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Research

Hepatic arterial infusion chemotherapy (HAIC) plus Lenvatinib and PD-1 inhibitors versus systemic chemotherapy for unresectable intrahepatic cholangiocarcinoma

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Abstract

Background Unresectable intrahepatic cholangiocarcinoma (iCCA) is characterized with dismal prognosis. Here, this study aimed to compare the efficacy and safety of hepatic arterial infusion chemotherapy (HAIC) combined with lenvatinib and PD-1 inhibitors versus systemic chemotherapy (SC) for unresectable iCCA.

Methods Patients with histologically confirmed unresectable iCCA from January 2020 to December 2022 at our center were retrospectively enrolled. Propensity score matching (PSM) method was used to balance clinicopathological information between two groups. The primary endpoints were overall survival (OS), progression-free survival (PFS), whereas the secondary endpoints included objective response rate (ORR), disease-control rate (DCR) and safety profiles. Factors affecting the survival were identified through univariate and multivariate analyses.

Results Eighty-six cases were included in this study. After PSM, there were 30 patients in each group. Compared to SC group, HAIC + Len + PD-1 inhibitor exhibited significantly improved OS (16.91 [95%CI: 11.6–28.4] months vs. 11.06 months [95%CI: 7.8–14.6 months], p = 0.011), PFS (11.17 months [95%CI: 7.0, 26.7] vs. 5.55 months [95%CI: 3.8, NA], p = 0.004), better ORR (56.7% vs. 23.3%, p = 0.008) and DCR (93.3% vs. 70.0%, p = 0.019). Multivariate analysis indicated that treatment arm of SC was a risk factor of worse OS and PFS, while uni-lobe tumor distribution, AST ≤ 40, CA19-9 level ≤ 39 were protective factors of worse OS. All adverse events were comparable and controllable between two groups.

Conclusions In conclusion, HAIC combined with lenvatinib and PD-1 blockade yields better tumor control and survival outcomes over SC for unresectable iCCA, with manageable adverse events as well.

Keywords Intrahepatic cholangiocarcinoma · Lenvatinib · PD-1 inhibitor · Hepatic arterial infusion chemotherapy · Systemic chemotherapy

Abbreviations

CI	Confidence interval
CR	Complete response

Qingyu Xu, Chendong Wang and Ran You contributed equally to this work.

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DCR	Disease-control rate
ECOG-PS	Eastern Cooperative Oncology Performance Status
HAIC	Hepatic arterial infusion chemotherapy
iCCA	Intrahepatic cholangiocarcinoma
LEN	Lenvatinib
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
PR	Partial response
RECIST	Response Evaluation Criteria in Solid Tumors.
SC	Systemic chemotherapy
TKI	Tyrosine kinase inhibitor
TACE	Transarterial chemoembolization
TRAEs	Treatment-related adverse events

1 Introduction

Intrahepatic cholangiocarcinoma (iCCA) is the second most common primary liver cancer, comprising up to 20% of all hepatic malignancies, with a rising global incidence[1, 2]. Surgical resection remains the only curative treatment for iCCA, while the majority of patients (60%-90%) are deemed unresectable due to the diagnosis at a locally advanced or metastatic stage[3]. Systemic chemotherapy (SC) regimen (gemcitabine and cisplatin) combined with durvalumab or not has been recommended as the first-line option for unresectable iCCA[4, 5]. Despite this, the prognosis of unresectable iCCA remains poor, with a 5-year over survival rate of approximately 9%[6].

Tumor immunotherapy, particularly immune checkpoint blockades targeting PD-(L)1 signaling pathway, has substantially improved survival outcomes across many types of cancer, although only a small proportion of solid tumor patients benefit from these therapies[7]. Lenvatinib, an oral small-molecule tyrosine kinase inhibitor (TKI) targeting vascular endothelial growth factor receptor (VEGFR) 1 to 3, fibroblast growth factor receptors (FGFR) 1 to 4, platelet-derived growth factor receptor-a (PDGFRa), RET, and KIT, has been approved as the first-line drug for advanced hepatocellular carcinoma (HCC)[8]. High levels of vascular endothelial growth factor (VEGF) and abnormal activation of the FGFR signaling pathway are frequently detected in iCCA[9]. Lenvatinib in combination with PD-1 inhibitors have achieved satisfactory tumor responses and extended survival outcomes in s spectrum of malignancies, including iCCA[10, 11].

Increasing evidence supports the feasibility and efficacy of locoregional therapies for the unresectable iCCA subgroup, such as transarterial chemoembolization (TACE), hepatic arterial infusion chemotherapy (HAIC), transarterial radioembolization (TARE) and microwave ablation (MWA) or radiofrequency ablation (RFA)[12–15]. Hepatic tumors may be particularly amenable to arterially directed therapies, without excessive non-target treatment. There is urgent need to explore more promising and effective combinational treatment strategies for unresectable iCCA.

Therefore, this study aims to compare the efficacy and safety of HAIC combined with lenvatinib and PD-1 inhibitors versus systemic chemotherapy for the treatment of unresectable iCCA.

2 Methods

2.1 Study population

Patients with unresectable iCCA from January 2020 to December 2022 at our center were retrospectively reviewed. Patients' demographic, clinical and laboratory data was collected. Patients were included if fulfilling the following criteria: 1) aged > = 18 years old; 2) with iCCA in contrast-enhanced Computed Tomography (CT) or Magnetic Resonance Imaging (MRI); 3) pathologically confirmed iCCA with tumor biopsy; 4) refusal or unsuitable for surgical resection; 5) with Eastern Cooperative Oncology Group (ECOG) score of 0 or 1; 6) with preserved hepatic function (Child–pugh A or B class). The exclusion criteria were as follow: 1) with other malignant tumors; 2) contraindicated to arterially directed therapy; 3) without complete follow-up data.

This study was approved by the Ethical Review Committee of our hospital and performed in accordance with the principles of the Declaration of Helsinki. The consent from patients were waived in this retrospective study.

2.2 HAIC procedure and treatment protocol

HAIC procedures were performed by physicians with more than 10 years of experience in interventional radiology. Following femoral artery puncture and catheterization, hepatic arteriography and superior mesenteric arteriography or potential extrahepatic angiography were performed. Then, the microcatheter tip was located to the proper hepatic artery for the administration of chemotherapeutic agents (Gemcitabine 800 mg/m^2, Cisplatin 25 mg/m^2) by artery infusion pump. HAIC treatment was repeated every 3 weeks and continued until disease progression or unacceptable toxicity.

Intravenously administered chemotherapeutic agents included gemcitabine (1000 mg/m^2) and cisplatin (25 mg/m^2) on days 1 and 8 of each 21-day cycle.

Lenvatinib was orally administered 2–3 days after HAIC, with 8 mg/12 mg/d. PD-1 inhibitors were intravenously administered every 3 weeks, including sintilimab, camrelizumab, pembrolizumab, and tislelizumab (as shown in Supplemental Table 1). Lenvatinib and PD-1 blockade were discontinued after tumor progression or the occurrence of intolerable toxicity effects.

2.3 Tumor response assessment and survival outcomes:

The primary endpoints were overall survival (OS, the duration from HAIC treatment to any-cause death) and progression-free survival (PFS, the duration between HAIC treatment to the first documentation of disease progression or any-cause death). Secondary endpoints were objective response rate (ORR, defined as the sum of complete response (CR) and partial response (PR)) and disease control rate (DCR, defined as the sum of CR, PR and stable disease (SD). Tumor response was evaluated based on the Modified Response Evaluation Criteria in Solid Tumors (mRECIST). Treatment-related adverse events (TRAEs) were recorded and assessed with National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

2.4 Statistical analysis

Categorical data were presented as counts and percentages and compared using the X^2 test or Fisher's exact test. Continuous variables were expressed as means ± standard deviations (SD) or medians with interquartile ranges. For normally distributed variables, Student's t-test was employed, whereas the Mann–Whitney U test was utilized for non-normally distributed variables. Kaplan–Meier analysis and log-rank tests were used to plot and compare the survival curves of overall survival (OS) and progression-free survival (PFS) between the two groups. Univariate and multivariate cox regression analyses were used to identify factor affecting OS and PFS. All statistical analyses were conducted with SPSS Statistics software (version 26.0, IBM Inc., Chicago, IL, USA) and R software (version 4.1.1). A two-sided P value < 0.05 indicated statistical significance.

3 Results

3.1 Patients' characteristics

A total of 86 patients (39 male, mean age, 65.8 years old) were included in this study, with 43 patients in HAIC-Len-PD1 arm and 40 patients in SC arm. After 1:1 propensity scored matching (PSM), there were 30 patients in the HAIC-Len-PD1 group and 30 patients in the SC group (Fig. 1). As illustrated in Table 1**,** the distribution of all characteristics was comparable between two groups after PSM.

Table 1 Demographic and clinical characteristics of all patients after propensity score matching

Characteristics	HAIC + Len + aPD1 (N = 30)	SC (N = 30)	P value
Sex			0.605
Male	15 (50.0%)	17 (56.7%)	
Female	15 (50.0%)	13 (43.3%)	
Age			0.605
≤ 60 years	15 (50.0%)	13 (43.3%)	
> 60 years	15 (50.0%)	17 (56.7%)	
ECOG PS			0.602
0	12 (40.0%)	14 (46.7%)	
1–2	18 (60.0%)	16 (53.3%)	
HBV			> 0.999
Negative	26 (86.7%)	26 (86.7%)	
Positive	4 (13.3%)	4 (13.3%)	
Child Pugh class			0.347
A	22 (73.3%)	25 (83.3%)	
B	8 (26.7%)	5 (16.7%)	
Intrahepatic tumor size			0.243
≤ 5 cm	6 (20.0%)	10 (33.3%)	
> 5 cm	24 (80.0%)	20 (66.7%)	
Intrahepatic tumor number			0.592
Single	10 (33.3%)	12 (40.0%)	
Multiple	20 (66.7%)	18 (60.0%)	
Tumor distribution			> 0.999
Uni-lobe	23 (76.7%)	23 (76.7%)	
Bi-lobe	7 (23.3%)	7 (23.3%)	
Vascular Invasion			0.781
Absence	21 (70.0%)	20 (66.7%)	
Presence	9 (30.0%)	10 (33.3%)	
LN metastasis			0.796
Absence	14 (46.7%)	15 (50.0%)	
Presence	16 (53.3%)	15 (50.0%)	
Distant metastasis			0.436
Absence	15 (50.0%)	12 (40.0%)	
Presence	15 (50.0%)	18 (60.0%)	
TNM stage			0.906
I	2 (6.7%)	2 (6.7%)	
II	7 (23.3%)	6 (20.0%)	
III	6 (20.0%)	4 (13.3%)	
IV	15 (50.0%)	18 (60.0%)	
WBC			0.472
≤ 3.5 *10^9/L	3 (10.0%)	6 (20.0%)	
> 3.5 *10^9/L	27 (90.0%)	24 (80.0%)	
Hb			0.793
≤ 130 g/L	18 (60.0%)	17 (56.7%)	
> 130 g/L	12 (40.0%)	13 (43.3%)	
PLT			0.488
≤ 125*10^9/L	4 (13.3%)	6 (20.0%)	
> 125*10^9/L	26 (86.7%)	24 (80.0%)	
ALT			0.417
≤ 40 U/L	12 (40.0%)	9 (30.0%)	
> 40 U/L	18 (60.0%)	21 (70.0%)	

Table 1 (continued)

Characteristics	HAIC + Len + aPD1 (N = 30)	SC (N = 30)	P value
AST			0.795
≤ 40 U/L	14 (46.7%)	13 (43.3%)	
˃ 40 U/L	16 (53.3%)	17 (56.7%)	
TBIL			0.592
≤ 17 umol/L	12 (40.0%)	10 (33.3%)	
˃ 17 umol/L	18 (60.0%)	20 (66.7%)	
ALB			0.766
˃ 35 g/L	23 (76.7%)	22 (73.3%)	
≤ 35 g/L	7 (23.3%)	8 (26.7%)	
Cr			> 0.999
≤ 88 umol/L	26 (86.7%)	27 (90.0%)	
˃ 88 umol/L	4 (13.3%)	3 (10.0%)	
CEA			> 0.999
≤ 3.4 ng/mL	4 (13.3%)	3 (10.0%)	
˃ 3.4 ng/mL	26 (86.7%)	27 (90.0%)	
CA199			0.436
≤ 39 U/L	15 (50.0%)	18 (60.0%)	
˃ 39 U/L	15 (50.0%)	12 (40.0%)	
PT			0.317
≤ 13 s	26 (86.7%)	23 (76.7%)	
˃ 13 s	4 (13.3%)	7 (23.3%)	

HAIC Hepatic arterial infusion chemotherapy, *Len* Lenvatinib, *aPD1* Anti-programmed death protein 1, *SC* systemic chemotherapy, *ECOG-PS* Eastern Cooperative Oncology Performance Status, *LN* lymph node, *WBC* white blood cell, *Hb* Hemoglobin, *PLT* platelet, *ALT* Alanine aminotransferase; *AST* Aspartate aminotransferase, *TBIL* Total bilirubin, *ALB* Albumin, *Cr* Creatine, *CEA* Carcinoembryonic antigen, *PT* Prothrombin time

3.2 OS and PFS

After a mean follow-up of 38.9 months, 23 patients (76.7%) in the HAIC-Len-PD1 group and 23 patients (76.7%) in the SC group died. Compared to the SC group, HAIC-Len-PD1 significantly prolonged the OS (16.91 [95%CI: 11.6–28.4] months vs. 11.06 months [95%CI: 7.8–14.6 months], p = 0.011) and the PFS (11.17 months [95%CI: 7.0, 26.7] vs. 5.55 months [95%CI: 3.8, NA], p = 0.004) (Fig. 2).

Subsequent univariate and multivariate analyses indicated that LN-metastasis (HR:2.14, 95%CI: 1.14–4.00, p = 0.018) was a risk factor for OS, while Hb > 130 g/L (HR: 0.52, 95%CI: 0.27–1.01, p = 0.053) was protective factors of OS (Table 2).

As visualized in the forest plot, HAIC-Len-PD1 treatment arm provided better OS and PFS outcomes in subgroups of age > 60 years old, intrahepatic tumor size > 5 cm, multiple intrahepatic lesions, tumor bi-lobe involvement, WBC count > 3.5*10^9/L, AST > 40 u/L, ALB > 35 g/L, CA19-9 < 39 u/ml and PT < 13 s (Fig. 3-4).

3.3 Tumor response

Compared to the SC group, HAIC-Len-PD1 triple combination group achieved a significantly improved ORR (56.7% vs. 23.3%, p = 0.008) and DCR (93.3% vs. 70.0%, p = 0.019) (Table 3).

3.4 Safety profiles

The most common TRAEs included: nausea or vomiting, abdominal pain, diarrhea, neurotoxicity, mucositis, infection, hypertension, weight loss, leukopenia, thrombocytopenia, neutropenia, anemia, hyponatremia, hypokalemia, elevated ALT, elevated AST, hyperbilirubinemia, elevated creatinine, abnormal thyroid function. The occurrence of leukopenia,

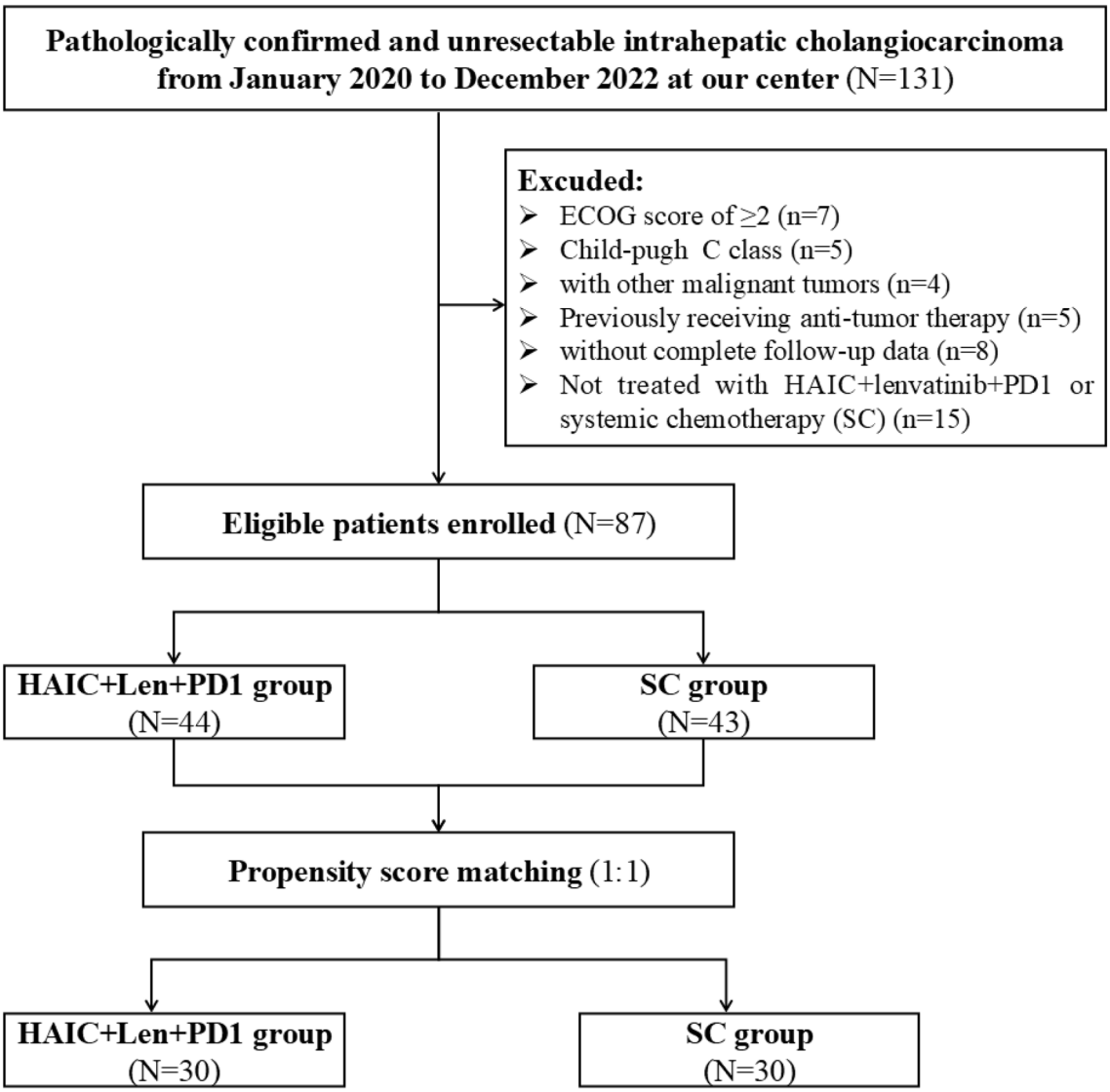


Fig. 1 The flowchart of patient selection

nausea and vomiting were higher in SC group. However, the incidence of hypertension was higher in the triple regimen group, which may be attributed to the uses of lenvatinib. There were no other differences about the rates of any grade or 3–4 grade TRAEs between two treatment groups (Table 4). No treatment-related deaths were observed in both two groups.

4 Discussion

The current retrospective study revealed that HAIC + Len + PD-1 inhibitor regimen exhibited significantly improved OS, PFS, as well as achieved better ORR and DCR compared to the SC regimen. Multivariate analysis indicated that the SC treatment arm was a risk factor of worse OS and PFS. In addition, LN-metastasis was a risk factor for OS, whereas Hb > 130 g/L was protective factors of OS. Additionally, all AEs were comparable and controllable between the two groups. We also compared the chemotherapeutic doses given IV and HAIC during a treatment cycle, finding that dose of chemotherapy drugs in the HAIC based treatment group (Gemcitabine: 1.3 ± 0.12 g vs. 3.2 ± 0.26 g; Cisplatin: 38.5 ± 7.1 mg vs. 79.8 ± 8.9 mg) was significantly lower than that in the systemic chemotherapy group.

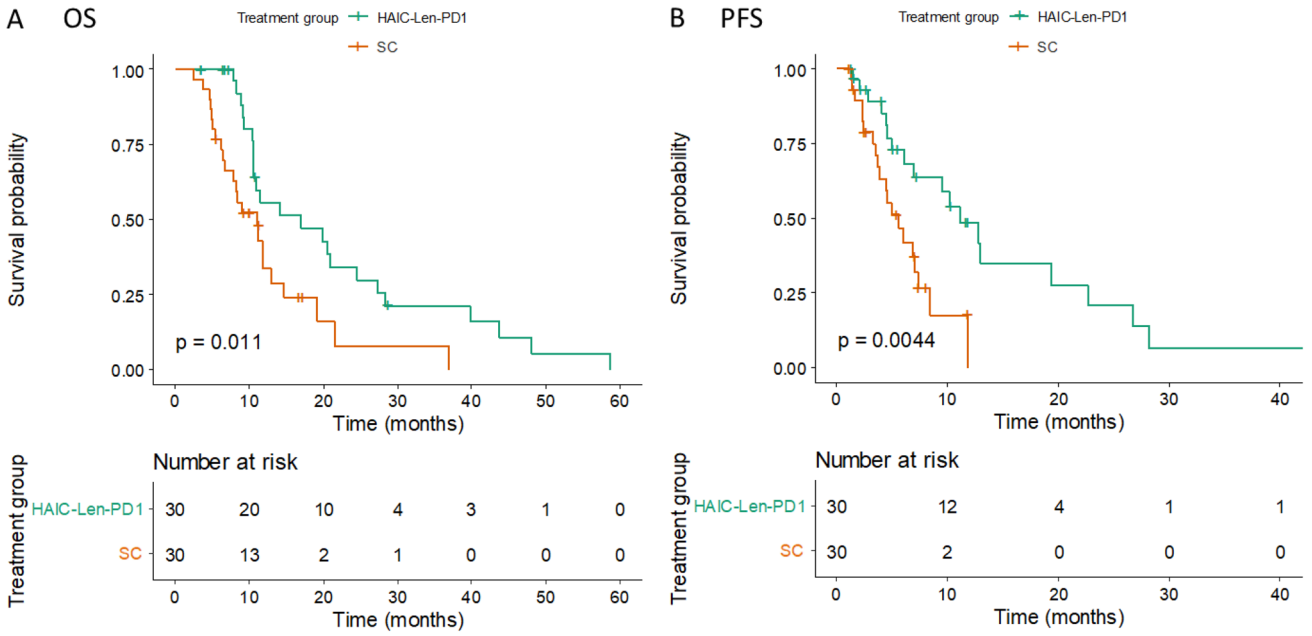


Fig. 2 Kaplan–Meier curves of patients between HAIC-Len-PD1 treatment group and SC treatment groups, **A** overall survival (OS) comparison, **B** progression-free survival (PFS) comparison

Subgroup analysis suggested patients with intrahepatic tumor size > 5 cm, multiple intrahepatic lesions or tumor bilobe involvement experienced longer OS with the HAIC-Len-PD1 triple combination therapy compared to the SC therapy. Hepatic arterial infusion of oxaliplatin, fluorouracil, and leucovorin has been reported to provide better tumor control and survival time over transarterial chemoembolization for HCC with large tumor burden (> 7 cm)[16]. Additionally, another study revealed that the addition of HAIC to lenvatinib and drug-eluting bead transarterial chemoembolization (DEB-TACE) significantly improved tumor response and OS in large HCC with portal vein tumor thrombosis (PVTT)[17]. Similar to HCC, we speculate that unresectable iCCA with a larger tumor burden may also benefit more from HAIC treatment.

High expression of VEGF and gene mutations of FGFR2, IDH1/2, HER2, WNT and EGFR have been frequently observed in cholangiocarcinoma, making it reasonable for the use of molecular targeted drugs. Lenvatinib administered alone has demonstrated considerable antitumor activity for unresectable CCA, while the ORR was only 11.5%[18]. Based on the results from global phase 3 TOPAZ1 trial and Keynote-966, immunotherapy combined with chemotherapy has been established as the first-line option that can significantly improve OS for advanced BTC [5, 19].

Several previous investigations have confirmed the efficacy of Lenvatinib and PD-1 inhibitors dual therapy in treating iCCA. A real-world cohort study involving 103 advanced iCCA patients who received lenvatinib and PD-1 blockade reported a median PFS of 5.9 months, a median OS of 11.4 months, an ORR of 18.4% and DCR of 80.6% [10]. Another retrospective study of 40 patients demonstrated that a combination of lenvatinib with the PD-1 inhibitor for chemorefractory advanced iCCA is also an effective treatment, with a median PFS of 5.83 months and OS of 14.30 months, ORR of 17.5%, DCR of 75.0% [11].

Additionally, numerous exploratory studies have been conducted to elaborate the effectiveness of triple combination therapy with locoregional therapy for CCA. In a study involving 28 patients with unresectable iCCA, lenvatinib plus durvalumab combined with FOLFOX-HAIC showed promising antitumor activity, with median PFS of 11.9 months and OS of 17.9 months, ORR of 65.2% (mRECIST) and 39.1% (RECIST1.1)[20]. FOLFOX-HAIC plus lenvatinib with PD-1 inhibitors for advanced CCA exhibited satisfactory anti-tumor efficacy, with median PFS of 6.5 months and OS of 16.0 months, ORR of 28.6% and DCR of 80.0% per RECIST1.1[21]. Another recent single-arm study demonstrated that FOLFOX-HAIC in combination with lenvatinib and PD-1 inhibitor in patients with advanced iCCA resulted in a median PFS of 9.40 months and and OS of 16.77 months, with an ORR of 47.8% and DCR of 91.3% per RECIST criteria. In addition, genetic, transcriptomic and immunohistochemistry data indicated that pre-existing high expression level of immune-related signatures and intra-tumoral CD8 + T cell density was associated with better clinical outcome[22].

In contrast to systemic chemotherapy with or without PD-(L)1 inhibitors, the triple combination therapy incorporating HAIC, lenvatinib, and PD-(L)1 inhibitors showcased favorable survival benefits and manageable adverse events for

Table 2 Univariate and multivariate analyses of prognostic factors affecting OS and PFS of patients

Variables	OS				PFS			
	Univariate Cox analysis		Multivariate Cox analysis		Univariate Cox analysis		Multivariate Cox analysis	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
Sex(male/female)	0.66 (0.36–1.23)	0.192			0.67 (0.35–1.30)	0.241		
Age(≤ 60y/ > 60y)	0.94 (0.52–1.69)	0.839			0.95 (0.50–1.81)	0.868		
ECOG-PS (0/1–2)	1.11 (0.61–2.00)	0.732			1.09 (0.57–2.07)	0.798		
HBV (Negative/Positive)	0.97 (0.38–2.49)	0.951			0.73 (0.25–2.10)	0.559		
Child–Pugh class (B/A)	1.02 (0.52–2.01)	0.943			0.89 (0.40–1.96)	0.767		
Intrahepatic Tumor size (> 5 cm/ ≤ 5 cm)	0.60 (0.31–1.16)	0.129			0.62 (0.29–1.30)	0.206		
Intrahepatic tumor number (single/multiple)	1.04 (0.57–1.91)	0.894			1.19 (0.60–2.36)	0.620		
Tumor distribution (Uni-lobe/Bi-lobe)	1.64 (0.85–3.14)	0.139			1.33 (0.63–2.79)	0.459		
Vascular Invasion (absence/presence)	0.61 (0.31–1.21)	0.159			0.62 (0.30–1.31)	0.213		
LN Metastasis (No/Yes)	1.82 (0.99–3.35)	0.053	2.14 (1.14–4.00)	0.018	1.57 (0.82–3.02)	0.176		
Distant metastasis (absence/presence)	0.73 (0.39–1.35)	0.313			0.79 (0.40–1.54)	0.486		
TNM stage (I/II/III/IV)								
II vs I	0.97 (0.30–3.16)	0.961			1.37 (0.37–5.00)	0.638		
III vs I	1.48 (0.44–4.98)	0.525			0.87 (0.19–3.92)	0.860		
IV vs I	0.82 (0.28–2.40)	0.714			0.90 (0.26–3.08)	0.867		
WBC (*10^9) (≤ 3.5/ > 3.5)	0.69 (0.32–1.49)	0.341			1.06 (0.37–3.03)	0.915		
Hb (g/L) (≤ 130/ > 130)	0.52 (0.28–0.97)	0.040	0.52 (0.27–1.01)	0.053	0.70 (0.36–1.34)	0.282		
PLT (*10^9/L) (≤ 125/ > 125)	2.04 (0.79–5.25)	0.139			2.21 (0.76–6.45)	0.148		
ALT (U/L) (≤ 40/ > 40)	1.11 (0.60–2.03)	0.746			1.21 (0.62–2.38)	0.578		
AST (U/L) (≤ 40/ > 40)	1.68 (0.90–3.11)	0.101			1.26 (0.66–2.40)	0.480		
TBIL (umol/L) (≤ 17/ > 17)	1.15 (0.62–2.15)	0.658			0.85 (0.43–1.66)	0.626		
ALB (g/L) (≤ 35/ > 35)	1.12 (0.58–2.16)	0.733			0.74 (0.37–1.48)	0.400		
Cr (umol/L) (≤ 88/ > 88)	0.68 (0.27–1.74)	0.423			0.89 (0.34–2.36)	0.822		
CEA (ng/mL) (≤ 3.4/ > 3.4)	0.70 (0.29–1.68)	0.428			0.71 (0.25–2.06)	0.529		
CA199 (U/L) (≤ 39/ > 39)	1.66 (0.91–3.04)	0.099	1.61 (0.86–3.05)	0.140	1.30 (0.68–2.50)	0.425		
PT (s) (≤ 13/ > 13)	0.61 (0.28–1.34)	0.219			0.69 (0.28–1.67)	0.407		

OS Overall survival, *PFS* Progression-free survival, *HR* Hazard ratio, *CI* confidence interval, *ECOG-PS* Eastern Cooperative Oncology Performance Status, *BCLC* Barcelona Clinic Liver Cancer, *AFP* α-fetoprotein, *PVTT* portal vein tumor thrombus, *TACE* transarterial chemoembolization, *HAIC* Hepatic arterial infusion chemotherapy, *Len* Lenvatinib, *ICIs* Immune checkpoint inhibitors

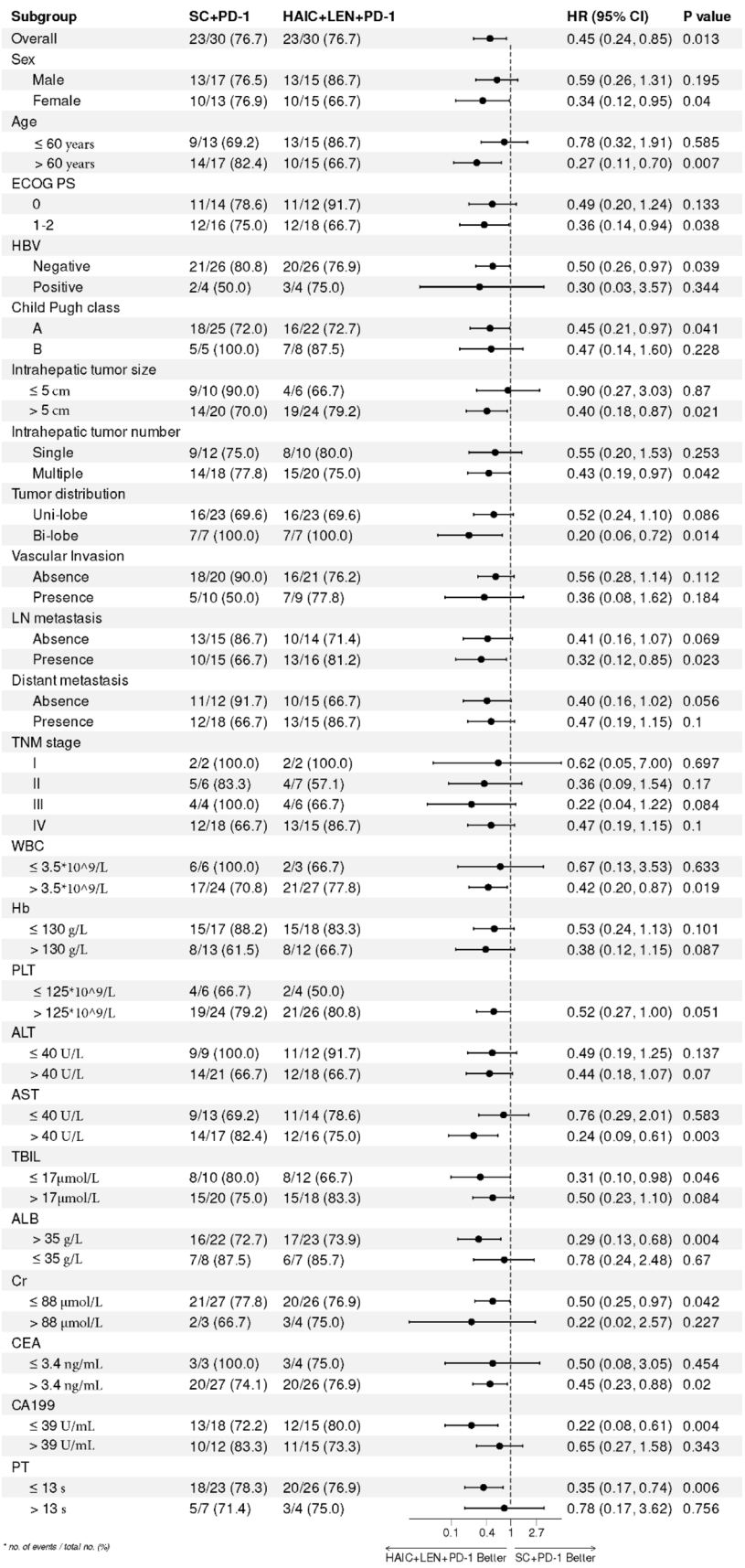
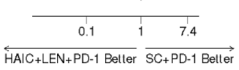


Fig. 3 Forest plot for overall survival between t HAIC-Len-PD1 treatment group and SC treatment groups. *SC* systemic chemotherapy, *HAIC* Hepatic arterial infusion chemotherapy, *LEN* Lenvatinib, *ECOG-PS* Eastern Cooperative Oncology Performance Status, *CI* confidence interval. LN, lymph node; *WBC* white blood cell, *Hb* Hemoglobin, *PLT* platelet, *ALT* Alanine aminotransferase, *AST* Aspartate aminotransferase, *TBIL* Total bilirubin, *ALB* Albumin, *Cr* Creatine, *CEA* Carcinoembryonic antigen, *PT* Prothrombin time

Subgroup	SC+PD-1	HAIC+LEN+PD-1	HR (95% CI)	P value
Overall	20/30 (66.7)	19/30 (63.3)	0.35 (0.17, 0.74)	0.006
Sex				
Male	11/17 (64.7)	12/15 (80.0)	0.50 (0.20, 1.25)	0.139
Female	9/13 (69.2)	7/15 (46.7)	0.19 (0.05, 0.73)	0.015
Age				
≤ 60 years	8/13 (61.5)	10/15 (66.7)	0.51 (0.18, 1.41)	0.193
> 60 years	12/17 (70.6)	9/15 (60.0)	0.24 (0.07, 0.77)	0.017
ECOG PS				
0	10/14 (71.4)	8/12 (66.7)	0.35 (0.12, 1.04)	0.058
1-2	10/16 (62.5)	11/18 (61.1)	0.42 (0.15, 1.17)	0.098
HBV				
Negative	18/26 (69.2)	17/26 (65.4)	0.40 (0.19, 0.87)	0.021
Positive	2/4 (50.0)	2/4 (50.0)		
Child Pugh class				
A	17/25 (68.0)	14/22 (63.6)	0.38 (0.16, 0.87)	0.022
B	3/5 (60.0)	5/8 (62.5)	0.20 (0.03, 1.24)	0.083
Intrahepatic tumor size				
≤ 5 cm	7/10 (70.0)	3/6 (50.0)	0.48 (0.10, 2.34)	0.363
> 5 cm	13/20 (65.0)	16/24 (66.7)	0.32 (0.13, 0.77)	0.011
Intrahepatic tumor number				
Single	7/12 (58.3)	6/10 (60.0)	0.37 (0.09, 1.51)	0.165
Multiple	13/18 (72.2)	13/20 (65.0)	0.35 (0.15, 0.85)	0.021
Tumor distribution				
Uni-lobe	16/23 (69.6)	12/23 (52.2)	0.32 (0.13, 0.76)	0.01
Bi-lobe	4/7 (57.1)	7/7 (100.0)	0.40 (0.09, 1.68)	0.211
Vascular Invasion				
Absence	13/20 (65.0)	14/21 (66.7)	0.60 (0.26, 1.35)	0.215
Presence	7/10 (70.0)	5/9 (55.6)	0.07 (0.01, 0.58)	0.014
LN metastasis				
Absence	11/15 (73.3)	9/14 (64.3)	0.25 (0.08, 0.84)	0.024
Presence	9/15 (60.0)	10/16 (62.5)	0.35 (0.12, 1.00)	0.051
Distant metastasis				
Absence	10/12 (83.3)	7/15 (46.7)	0.15 (0.04, 0.55)	0.004
Presence	10/18 (55.6)	12/15 (80.0)	0.59 (0.23, 1.54)	0.281
TNM stage				
I	1/2 (50.0)	2/2 (100.0)	0.71 (0.04, 11.79)	0.809
II	6/6 (100.0)	4/7 (57.1)	0.19 (0.04, 0.94)	0.042
III	3/4 (75.0)	1/6 (16.7)		
IV	10/18 (55.6)	12/15 (80.0)	0.59 (0.23, 1.54)	0.281
WBC				
≤ 3.5*10^9/L	4/6 (66.7)	0/3 (0.0)		
> 3.5*10^9/L	16/24 (66.7)	19/27 (70.4)	0.36 (0.16, 0.80)	0.012
Hb				
≤ 130 g/L	12/17 (70.6)	11/18 (61.1)	0.35 (0.13, 0.90)	0.029
> 130 g/L	8/13 (61.5)	8/12 (66.7)	0.40 (0.12, 1.30)	0.126
PLT				
≤ 125*10^9/L	4/6 (66.7)	2/4 (50.0)		
> 125*10^9/L	16/24 (66.7)	17/26 (65.4)	0.41 (0.19, 0.89)	0.024
ALT				
≤ 40U/L	5/9 (55.6)	9/12 (75.0)	0.53 (0.16, 1.76)	0.299
> 40U/L	15/21 (71.4)	10/18 (55.6)	0.26 (0.09, 0.71)	0.009
AST				
≤ 40U/L	10/13 (76.9)	9/14 (64.3)	0.41 (0.14, 1.24)	0.116
> 40U/L	10/17 (58.8)	10/16 (62.5)	0.25 (0.08, 0.74)	0.013
TBIL				
≤ 17μmol/L	8/10 (80.0)	6/12 (50.0)	0.21 (0.05, 0.80)	0.023
> 17μmol/L	12/20 (60.0)	13/18 (72.2)	0.44 (0.18, 1.11)	0.082
ALB				
≤ 35g/L	6/8 (75.0)	6/7 (85.7)	0.87 (0.26, 2.88)	0.814
> 35g/L	14/22 (63.6)	13/23 (56.5)	0.25 (0.09, 0.65)	0.004
Cr				
≤ 88μmol/L	17/27 (63.0)	17/26 (65.4)	0.44 (0.20, 0.97)	0.043
> 88μmol/L	3/3 (100.0)	2/4 (50.0)	0.47 (0.06, 3.44)	0.454
CEA				
≤ 3.4ng/mL	2/3 (66.7)	2/4 (50.0)	0.39 (0.04, 4.39)	0.449
> 3.4ng/mL	18/27 (66.7)	17/26 (65.4)	0.34 (0.15, 0.76)	0.009
CA199				
≤ 39U/mL	12/18 (66.7)	11/15 (73.3)	0.25 (0.09, 0.70)	0.009
> 39U/mL	8/12 (66.7)	8/15 (53.3)	0.50 (0.17, 1.45)	0.202
PT				
≤ 13 s	15/23 (65.2)	18/26 (69.2)	0.37 (0.16, 0.85)	0.019
> 13 s	5/7 (71.4)	1/4 (25.0)		



* no. of events / total no. (%)

Fig. 4 Forest plot for progression-free survival between the HAIC-Len-PD1 treatment group and SC treatment groups. *SC* systemic chemotherapy, *HAIC* Hepatic arterial infusion chemotherapy, *LEN* Lenvatinib, *ECOG-PS* Eastern Cooperative Oncology Performance Status, *CI* confidence interval. *LN* lymph node, *WBC* white blood cell, *Hb* Hemoglobin, *PLT* platelet, *ALT* Alanine aminotransferase, *AST* Aspartate aminotransferase, *TBIL* Total bilirubin, *ALB* Albumin, *Cr* Creatine, *CEA* Carcinoembryonic antigen, *PT* Prothrombin time

Table 3 Tumor response

Tumor response	HAIC + Len + aPD1 (N = 30)	SC (N = 30)	P value
Complete response	0 (0%)	0 (0%)	1.000
Partial response	17 (56.7%)	7 (23.3%)	
Stable disease	11 (36.7%)	14 (46.7%)	
Progressive disease	2 (6.7%)	9 (30.0%)	
ORR	17 (56.7%)	7 (23.3%)	0.008
DCR	28 (93.3%)	21 (70.0%)	0.019

HAIC Hepatic arterial infusion chemotherapy, *Len* Lenvatinib, *aPD1* Anti-programmed death protein 1, *SC* systemic chemotherapy, *ORR* objective response rate, *DCR* disease control rate

Table 4 Treatment-related adverse events in the two groups

Adverse events	Any grade		P-value	Grade3-4		P-value
	HAIC + Len + aPD1 (N = 30)	SC (N = 30)		HAIC + Len + aPD1 (N = 30)	SC (N = 30)	
Diarrhea	2 (6.7%)	4 (13.3%)	0.671	0 (0.0%)	0 (0.0%)	1.000
Abdominal pain	4 (13.3%)	9 (30.0%)	0.117	1 (3.3%)	1 (3.3%)	1.000
Nausea and vomiting	3 (10.0%)	10 (33.3%)	0.028	0 (0.0%)	3 (10.0%)	0.273
Hypertension	8 (26.7%)	1 (3.3%)	0.026	2 (6.7%)	0 (0.0%)	0.492
Neurotoxicity	2 (6.7%)	3 (10.0%)	1.000	0 (0.0%)	0 (0.0%)	1.000
Mucositis	4 (13.3%)	1 (3.3%)	0.353	0 (0.0%)	0 (0.0%)	1.000
Infection	0 (0.0%)	0 (0.0%)	1.000	0 (0.0%)	0 (0.0%)	1.000
Weight loss	6 (20.0%)	5 (16.7%)	0.739	0 (0.0%)	0 (0.0%)	1.000
Leukopenia	4 (13.3%)	12 (40.0%)	0.020	0 (0.0%)	2 (6.7%)	0.492
Thrombopenia	4 (13.3%)	9 (30.0%)	0.117	0 (0.0%)	5 (16.7%)	0.492
Neutropenia	8 (26.7%)	4 (13.3%)	0.197	3 (10.0%)	1 (3.3%)	0.612
Anemia	11 (36.7%)	7 (23.3%)	0.260	2 (6.7%)	1 (3.3%)	1.000
Hyponatremia	4 (13.3%)	3 (10.0%)	1.000	0 (0.0%)	0 (0.0%)	1.000
Hypokalemia	2 (6.7%)	3 (10.0%)	1.000	0 (0.0%)	0 (0.0%)	1.000
Elevated transaminases	12 (40.0%)	7 (23.3%)	0.165	2 (6.7%)	1 (3.3%)	1.000
Hyperbilirubinemia	5 (16.7%)	4 (13.3%)	1.000	1 (3.3%)	1 (3.3%)	1.000
Elevated creatinine	3 (10.0%)	1 (3.3%)	0.612	0 (0.0%)	0 (0.0%)	1.000
Abnormal thyroid function	15 (50.0%)	9 (30.0%)	0.114	4 (13.3%)	1 (3.3%)	0.353

HAIC Hepatic arterial infusion chemotherapy, *Len* Lenvatinib, *aPD1* Anti-programmed death protein 1, *SC* systemic chemotherapy

Supplemental Table 1: The detailed information about PD-1 inhibitors administration protocol

unresectable iCCA[23]. However, an interesting multicenter study revealed that PD-1 inhibitor plus lenvatinib and Gemox chemotherapy provide more potent efficacy than Len + PD-1 + FOLFOX-HAIC for 60 advanced BTC (median PFS 13.7 vs 6.0 months, median OS 23.8 vs 11.6 months, ORR 73.3 vs 30.0%, DCR 96.7 vs 96.7%)[24]. Nevertheless, the data specific to the iCCA subgroup were not disclosed in this study.

Inspired by the study by Yang et al., which demonstrated that the HAIC regimen provides better intrahepatic tumor control for unresectable iCCA compared to systemic chemotherapy[25], our study is the first attempt to directly compare HAIC(G + C) plus Len and PD-1 inhibitors versus Systemic chemotherapy (G + C) for unresectable iCCA. Furthermore, the administration dosage of G + C in HAIC-Len-PD1 therapy group in our study was about fifty percent of standardized dose of systemic chemotherapy, yet it could yield better outcomes. Compared to systemic chemotherapy, trans-arterial chemotherapy targetedly deliver higher concentrations of chemotherapeutic agents directly to the tumor site, thereby minimizing the systemic exposure to chemotherapy and reducing side effects.

As depicted in the KM survival curve, OS rates in median follow-up of 39 months are the same in both groups, however, the timing distribution of these events differ. The deaths in HAIC-LEN-PD1 group are concentrated towards the later stages of follow-up, while in the SC group they are concentrated in the early stages. Even with identical ultimate mortality rates, the 6-month prolongation of median overall survival (OS) holds significant clinical importance for patients with advanced intrahepatic cholangiocarcinoma (iCCA). Incorporating other important endpoints (PFS, ORR, DCR) to evaluate therapeutic superiority, the HAIC combined with targeted-immunotherapy group demonstrating significant improvements in both disease control rate and objective response rate compared to systemic chemotherapy. Mechanically, this multimodal synergy could lead to sustained survival benefits during medium-to-long term follow-up in the combination therapy group. While systemic chemotherapy regimens demonstrate modest efficacy in iCCA, their monotherapeutic mechanism of action lacks immunomodulatory properties. Furthermore, systemic toxicity may constrain treatment intensity and duration. Although chemotherapy may achieve rapid tumor shrinkage in the early phase, its limited capacity for durable disease control often results in higher risk of subsequent progression during later stages.

Several potential synergistic mechanisms might exist in the HAIC + Len + PD1 inhibitor regimen. Lenvatinib has the ability to enhance T-cell infiltration within the tumor microenvironment[26]. Tumor necrosis and the amplified release of tumor-associated antigens induced by HAIC and TKIs significantly upregulate the PD-L1 expression, further enhancing the efficacy of immunotherapy [27–29]. Furthermore, the combined strategy can overcome the resistance mechanisms inherent to monotherapies. Consequently, the combination treatment holds promise for potentiating the anti-tumor effects in unresectable iCCA.

Several limitations should be noted in the current study. Firstly, this is a small-sample retrospective and non-randomized study conducted at a single center. Therefore, potential selection bias can't be ignored. In the future, large-scale, multicenter and prospective studies are warranted to validate the results. Secondly, systemic chemotherapy combined with immunotherapy (Durvalumab) has also been approved as the first-line option for unresectable or advanced biliary tract cancer. Further prospective and randomized clinical trials are warranted to directly compare HAIC-based triple therapy (HAIC-Len-PD1) with systemic chemotherapy plus immunotherapy. Lastly, different types of PD-1 inhibitors were used in this study, which may affect the interpretation of current results. Furthermore, the limited number of cases make it difficult to conduct the stratification according to the different anti-PD1 agents.

5 Conclusions

In conclusion, HAIC combined with lenvatinib and PD-1 blockade yields better tumor control and survival outcomes over systemic chemotherapy for unresectable iCCA, with manageable adverse events. Further prospective studies are needed to verify the efficacy and safety of this treatment regimen.

Author contributions Qingyu Xu, Ran You and Chendong Wang contributed equally to this work. Guowen Yin, Qingyu Xu designed the study, performed the experiments, and wrote the manuscript. Ran You, Chendong Wang conducted examinations. Bin Leng, Zeyu Yu, Ya Lu and Lingfeng Diao collected the data. Qingyu Xu, Ran You and Chendong Wang provided hepatological advice and edited the manuscript. Guowen Yin revised the manuscript for important intellectual content.

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Data availability The data used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate The study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments and was approved by the Ethics Committee of Jiangsu Cancer Hospital.

Consent for publication The consents from participants were waived in this retrospective study, which was approved by our ethics committee (KY-2024-083).

Competing interests The author reports no conflicts of interest in this work.

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