (74.4)	
D-TACE	15 (21.7)	17 (32.7)		10 (25.6)	10 (25.6)	

Unless otherwise indicated, the data are expressed as the number (%). AFP, alpha-fetoprotein; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; c-TACE, conventional transarterial chemoembolization; D-TACE, drug-eluting beads transarterial chemoembolization; PALB, prealbumin; PLT, platelet; PSM, propensity score matching; PT, prothrombin time; TACE, transarterial chemoembolization; TBIL, total bilirubin.

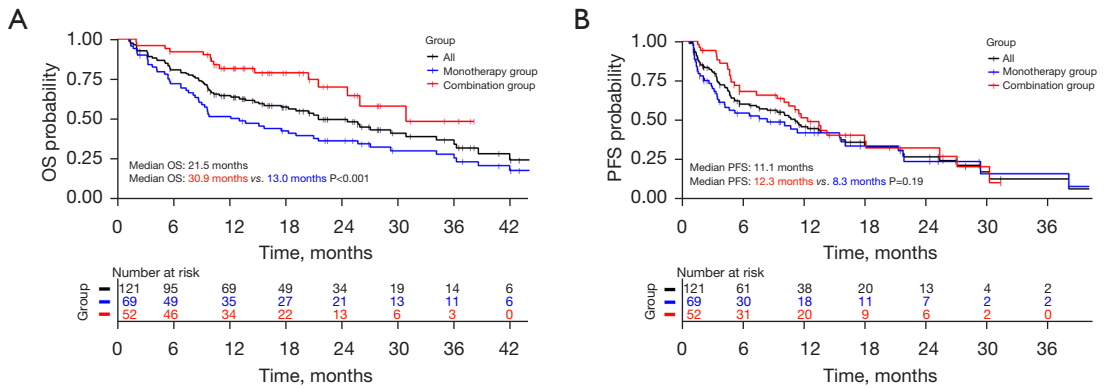

Figure 2 Kaplan-Meier analysis of OS and PFS before PSM. (A) OS for the entire cohort, combination group, and monotherapy group; (B) PFS for the entire cohort, combination group, and monotherapy group. OS, overall survival; PFS, progression-free survival; PSM, propensity score matching.

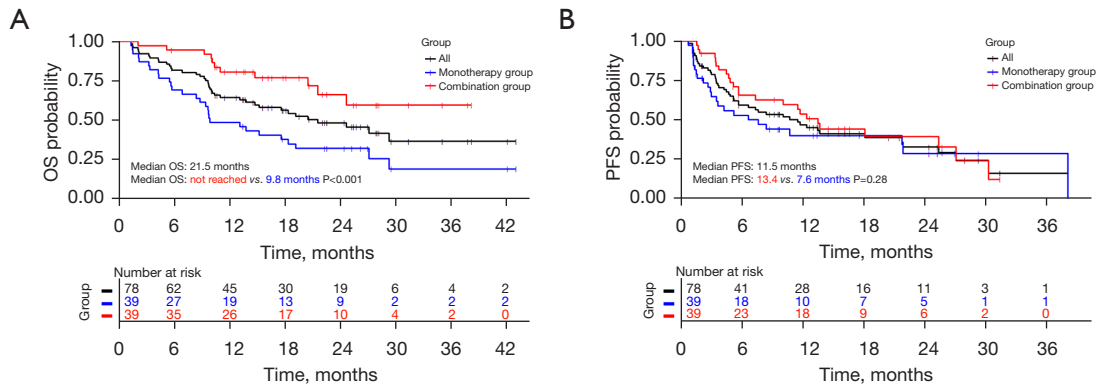

Figure 3 Kaplan-Meier analysis of OS and PFS after PSM. (A) OS for the entire cohort, combination group, and monotherapy group; (B) PFS for the entire cohort, combination group, and monotherapy group. OS, overall survival; PFS, progression-free survival; PSM, propensity score matching.

Table 2 Summary of best response based on the mRECIST

Tumor response	Before PSM			After PSM		
	Monotherapy group (N=69)	Combination group (N=52)	P	Monotherapy group (N=39)	Combination group (N=39)	P
CR	3 (4.3)	6 (11.5)	0.17	3 (7.7)	4 (10.3)	>0.99
PR	20 (29.0)	26 (50.0)	0.02	9 (23.1)	19 (48.7)	0.02
SD	30 (43.5)	16 (30.8)	0.15	17 (43.6)	12 (30.8)	0.24
PD	16 (23.2)	4 (7.7)	0.02	10 (25.6)	4 (10.3)	0.08
ORR	23 (33.3)	32 (61.5)	0.002	12 (30.8)	23 (59.0)	0.01
DCR	53 (76.8)	48 (92.3)	0.02	29 (74.4)	35 (89.7)	0.08

Unless otherwise indicated, the data are expressed as the number (%). CR, complete response; DCR, disease control rate; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; PD, progressive disease; PR, partial response; PSM, propensity score matching; SD, stable disease.

Table 3 Univariate and multivariate analyses of prognostic factors for OS

Characteristics	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Gender (female/male)	1.14 (0.54–2.39)	0.73		
Age (<55/≥55 years)	0.97 (0.59–1.60)	0.92		
Cirrhosis (no/yes)	2.43 (1.05–5.64)	0.04	1.65 (0.68–4.06)	0.27
Child-Pugh score (A/B)	2.14 (1.21–3.78)	0.009	0.70 (0.35–1.41)	0.32
Hepatitis B surface antigen (negative/positive)	1.11 (0.51–2.43)	0.80		
Hepatitis C virus antibody (negative/positive)	1.18 (0.29–4.88)	0.81		
Long-term alcohol consumption (no/yes)	1.20 (0.65–2.20)	0.56		
Largest tumor diameter (<5/≥5 cm)	0.84 (0.49–1.45)	0.54		
Tumor number (<4/≥4)	1.30 (0.79–2.13)	0.30		
Confined to hemihepatic lobe (no/yes)	1.03 (0.59–1.80)	0.91		
Beyond up-to-7 criteria (no/yes)	1.05 (0.52–2.11)	0.90		
AFP (<400/≥400 ng/mL)	1.33 (0.82–2.17)	0.25		
TBIL (<17.1/≥17.1 μmol/L)	1.04 (0.63–1.71)	0.89		
ALT (<40/≥40 U/L)	1.54 (0.94–2.54)	0.09		
AST (<40/≥40 U/L)	1.92 (1.00–3.68)	0.049	1.57 (0.79–3.13)	0.20
ALP (<90/≥90 U/L)	2.33 (1.23–4.41)	0.009	1.97 (1.02–3.83)	0.045
ALB (≥30/<30 g/L)	1.70 (0.94–3.09)	0.08		
PALB (≥140/<140 mg/L)	3.31 (1.98–5.51)	<0.001	2.85 (1.52–5.35)	0.001
PT (≤13.0/>13.0 s)	1.44 (0.88–2.34)	0.14		
PLT (≥100/<100×10^9/L)	1.06 (0.54–2.09)	0.87		
Number of TACEs (≤3/>3)	0.58 (0.29–1.19)	0.14		
TACE technique (c-TACE/D-TACE)	1.22 (0.71–2.10)	0.48		
Treatment (TACE/TACE + LEN + ICIs)	0.36 (0.20–0.65)	<0.001	0.36 (0.20–0.64)	<0.001

The multivariable analysis included the variables with a P value <0.05 from the univariable analysis. AFP, alpha-fetoprotein; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; CI, confidence interval; c-TACE, conventional TACE; D-TACE, drug-eluting beads TACE; HR, hazard ratio; ICIs, immune checkpoint inhibitors; LEN, lenvatinib; OS, overall survival; PALB, prealbumin; PT, prothrombin time; PLT, platelet; TACE, transarterial chemoembolization; TBIL, total bilirubin.

P=0.045) were identified as an independent risk factor for OS. The subgroup analysis revealed that in most of the pre-specified subgroups, TACE combined with lenvatinib plus ICIs treatment provided a longer OS benefit than TACE alone, with non-significant P for interaction, indicating consistency across different stratification results (*Figure 4*).

Safety

In the study, 74 of the 121 patients (61.2%) experienced AEs due to any cause (*Table 4*). The incidence of AEs in the combination group was higher than that in the monotherapy group [36/52 patients (69.2%) *vs.* 38/69 patients (55.1%), P=0.11]. The most common AEs in both the combination group and the monotherapy group were abdominal pain [21/52 patients (40.4%) *vs.* 23/69 patients (33.3%), P=0.43], followed by increased ALT [16/52 patients (30.8%) *vs.* 20/69 patients (29.0%), P=0.83] and increased AST [15/52 patients (28.8%) *vs.* 18/69 patients (26.1%), P=0.74]. Additionally, 8 of 52 patients (15.4%)

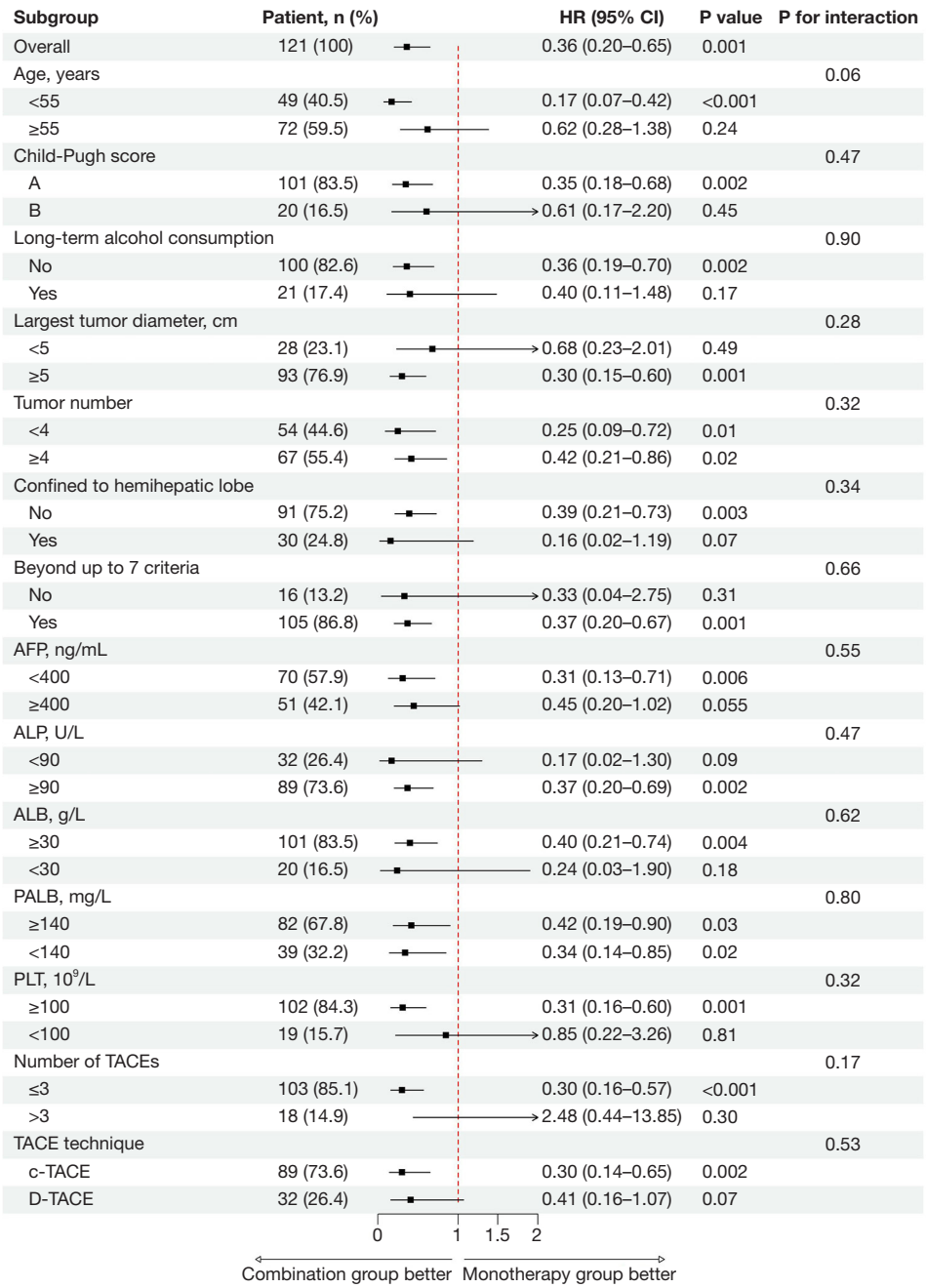

Figure 4 Subgroup analysis of OS. AFP, alpha-fetoprotein; ALB, albumin; ALP, alkaline phosphatase; CI, confidence interval; c-TACE, conventional TACE; D-TACE, drug-eluting beads TACE; HR, hazard ratio; OS, overall survival; PALB, prealbumin; PLT, platelet; TACE, transarterial chemoembolization.

in the combination group, and 4 of 69 patients (5.8%) in the monotherapy group experienced grade 3 or 4 AEs (P=0.08). Grade 3 or 4 AEs occurred rarely, and no grade 5 AEs were observed. The frequency and severity of AEs were similar between the two groups, and symptoms were alleviated by dose reduction, drug discontinuation, and symptomatic treatment. However, it should be noted that of the 52 patients in the combination group, 3 (5.8%) had

Table 4 AEs from any cause

AE	Any grade, n (%)			Grade 3–4, n (%)		
	Monotherapy group (N=69)	Combination group (N=52)	P	Monotherapy group (N=69)	Combination group (N=52)	P
All	38 (55.1)	36 (69.2)	0.11	4 (5.8)	8 (15.4)	0.08
Fatigue	7 (10.1)	4 (7.7)	0.64	0	0	–
Fever	2 (2.9)	4 (7.7)	0.40	0	0	–
Abdominal pain	23 (33.3)	21 (40.4)	0.43	0	0	–
Nausea	8 (11.6)	7 (13.5)	0.76	0	0	–
Abdominal distention	9 (13.0)	7 (13.5)	0.95	0	0	–
Diarrhea	0	2 (3.8)	0.18	0	0	–
Elevated ALT	20 (29.0)	16 (30.8)	0.83	3 (4.3)	2 (3.8)	>0.99
Elevated AST	18 (26.1)	15 (28.8)	0.74	2 (2.9)	2 (3.8)	>0.99
Hyperbilirubinemia	6 (8.7)	3 (5.8)	0.80	0	2 (3.8)	0.18
Chest distress	2 (2.9)	1 (1.9)	>0.99	0	0	–
Leukopenia	1 (1.4)	3 (5.8)	0.31	0	1 (1.9)	0.43
Thrombocytopenia	2 (2.9)	2 (3.8)	>0.99	0	0	–
Rash	0	2 (3.8)	0.18	0	0	–
Gastrointestinal bleeding	0	3 (5.8)	0.08	0	2 (3.8)	0.18
Pneumonia	0	1 (1.9)	0.43	0	1 (1.9)	0.43
Enteritis	0	1 (1.9)	0.43	0	0	–

AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase.

gastrointestinal bleeding, and 1 (1.9%) had pneumonia, all of which led to interruptions in the patients' medication and prolonged hospital stays.

Discussion

The current commonly held view is that surgical treatment can prolong the OS of BCLC-B stage patients. However, there is a lack of comparative studies on interventional therapy, and the combination of interventional therapy with targeted immunotherapy for BCLC-B stage patients. TACE can induce a hypoxic microenvironment, and postoperatively, the expression level of vascular endothelial growth factor increases, leading to enhanced tumor angiogenesis and the formation of an immunosuppressive tumor environment. This environment hinders the maturation and function of dendritic cells, and increases the recruitment of T regulatory cells and myeloid-derived suppressor cells (21). Additionally, TACE can increase the expression of programmed cell death protein 1/programmed death-ligand 1 in HCC, leading to the formation of a tumor-promoting immune escape mechanism (22). Therefore, the efficacy of using TACE alone for the treatment of intermediate-stage HCC is not ideal.

Lenvatinib is a multitarget tyrosine kinase inhibitor that can inhibit various kinases associated with tumor growth and angiogenesis, counteracting the angiogenesis-induced post-TACE, promoting vascular normalization, and modulating the tumor immune microenvironment. It may restore antitumor activity and enhance the immunological response of ICIs in HCC (23,24). Therefore, the combined use of TACE with lenvatinib and ICIs may produce synergistic antitumor activity, which could help improve the clinical prognosis of intermediate BCLC-B stage HCC patients.

Our study results revealed that the combination of TACE with lenvatinib plus ICIs treatment improved the outcomes of BCLC-B stage HCC patients, and the safety profile was acceptable. The combination group had a

median OS of 30.9 months (95% CI: 24.6–not reached), a 1-year OS rate of 81.7%, a 2-year OS rate of 70.0%, a 3-year OS rate of 48.4%, and a median PFS of 12.3 months (95% CI: 10.0–25.3), all of which were better than those of the monotherapy group. After PSM, the median OS of the combination group was not reached (95% CI: 24.6–not reached), but the 1-year OS rate was 80.8%, the 2-year OS rate was 66.4%, the 3-year OS rate was 59.8%, and the median PFS was 13.4 months (95% CI: 7.3–not reached).

In a retrospective study focusing on intermediate-stage HCC, the median OS of the group treated with TACE combined with lenvatinib was 28.0 months, and the median PFS was 8.2 months (25). Recently, the results of the EMERALD-1 study were officially published, demonstrating that the median PFS for patients treated with durvalumab plus bevacizumab plus TACE was 15.0 months, significantly improving the PFS of patients with uHCC compared to the placebo control group (26). Similarly, the results of another clinical trial, the LEAP-012 study, showed that the median PFS for patients with unresectable, non-metastatic HCC treated with TACE in combination with lenvatinib and pembrolizumab reached 14.6 months, demonstrating a statistically significant prolongation in PFS compared to those receiving placebo + TACE (27). In terms of PFS data, our research results are in line with those of the EMERALD-1 and LEAP-012 studies, suggesting that the positive outcomes observed in BCLC-B stage patients treated with the combination therapy of TACE with lenvatinib plus ICIs are not fortuitous. A study has reported that the median OS times of BCLC-B1 to B4 stage patients, classified under the Bolondi staging criteria, who underwent hepatectomy, were 75, 28, 9.5, and 8 months, respectively (28). This is also similar to the results of a Japanese study that reported that based on the Kinki criteria, the median OS of patients with BCLC-B1 to B2 stages after hepatectomy were 7.9 years and 3.1 years, respectively (29). In a previous study, we found that the median OS time after surgical treatment for BCLC-B stage patients who beyond the up-to-7 criteria reached 45 months, with a 1-year OS rate of 81.3%, a 2-year OS rate of 68.8%, and a 3-year OS rate of 57.9% (30). In the present study, the survival prognosis of the BCLC-B patients who received the combined treatment appeared to be slightly inferior to that of those who received the surgical treatment. However, among the patients who received the combined treatment, 90.4% beyond the up-to-7 criteria, and 80.8% had tumors growing in both the right and left lobes of the liver. Most of these patients were predicted to have insufficient residual liver function postoperatively, and faced high surgical difficulty; thus, such patients were not suitable for direct surgical treatment.

Compared with TACE alone, the excellent OS time achieved by the patients who received the combination therapy of TACE with lenvatinib plus ICIs in this study confirmed the superior efficacy of combined treatment in clinical practice. We found that the combined treatment significantly improved the survival prognosis of the BCLC-B patients who face difficulty undergoing surgical treatment, and it should also be considered as a preoperative neoadjuvant treatment. Additionally, the combined treatment also produced an advantage in terms of the ORR. Before and after PSM, the ORRs of patients receiving TACE combined with lenvatinib plus ICIs treatment were 61.5% and 59.0%, respectively, indicating that more than half of the patients benefited from the combined treatment. In terms of PFS, the PFS of the combined treatment group was longer than that of the TACE alone group (before PSM: 12.3 *vs.* 8.3 months, P=0.19; after PSM: 13.4 *vs.* 7.6 months, P=0.28). However, no significant statistical difference was found, which is inconsistent with the findings of most other studies (31,32). This discrepancy might be due to poorer baseline characteristics; larger and multifocal disseminated tumor lesions make it more likely that new lesions will appear in the liver, leading to tumor progression. However, patients with a heavier tumor burden may be more suitable for a combined treatment than a TACE alone treatment.

In the subgroup analyses, we observed that the combined treatment had an advantage in extending survival compared to TACE alone across different subgroups, particularly in those who beyond the up-to-7 criteria, and those with tumors not confined to hemihepatic lobe. The combined treatment significantly prolonged the survival of these patients, indicating that the concurrent action of TACE with lenvatinib and ICIs was also effective in HCC that is considered more aggressive. This may be because large and multifocal tumors often exhibit heterogeneity, such that tumors in different locations may exhibit different molecular characteristics and biological behaviors. Combined treatment can target multiple pathways, reducing tumor evasion and the development of resistance due to repeated interventions with TACE. These favorable results may be due to the potential synergistic antitumor effects of combined treatment.

In this study, all the AEs associated with the combined treatment of TACE with lenvatinib plus ICIs and with TACE alone were controllable, and no AEs leading to death

were observed. Additionally, the incidence and severity of AEs were comparable between the two groups. The combined group experienced an increase in AEs compared to the monotherapy group; however, this may be attributed to the pharmacological effects of lenvatinib and the ICIs, such as camrelizumab and tislelizumab, and it did not significantly increase the risk of AEs. Thus, the safety of the combined treatment of TACE with lenvatinib plus ICIs was found to be acceptable for patients with BCLC-B stage HCC.

In terms of the liver function indicators we monitored, the incidence of elevated aminotransferase events in the combined treatment group did not increase significantly [elevated ALT: 16/52 cases (30.8%) *vs.* 20/69 cases (29.0%), P=0.83; elevated AST: 15/52 cases (28.8%) *vs.* 18/69 cases (26.1%), P=0.74]. This suggests that the addition of lenvatinib plus ICIs to TACE did not synergistically exacerbate the liver function of patients. Thus, patients who have undergone combined treatment will have sufficient liver function reserve to receive other treatments, including partial hepatectomy and local radiotherapy.

This study had several limitations. First, it was a single-center retrospective study, which might have led to potential selection bias, and caused inherent limitations. Second, the sample size of patients included in this study was small, which might have introduced selection bias for the patients receiving specific therapies, and due to individual differences, the dose, frequency, and interval of TACE could not be standardized, which might have affected the efficacy. Third, the follow-up time for OS in this study was relatively short, which led to a lack of long-term survival data. Therefore, it is necessary to conduct prospective studies in the future to confirm the efficacy of the triple combination therapy.

Conclusions

In conclusion, our results indicated that in BCLC-B stage HCC patients, the combination of TACE with lenvatinib plus ICIs treatment was more effective than TACE alone, and it was not inferior to surgical treatment in terms of OS in specific BCLC-B subgroups. This combined treatment was found to improve the prognosis of BCLC-B stage HCC patients and to have an acceptable safety profile. The efficacy of this combined treatment still needs to be further validated in randomized controlled trials with large sample sizes and long-term follow-up to assess the effects of adding lenvatinib and ICIs to TACE.

Acknowledgments

None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-2025-33/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-2025-33/dss

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-2025-33/prf

Funding: None.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-2025-33/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Board of Ethics Committee of Guangxi Medical University Cancer Hospital (No. LW2024119) and informed consent was taken from all the patients.

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Cite this article as: Yao Y, Nong X, Liang JC, Zhang YM, Zhang ZM. Real-world effectiveness and safety of TACE combined with lenvatinib plus immune checkpoint inhibitors in patients with BCLC-B stage hepatocellular carcinoma. J Gastrointest Oncol 2025;16(1):176-190. doi: 10.21037/jgo-2025-33