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RALOX-HAIC (raltitrexed + oxaliplatin) combined with lenvatinib improves survival and safety in elderly patients with unresectable hepatocellular carcinoma

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Abstract

Objective To explore the efficacy and safety of RALOX-HAIC (raltitrexed plus oxaliplatin) combined with lenvatinib in the treatment of elderly patients with unresectable hepatocellular carcinoma (uHCC), aiming to provide a safer and more effective therapeutic strategy for this patient population.

Materials and methods A retrospective analysis was conducted on the clinical data of 82 elderly patients with uHCC who received treatment in the Department of Interventional Radiology at Wuhan Union Hospital from January 2019 to December 2022. Patients were divided into two groups based on their treatment strategy: HAIC + Lenvatinib group ($N = 39$) and TACE group ($N = 43$). The primary endpoints were the objective response rate (ORR), disease control rate (DCR), overall survival (OS), and progression-free survival (PFS) in the two groups. The secondary endpoint was the incidence of treatment-related adverse events in both groups.

Results The ORR and DCR after treatment were higher in the HAIC + Lenvatinib group compared to the TACE group (61.5% vs. 37.2%, 82.1% vs. 58.1%, $P < 0.05$). The HAIC + Lenvatinib group had a longer median progression-free survival (mPFS,9.2 months vs. 4.6 months, $P < 0.001$) and median overall survival(mOS, 18.1 months vs. 10.6 months, $P < 0.001$) compared to the TACE group. The incidence of abdominal pain and fever was significantly higher in the TACE group than in the HAIC + Lenvatinib group (including all grades and grades 3/4, $P < 0.05$). The incidence of hand-foot syndrome (all grades) was higher in the HAIC + Lenvatinib group compared to the TACE group (15.4% vs. 0.0%, $P = 0.009$), but there was no significant difference in the incidence of grade 3/4 hand-foot syndrome between the two groups (2.6% vs. 0.0%, $P = 0.476$).

Conclusion This study demonstrates that RALOX-HAIC combined with lenvatinib provides superior survival outcomes and tolerability compared to TACE alone in elderly patients (≥ 70 years) with unresectable HCC. This combination therapy may be a feasible and safe option for improving the prognosis of elderly patients with uHCC.

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors, accounting for approximately 75–85% of all primary liver malignancies [1]. According to the latest Global Cancer Statistics 2022 (GLOBOCAN), HCC remains the 6th most common cancer globally and the 3rd leading cause of cancer-related mortality [2] posing a severe threat to public health and life. Surgical resection remains curative for fewer than 30% of patients with hepatocellular carcinoma (HCC) [3]. Geriatric patients face further restricted surgical candidacy due to multimorbidity burden, necessitating optimized management strategies for unresectable HCC (uHCC) in this population. Transarterial chemoembolization (TACE) constitutes a mainstay therapy for uHCC [4], endorsed as first-line treatment in Barcelona Clinic Liver Cancer (BCLC) stage B by international guidelines for its ability to delay progression and extend survival [5]. Emerging evidence supports TACE's survival benefit in selected BCLC stage C patients [6, 7]; however, procedure-related complications remain significant. These include post-embolization syndrome (manifesting as abdominal pain, pyrexia, nausea/vomiting), infectious complications, biliary tract injuries, gallbladder perforation, and hepatotoxicity ranging from liver dysfunction to fulminant hepatic failure [8, 9]. Such adverse events disproportionately impact elderly patients, potentially precipitating cardiovascular events, gastrointestinal hemorrhage, hepatic abscess formation, or life-threatening sequelae. Hepatic arterial infusion chemotherapy (HAIC) has emerged as a promising alternative for uHCC management [10, 11]. This locoregional therapy delivers chemotherapeutics directly into the hepatic artery, achieving suprapharmacological tumor exposure while minimizing systemic drug distribution. The hepatic first-pass effect substantially reduces systemic toxicity [12, 13]. Clinical trials evaluating HAIC regimens - particularly those incorporating FOLFOX-based protocols - demonstrate notable efficacy in treating large tumors and portal vein tumor thrombus (PVTT) [14, 15]. Notably, HAIC exhibited a lower incidence of treatment-related Adverse events (AEs) with superior tolerability profile compared to sorafenib [16].Given these considerations, our institution has developed a novel therapeutic strategy combining HAIC with molecular targeted therapy for elderly patients with uHCC. Traditional FOLFOX-based HAIC protocols require prolonged continuous infusion (48 h) [17], which poses significant tolerability challenges in geriatric populations. To optimize treatment feasibility, we implemented a modified HAIC regimen utilizing oxaliplatin combined with raltitrexed (RALOX). As a folate analog antimetabolite targeting thymidylate synthase (TS) [18, 19], raltitrexed demonstrates a substantially extended plasma half-life (198 h) compared to 5-fluorouracil (5-FU) [20, 21]. This pharmacokinetic advantage allows us to deliver RALOX-HAIC with a concise 3-hour raltitrexed infusion cycle, overcoming the procedural burden associated with conventional FOLFOX-based regimens. Shiguang Chen et al. demonstrated that RALOX-HAIC achieves superior objective response rates (ORR) and extends overall survival (OS) compared to TACE in patients with locally advanced HCC, while maintaining comparable safety profiles [22]. Lenvatinib, a multitarget tyrosine kinase inhibitor (TKI) endorsed by major clinical guidelines as first-line therapy for HCC [23–25], gained FDA approval in 2017 based on the REFLECT phase III trial demonstrating non-inferiority to sorafenib [26]. Although its favorable safety profile (low incidence of grade ≥ 3 AEs) and manageable tolerability make it an attractive candidate for elderly patients [27, 28], its efficacy in this population remains under investigation. Through a retrospective analysis of clinical data from our center, this study aims to explore the efficacy and safety of RALOX-HAIC (raltitrexed + oxaliplatin) combined with lenvatinib in the treatment of elderly patients with uHCC, with the goal of providing safer and more effective treatment strategies for this patient population.

Materials and methods

General information

Clinical data were collected from 82 elderly patients with uHCC who were treated at Union Hospital, affiliated with Tongji Medical College of Huazhong University of Science and Technology, between January 2019 and December 2022. The inclusion criteria were as follows: (1) Histologically or radiologically confirmed diagnosis of HCC [29]; (2) Multidisciplinary evaluation determining the tumor as unresectable; (3) Age > 70 years; (4) Child-Pugh class A-B liver function, Eastern Cooperative Oncology Group (ECOG) performance status score of 0–1; (5) History of liver cirrhosis; (6) No prior radiotherapy, chemotherapy, targeted therapy, or immunotherapy for HCC. The exclusion criteria included: (1) Tumor thrombus involving bilateral first-order branches of the portal vein or the main trunk of the portal vein with few collateral circulations; (2) Severe abnormalities in cardiac, pulmonary, renal, hematologic, neurologic, or coagulation systems; (3) Presence of primary or metastatic malignancies in other sites; (4) Allergy to iodinated

contrast agents, chemotherapeutic agents, or lenvatinib; (5) Expected survival < 3 months; (6) Incomplete clinical follow-up data. Patients were divided into two groups based on the treatment received(Fig. 1): the HAIC + Lenvatinib group ($N = 39$) and the TACE group ($N = 43$). Baseline data collected for both groups included gender, age, cause of cirrhosis, preoperative Child-Pugh classification of liver function, ECOG score, AFP level, BCLC stage, PVTT, history of hypertension, history of diabetes, total bilirubin, ALT, AST, white blood cell count(WBC), red blood cell count(RBC), and platelet count(PLT). Laboratory and imaging evaluations were conducted within 14 days before treatment initiation to capture stable pretreatment disease characteristics. Complete blood count, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), bilirubin, and Alpha-fetoprotein (AFP) levels were measured. Contrast-enhanced CT (or MRI for iodinated contrast-contraindicated patients) was performed to assess tumor burden and vascular invasion. Two independent radiologists blinded to treatment allocation reviewed all images.

Methods

TACE Procedure[30]

Conventional TACE (C-TACE) was performed via the femoral artery approach. Digital subtraction angiography (DSA) was conducted to delineate tumor-feeding arteries. A 2.7 F microcatheter was advanced superselectively into the target vessel. Sequential embolization was performed by injecting an iodized oil + epirubicin emulsion (20 mg of epirubicin is administered per 5 mL of iodized oil, with a total iodized oil volume ranging from 5 to 15 mL.) followed by 300–500-μm gelatin sponge particles until complete cessation of blood flow in the tumor-feeding artery was achieved.

HAIC Procedure[31]

Following femoral artery access, digital subtraction angiography (DSA) was performed to delineate tumor-feeding arteries. If extrahepatic arterial collaterals supplying the tumor were identified, metallic coils were deployed for embolization. The microcatheter was selectively advanced into the proper hepatic artery, left hepatic artery, or right hepatic artery based on tumor location and secured in place. A continuous infusion regimen was administered via the indwelling catheter: Oxaliplatin 100 mg was dissolved in 250 mL of 5% dextrose solution and administered as a slow hepatic arterial infusion over 2 h via catheter, followed by Raltitrexed 4 mg dissolved in 250 mL of 0.9% sodium chloride solution, infused slowly into the hepatic artery over 3 h.

Lenvatinib treatment

Oral lenvatinib was initiated at 8 mg daily. Dose reduction to 4 mg daily was permitted in cases of grade ≥ 3 adverse events. No patients required discontinuation of lenvatinib due to intolerable AEts in this study.

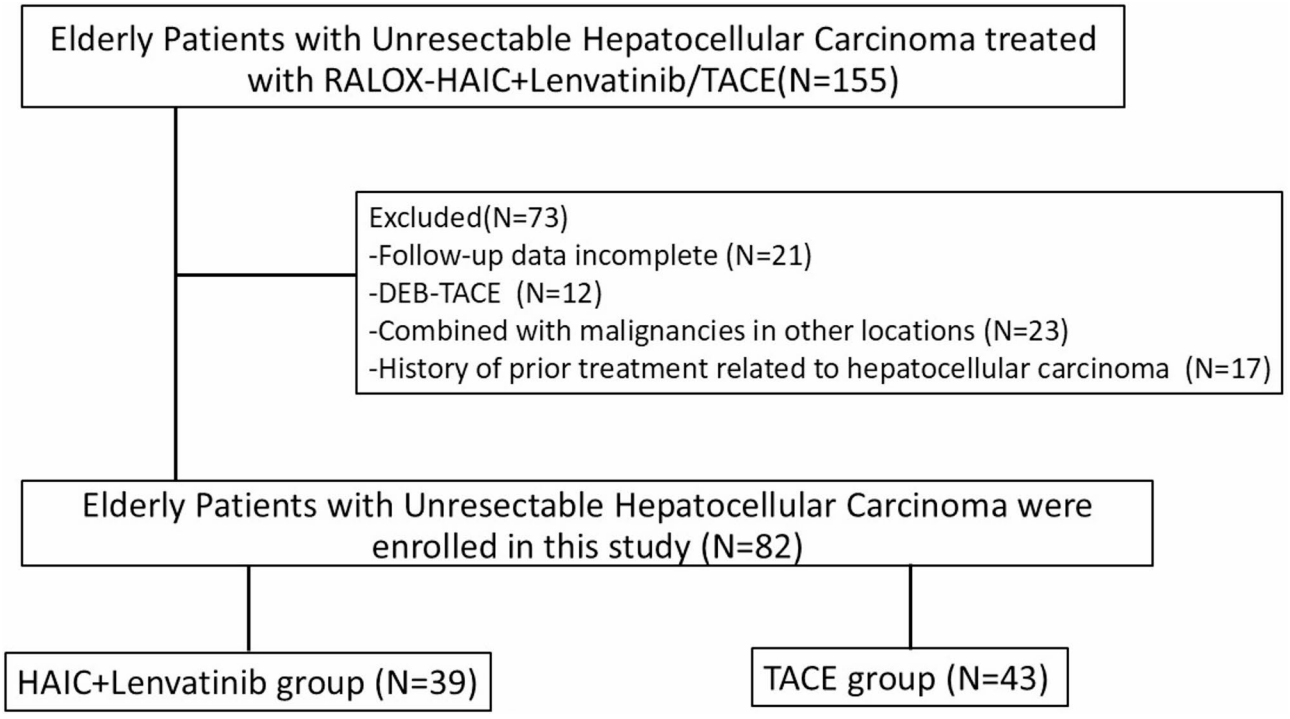

Fig. 1 Patient selection flowchart

Patients underwent clinical evaluation, laboratory testing (complete blood count, liver function tests), and contrast-enhanced CT/MRI every 4 weeks. Radiographic response was reassessed, with repeat interventions scheduled for persistent viable tumor. The median follow-up duration was 18 months (interquartile range: 6–30 months). Patients lost to follow-up were censored at their last known alive date.

Outcome measures

Primary Endpoints:

(1) Tumor Response: Evaluated using The modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria [32], categorized as: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD).
(2) Efficacy Metrics: Objective response rate (ORR = CR + PR) and disease control rate (DCR = CR + PR + SD).
(3) Survival Outcomes: Median progression-free survival (PFS) and overall survival (OS).

Secondary Endpoints:

(1) Laboratory Parameters: Changes in liver function (total bilirubin, ALT, AST) and hematologic indices (platelets, WBC, RBC) at 3 months.
(2) Safety Profile: Incidence of treatment-related adverse events (TRAEs) graded per CTCAE v5.0 [33].

Statistical methods

Data were analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Categorical variables were compared using chi-square or Fisher's exact tests. Continuous variables were assessed with Student's t-test or Mann-Whitney U test. Survival curves were generated via the Kaplan-Meier method and compared using the log-rank test. A two-tailed $P < 0.05$ was considered statistically significant. Missing data were addressed using multiple imputation techniques.

Results

Baseline characteristics

As shown in Table 1, no statistically significant differences were observed between the two groups in terms of gender distribution, age, etiology of cirrhosis, preoperative Child-Pugh class, ECOG performance status, alpha-fetoprotein (AFP) levels, portal vein tumor thrombosis status, BCLC stage, hypertension history, diabetes history, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), white blood cell count, red blood cell count, or platelet count (all $p > 0.05$).

Post-treatment hematological parameters

At 3-month follow-up, no significant intergroup differences were found in total bilirubin, ALT, AST, white blood cell (WBC), or red blood cell (RBC) levels (all $p > 0.05$, Table 2). However, platelet counts were significantly lower in the HAIC + Lenvatinib group compared to the TACE group (71.7 ± 26.6 G/L vs. 83.5 ± 25.5 G/L; $p = 0.043$).

Tumor response evaluation

The HAIC + Lenvatinib cohort demonstrated superior tumor response compared to the TACE group (Table 3). CR and PR rates were significantly higher in the combination group ($p = 0.027$). ORR was 61.5% (24/39) versus 37.2% (16/43; $p = 0.046$), while DCR reached 82.1% (32/39) versus 58.1% (25/43; $p = 0.030$).

Survival outcomes

mPFS (Table 4; Fig. 2): RALOX-HAIC + Lenvatinib group, 9.2 months (95%CI 7.8–10.7 months); TACE group, 4.6 months (95%CI 4.0-5.4 months); $P < 0.001$.

mOS (Table 4; Fig. 3)): RALOX-HAIC + Lenvatinib group, 18.1 months (95%CI 15.0-21.1 months); TACE group, 10.6 months (95%CI 8.7–12.5 months); $P < 0.001$.

Treatment-related adverse events

As summarized in Table 5, no significant differences emerged in vomiting, diarrhea, anorexia, or fatigue incidence (all $p > 0.05$). The TACE group exhibited markedly higher rates of abdominal pain (51.2% vs. 20.5%; $p = 0.006$) and fever (32.6% vs. 7.7%; $p = 0.006$) across all severity grades. While hand-foot reaction incidence was higher in the HAIC + Lenvatinib group (15.4% vs. 0.0%; $p = 0.009$), no significant difference was observed for grade ≥ 3 events (2.6% vs. 0.0%; $p = 0.476$). Although blood pressure elevation occurred more frequently in the combination group (all grades: 23.1% vs. 7.0%; grade ≥ 3: 7.7% vs. 2.3%), these differences did not reach statistical significance ($p = 0.059$ and $p = 0.342$, respectively).

Definition

Blood pressure elevation was defined as new-onset hypertension or worsening of pre-existing hypertension (previously controlled) during treatment.

Discussion

The lack of early-stage clinical manifestations combined with age-related attenuation in symptom perception frequently results in delayed diagnosis among elderly patients, who typically present with intermediate or advanced disease stages [34, 35]. Furthermore, this population demonstrates a higher prevalence of common comorbidities including hypertension, type 2 diabetes mellitus, and cardiopulmonary dysfunction, which often

Table 1 Comparison of baseline characteristics between the two groups

			Group				
			HAIC + Lenvatinib group(*N* = 39)	TACE group(*N* = 43)	Chi-Square Tests(*p*-value)		t-test(*p*-value)
					Fisher's Exact Test	Pearson Chi-Square	
Gender	Female	n (%)	12 (30.8%)	9 (20.9%)	0.325		
	Male	n (%)	27 (69.2%)	34 (79.1%)			
Etiology of cirrhosis	Hepatitis B	n (%)	26 (66.7%)	31 (72.1%)		0.528	
	Hepatitis C	n (%)	10 (25.6%)	7 (16.3%)			
	others	n (%)	3 (7.7%)	5 (11.6%)			
Pre-treatment ECOG	0	n (%)	27 (69.2%)	28 (65.1%)	0.815		
	1	n (%)	12 (30.8%)	15 (34.9%)			
Pre-treatment liver function	Child A	n (%)	26 (66.7%)	31 (72.1%)	0.637		
	Child B	n (%)	13 (33.3%)	12 (27.9%)			
BCLC staging	B	n (%)	25 (64.1%)	26 (60.5%)	0.821		
	C	n (%)	14 (35.9%)	17 (39.5%)			
Portal vein tumor thrombus	No	n (%)	26 (66.7%)	32 (74.4%)	0.475		
	Yes	n (%)	13 (33.3%)	11 (25.6%)			
AFP	< 400 μg/L	n (%)	11 (28.2%)	10 (23.3%)	0.623		
	≥ 400 μg/L	n (%)	28 (71.8%)	33 (76.7%)			
Hypertension	No	n (%)	14 (35.9%)	18 (41.9%)	0.653		
	Yes	n (%)	25 (64.1%)	26 (58.1%)			
Diabetes	No	n (%)	27 (69.2%)	27 (62.8%)	0.643		
	Yes	n (%)	12 (30.8%)	16 (37.2%)			
Age(Years)	Mean ± SD		75.5 ± 5.9	73.5 ± 5.6			0.119
Tumor size (cm)	Mean ± SD		8.2 ± 3.1	7.5 ± 2.8			0.211
Number of nodules	Mean ± SD		2.8 ± 1.2	2.5 ± 1.1			0.193
Pre-treatment bilirubin(μmol/L)	Mean ± SD		14.44 ± 6.85	15.27 ± 6.64			0.581
Pretreatment ALT(U/L)	Mean ± SD		42.1 ± 26.2	40.1 ± 22.1			0.707
Pretreatment AST(U/L)	Mean ± SD		33.0 ± 17.1	38.2 ± 21.8			0.241
Pretreatment WBC(G/L)	Mean ± SD		3.43 ± 1.22	3.69 ± 1.15			0.325
Pretreatment RBC(T/L)	Mean ± SD		3.84 ± 0.63	4.03 ± 0.70			0.196
Pretreatment PLT(G/L)	Mean ± SD		115.2 ± 48.8	100.1 ± 33.6			0.108

Table 2 Comparison of blood parameters between the two groups after three months of treatment

		Group		t-test(*p*-value)
		HAIC + Lenvatinib group(*N* = 39)	TACE group(*N* = 43)	
Post-treatment bilirubin(μmol/L)	Mean ± SD	18.15 ± 7.38	19.26 ± 9.29	0.549
Post-treatment ALT(U/L)	Mean ± SD	57.2 ± 30.2	65.1 ± 32.6	0.261
Post-treatment AST(U/L)	Mean ± SD	61.2 ± 32.4	55.5 ± 34.8	0.449
Post-Treatment WBC(G/L)	Mean ± SD	3.24 ± 1.36	3.33 ± 1.25	0.729
Post-Treatment RBC(T/L)	Mean ± SD	3.72 ± 0.71	3.68 ± 0.77	0.835
Post-Treatment PLT(G/L)	Mean ± SD	71.7 ± 26.6	83.5 ± 25.5	0.043

render surgical resection infeasible [36]. Consequently, developing safe, evidence-based therapeutic strategies to enhance survival outcomes and maintain quality of life remains a critical priority for clinicians managing elderly uHCC patients [37]. The chemotherapeutic agents injected via the catheter can inhibit tumor cell proliferation and induce apoptosis, while the embolization of the tumor's arterial blood supply leads to ischemia, hypoxia, and necrosis of the tumor tissue [38]. The TACE group demonstrated an ORR of 37.2% and DCR of 58.1%, with mPFS and mOS of 4.6 and 10.6 months respectively, consistent with data reported in other studies. Matan J. Cohen et al. [39] reported that among 102 HCC patients who received TACE as the only treatment, 10 patients (9.8%) were older than 80 years at diagnosis; 13 patients (12.7%) were aged 75–80 years, and 45 patients (44.1%) were aged 65–75 years. The 1-year, 2-year, and 3-year survival rates were 83%, 66%, and 48% in patients aged 65–75 years, and 86%, 41%, and 23% in patients aged ≥ 75 years, respectively. Despite its efficacy in uHCC, TACE

Table 3 Tumor response evaluation between the two groups

			Group		Chi-Square Tests(*p*-value)	
			HAIC + Lenvatinib group(*N* = 39)	TACE group(*N* = 43)	Pearson Chi-Square	Fisher's Exact Test
Tumor response	CR	n (%)	9 (23.1%)	2 (4.7%)	0.027	
	PR	n (%)	15 (38.5%)	14 (32.5%)		
	SD	n (%)	8 (20.5%)	9 (20.9%)		
	PD	n (%)	7 (17.9%)	18 (41.9%)		
ORR		n (%)	24 (61.5%)	16 (37.2%)		0.046
DCR		n (%)	32 (82.1%)	25 (58.1%)		0.030

Table 4 Comparison of OS and PFS between the two groups

	Gruop	Median(months)	95% Confidence Interval		Log Rank (Mantel-Cox) (p-value)
			Lower Bound	Upper Bound	
PFS	HAIC + Lenvatinib group	9.2	7.8	10.7	< 0.001
	TACE group	4.6	4.0	5.4	
OS	HAIC + Lenvatinib group	18.1	15.0	21.1	< 0.001
	TACE group	10.6	8.7	12.5	

is associated with a high burden of AEs-notably abdominal pain (51.2%), fever (32.6%), and vomiting (30.2%) in our cohort-that pose significant tolerability challenges for elderly patients [40–41]. H-F Hu et al. [42] reported on 5,436 HCC patients treated with TACE at 48 medical centers, noting that the common complications related to TACE treatment were nausea (25.77%), fever (31.53%), vomiting (20.99%), and hepatic pain (40.67%).

This study investigates the therapeutic potential of HAIC combined with lenvatinib for managing unresectable HCC in this vulnerable population. Hepatocellular carcinoma exhibits a unique hemotropism favoring

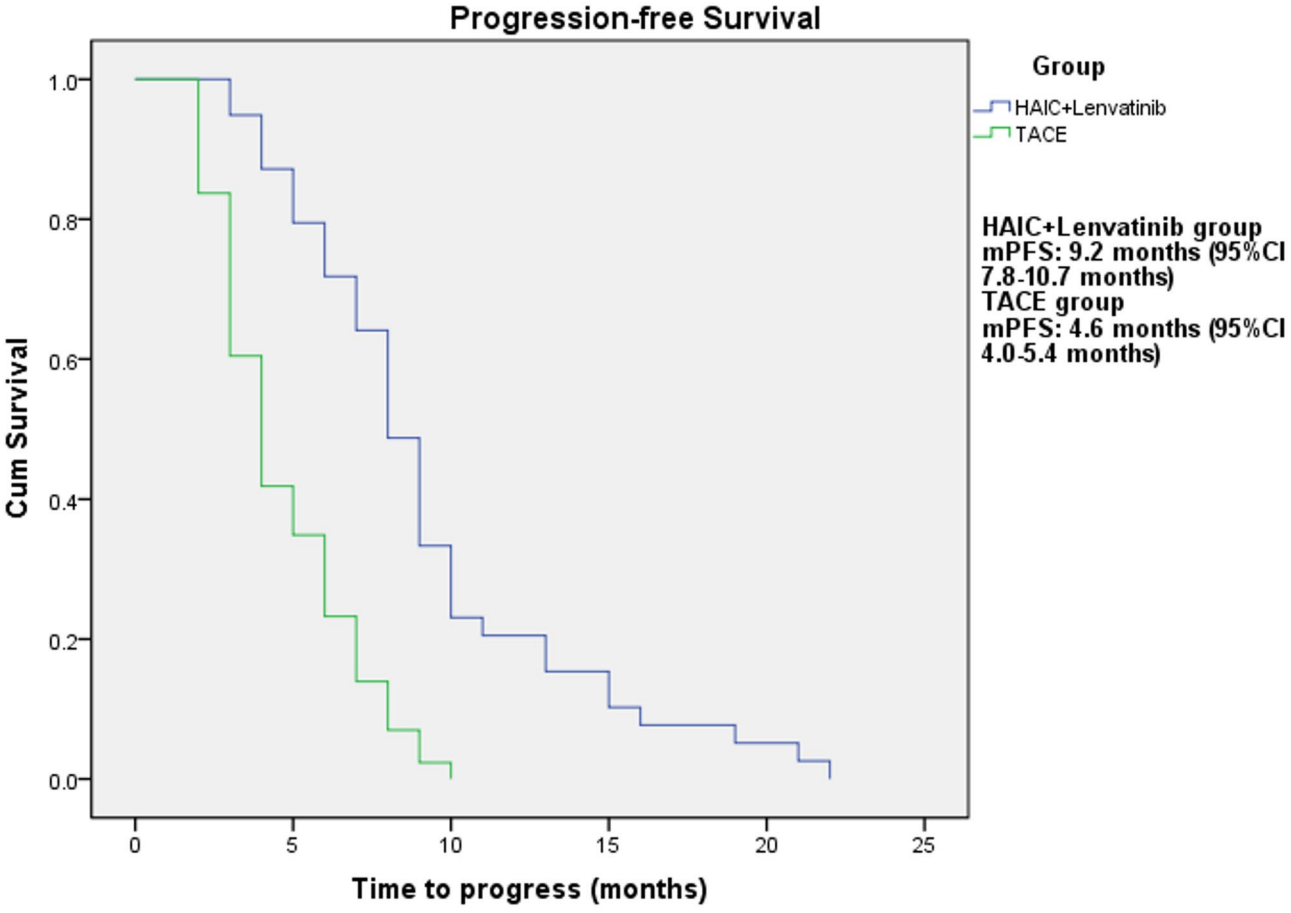

Fig. 2 Progression-free survival time in the two groups. mPFS: RALOX-HAIC + Lenvatinib group, 9.2 months (95%CI 7.8–10.7 months); TACE group, 4.6 months (95%CI 4.0-5.4 months)

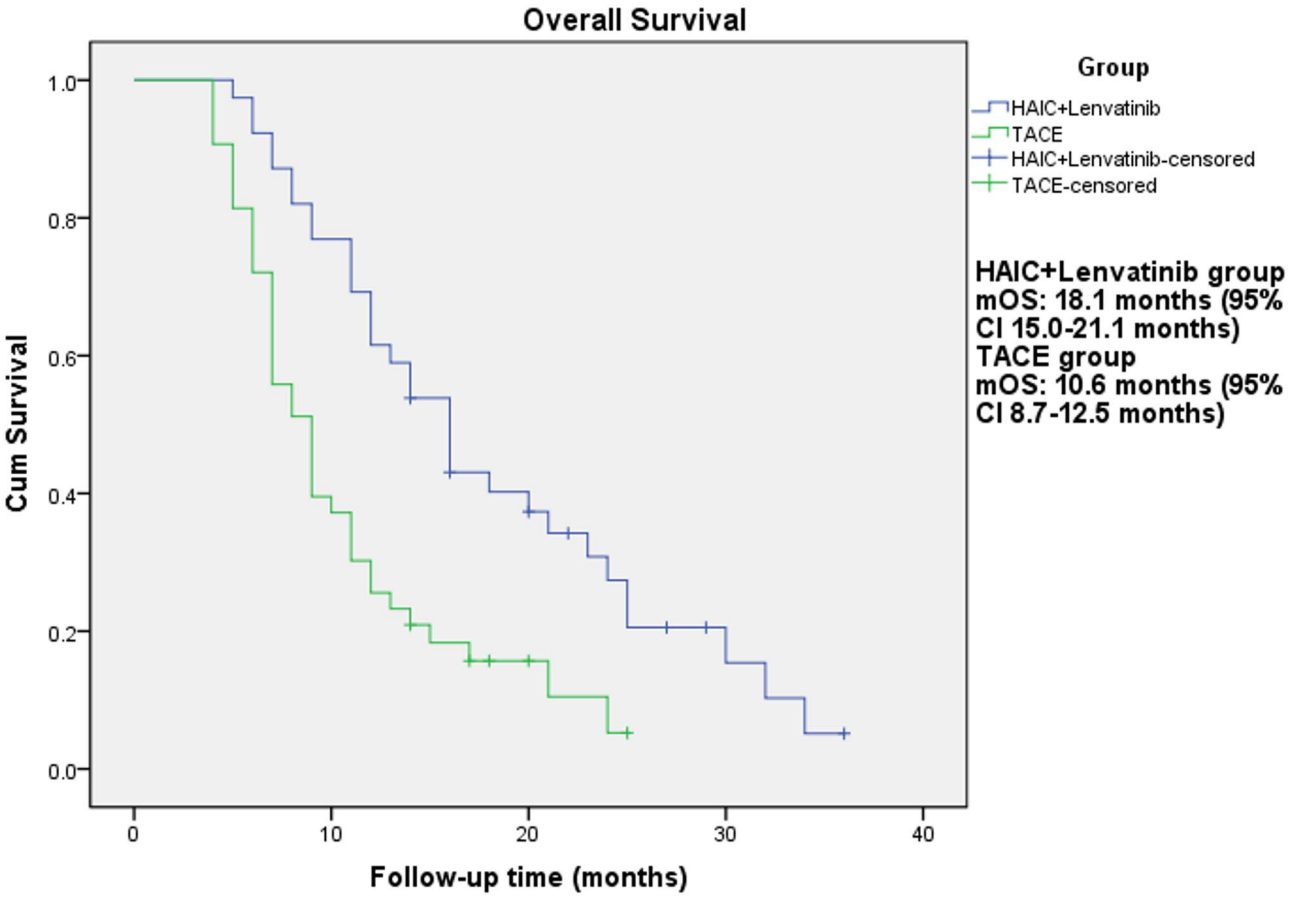

Fig. 3 Overall survival of patients in two groups. mOS: RALOX-HAIC + Lenvatinib group, 18.1 months (95%CI 15.0-21.1 months); TACE group, 10.6 months (95%CI 8.7–12.5 months)

Table 5 Incidence of post-treatment adverse events in both groups

Adverse events	Group				Chi-Square Tests(*p*-value)	
	HAIC + Lenvatinib group(*N* = 39)		TACE group(*N* = 43)			
	All grades, *n* (%)	Grade ≥ 3, *n* (%)	All grades, *n* (%)	Grade ≥ 3, *n* (%)	All grades	Grade ≥ 3
Abdominal pain	8 (20.5%)	2 (5.1%)	22 (51.2%)	10 (23.3%)	0.006	0.028
Fever	3 (7.7%)	0 (0.0%)	14 (32.6%)	8 (18.6%)	0.006	0.006
Vomiting	7 (17.9%)	2 (5.1%)	13 (30.2%)	5 (11.6%)	0.212	0.436
Elevated blood pressure	9 (23.1%)	3 (7.7%)	3 (7.0%)	1 (2.3%)	0.059	0.342
Diarrhea	3 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.103	N/A
Hand-foot syndrome	6 (15.4%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	0.009	0.476
Fatigue	5 (12.8%)	1 (2.6%)	4 (9.3%)	1 (2.3%)	0.730	1.000
Anorexia	4 (10.3%)	1 (2.6%)	6 (14.0%)	0 (0.0%)	0.741	0.476

hepatic arterial perfusion, enabling HAIC to deliver high-concentration chemotherapeutics directly into tumor parenchyma through selective arterial infusion [43]. This locoregional approach achieves suprapharmacological drug exposure with minimal systemic distribution, thereby enhancing antitumor efficacy while mitigating chemotherapy-related toxicities—a critical consideration in geriatric oncology. Emerging evidence supports HAIC's role in uHCC management, demonstrating both clinical effectiveness and favorable safety profiles [43]. In a recent head-to-head comparison by Ji Hoon Kim et al. [44], 193 HAIC-treated patients exhibited comparable overall survival (OS) and progression-free survival (PFS) parameters to 114 patients receiving atezolizumab/bevacizumab combination therapy ($p > 0.05$). Similarly, Jaejun Lee et al.'s propensity score-matched analysis [45] revealed no significant differences in mPFS (3.6 vs. 4.0 months; $p = 0.706$) or mOS (10.8 vs. 7.9 months; $p = 0.106$) between HAIC and lenvatinib monotherapy. Notably, the HAIC group demonstrated superior liver

functional preservation at best response evaluation, suggesting potential advantages in maintaining treatment tolerance for elderly patients.The conventional HAIC protocol traditionally employs the FOLFOX regimen, which necessitates a 48-hour continuous infusion of 5-fluorouracil (5-FU) due to its time-dependent cytotoxic kinetics. However, this prolonged procedural duration poses significant compliance challenges in geriatric populations, frequently compromising treatment adherence. In this study, we implemented a RALOX (oxaliplatin + raltitrexed)-based HAIC protocol to address these limitations. Raltitrexed, a folate analog antimetabolite with specificity for thymidylate synthase (TS), induces DNA strand breaks and apoptosis through irreversible enzyme inhibition. Unlike 5-FU, raltitrexed undergoes cellular uptake via the reduced folate carrier (RFC1) and subsequent polyglutamation by folylpolyglutamate synthetase (FPGS). This metabolic activation process results in significantly enhanced TS inhibition potency and prolonged enzymatic suppression duration, thereby augmenting its antineoplastic activity. The extended plasma half-life of raltitrexed (198 h) compared to 5-FU (approximately 20 min) allows for a substantially abbreviated infusion duration (3 h) in our RALOX-HAIC protocol. This pharmacokinetic advantage enables us to maintain therapeutic drug exposure levels while overcoming the compliance barriers associated with traditional FOLFOX-based regimens. Importantly, this modified dosing schedule preserves comparable antitumor efficacy with enhanced patient comfort and mobility, making it particularly suitable for elderly patients with limited procedural tolerance. Mengya Zang et al. [46] reported on 82 patients with uHCC who received HAIC treatment; 40 patients received FOLFOX-HAIC, and 42 patients received RALOX-HAIC. The two groups showed no significant differences in ORR and DCR (41.5% vs. 41.5%, 87.5% vs. 85.5%), with similar mPFS and mOS (10.7 months vs. 10.2 months, $P = 0.41$; 20.3 months vs. 17.7 months, $P = 0.50$). Our results are consistent with the multicenter phase II trial by Shiguang Chen et al., which showed that RALOX-HAIC achieved a median OS of 22.5 months in patients with PVTT [47]. The combination of HAIC and lenvatinib may synergistically enhance antitumor activity through vascular normalization and targeted inhibition of the RAF-MEK-ERK pathway.

While HAIC demonstrates moderate efficacy in uHCC, its standalone application shows limited treatment depth. Yangyang Li et al. [48] demonstrated superior survival outcomes in 453 patients receiving HAIC + PD-1 inhibitors versus 221 HAIC monotherapy recipients, with significantly prolonged mPFS and mOS. Combinatorial approaches gained further support through Yin Long et al.'s [49] meta-analysis showing HAIC-sorafenib combination therapy improved OS (HR 0.56, $P < 0.01$), PFS (HR 0.44, $P < 0.01$), and ORR (RR 3.77, $P < 0.01$) compared to sorafenib alone in advanced HCC. Building on these findings, our study employed RALOX-HAIC combined with lenvatinib. HAIC delivers high-dose chemotherapy directly to the hepatic artery, inducing tumor necrosis and hypoxia. This upregulates hypoxia-inducible factor-1α (HIF-1α), which stimulates angiogenesis via VEGF secretion. Lenvatinib, a multi-kinase inhibitor targeting VEGFR1-3, PDGFRα, and FGFR1-4, blocks this compensatory angiogenesis, thereby amplifying tumor ischemia and chemosensitivity. Our analysis revealed marked survival benefits: HAIC + lenvatinib group achieved significantly longer mPFS (9.2 vs. 4.6 months, $P < 0.001$, Fig. 2) and mOS (18.1 vs. 10.6 months, $P < 0.001$, Fig. 3) compared to TACE. Consistent with our results, Masafumi Ikeda et al. [50] reported 64.7% ORR (mRECIST) with HAIC + lenvatinib, while De-Di Wu et al. [51] associated early hepatic artery contraction with improved short-term outcomes in 67 patients. The common AEs of lenvatinib treatment include hypertension, hand-foot syndrome, fatigue, diarrhea, etc [52]. Although most studies have reported that the majority of patients can tolerate the AEs associated with lenvatinib, the efficacy and safety of lenvatinib in elderly patients require further clinical validation [53]. Therefore, this study aimed to explore the use of HAIC combined with lenvatinib in elderly patients with uHCC. In our study, 6 patients (15.4%) in the HAIC + Lenvatinib group experienced hand-foot syndrome. One of these cases was grade 3, and after adjusting the lenvatinib dose to 4 mg/day, the symptoms significantly improved. Additionally, 9 patients (23.1%) in the HAIC + Lenvatinib group experienced hypertension after treatment, requiring the initiation or adjustment of antihypertensive medications for blood pressure control. Although the incidence was higher than in the TACE group (7.0%), the difference between the two groups was not statistically significant ($p = 0.059$). Notably, the HAIC + Lenvatinib combination demonstrated a favorable safety profile with no severe cardiovascular or cerebrovascular events observed. After three months of treatment, thrombocytopenia emerged as the most common hematologic AE in this group (71.7 ± 26.6 G/L), though remained within safe thresholds without bleeding complications. Comparative analysis revealed significantly lower platelet levels in the HAIC + Lenvatinib group versus TACE ($p = 0.043$).ZhiCheng Lai et al. [54] reported on 36 patients receiving lenvatinib, toripalimab, and HAIC, where the most common AEs were thrombocytopenia, elevated AST, and hypertension. Similarly, Baojiang Liu et al. [55] documented comparable AE profiles in RALOX-HAIC post-TACE patients, with acceptable tolerability. In our cohort, the HAIC + Lenvatinib group exhibited significantly lower incidences of pain (20.5%, $p = 0.006$) and fever (7.7%, $p = 0.006$) compared to

TACE, while nausea/vomiting rates remained non-significantly different ($p = 0.212$). No differences were observed for diarrhea, fatigue, or anorexia between groups ($p > 0.05$). These results contribute to the growing body of evidence suggesting HAIC-based regimens may offer superior safety profiles in elderly uHCC patients, as supported by Shun-Yu Kong et al.'s [56] meta-analysis demonstrating lower AE incidence in HAIC versus TACE.

This retrospective, single-center study has several limitations: (1) Selection bias: Patients were treated at a single high-volume center, which may not reflect real-world settings. (2) Missing data: Imputation methods could introduce residual biases. (3) Short follow-up duration: The median follow-up was 18 months, insufficient to capture long-term toxicities. (4) Future directions: Multicenter, randomized trials are needed to validate our findings and explore the combination's role in first-line therapy.

Conclusion

In elderly patients with uHCC, the RALOX-HAIC combined with lenvatinib group demonstrated higher ORR and DCR, as well as longer mPFS and mOS, compared to the TACE group. The RALOX-HAIC combined with lenvatinib group did not experience any severe treatment-related AEs, and the incidences of abdominal pain, fever, and vomiting were lower than in the TACE group, indicating better patient tolerance and compliance. In summary, this study demonstrates that RALOX-HAIC combined with lenvatinib provides superior survival outcomes and tolerability compared to TACE alone in elderly patients (≥ 70 years) with unresectable HCC., and this combination therapy may represent a feasible and safe option for improving the prognosis of these patients.

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Author contributions
Haohao Lu and Qing Fu contributed to the conception and design of the work, the acquisition, analysis of data, as well as manuscript writing. Ya Gao contributed to the design of the work. Dongqiao Xiang contributed to the acquisition, analysis of data. Xiangwen Xia contributed to analysis, interpretation of data, and manuscript writing.

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Data availability
The datasets used during the current study are available from the corresponding author upon request.

Declarations

Ethics approval and consent to participate
The medical ethics committee at Union Hospital, Tongji Medical College, Huazhong University of science and technology, Wuhan, Hubei Province approved the retrospective study(Approval No.S20240143). The requirement for informed consent was waived by the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of science and technology due to the retrospective nature of the study. During follow-up, we informed patients about the study and they agreed to use their data. We confirmed that all methods were performed in accordance with the relevant guidelines and Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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