Original Article

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Chemotherapy combined targeted therapy has a potential benefit on the survival of advanced intrahepatic cholangiocarcinoma

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SUMMARY: The treatment strategies and outcomes for advanced intrahepatic cholangiocarcinoma (ICC) are restricted. The treatment modalities and effectiveness of local interventional chemotherapy and systemic chemotherapy remain indeterminate. The objective of this study is to explore and assess the influence of different chemotherapy methods on the prognosis of patients with advanced ICC. A retrospective investigation was carried out at two research centers. The recruited patients were divided into the systemic chemotherapy cohort and the local chemotherapy cohort (Transarterial Chemoembolization, TACE). The primary endpoint of this study was overall survival (OS), while the secondary endpoints encompassed progression free survival (PFS), response rate (RR), and adverse events (AE). From January 2014 to January 2024, a total of 124 patients were included. Systemic/local chemotherapy combined with targeted therapy exhibited superior survival performance compared to chemotherapy alone. Additionally, patients with lesions confined to the liver and large tumors (> 6 cm) obtained better survival benefits from systemic chemotherapy. There was no significant disparity in grade 3 or more severe adverse events between the two groups. Whether it is systemic chemotherapy or TACE, combining them with targeted therapy can confer significant therapeutic advantages to patients with advanced ICC. ICC patients with a higher tumor burden may attain better therapeutic outcomes by selecting systemic chemotherapy.

Keywords: intrahepatic cholangiocarcinoma, liver malignant tumor, transarterial chemoembolization, local chemotherapy, systemic chemotherapy, targeted therapy, immunotherapy

1. Introduction

Intrahepatic cholangiocarcinoma (ICC), originating from the secondary branches of the bile duct, stands as the second most prevalent malignant tumor of the biliary tract, accounting for 10%-15% of primary liver cancers (*1*). In recent years, a notable upsurge in the incidence of ICC has been observed globally (*2*). Surgical resection represents the sole therapeutic approach with the potential to cure ICC patients. Nevertheless, in China, merely 20% of patients present indications for radical resection at the time of initial diagnosis (*3*). Among patients undergoing radical resection, the median survival period is 27 months, and the 5-year survival rate stands at 31% (*4*). Conversely, patients undergoing systemic chemotherapy exhibit a median overall survival of less than 1 year, and in the absence of treatment, the median survival is less than 5 months (*5,6*).

For patients with locally advanced or metastatic ICC, there exists no unified standard treatment protocol. Historically, systemic treatment for advanced biliary tract cancer (BTC) was confined to chemotherapy. A phase III clinical study from the United Kingdom, namely ABC-02, compared gemcitabine plus cisplatin with gemcitabine monotherapy in the treatment of locally advanced or metastatic BTC. Gemcitabine combined with cisplatin (GC) demonstrated a significant survival advantage and was established as the standard treatment regimen for BTC in first-line systemic therapy (*5*). Notably, a multicenter comparative study in Japan also verified the efficacy and safety of the GC treatment regimen in Japanese BTC patients, and it was adopted as the standard treatment regimen for BTC (*7*). Subsequently, in a randomized phase III study carried out in Japan to explore diverse first-line treatment options for BTC, the GC treatment regimen was compared with gemcitabine combined with tegafur-uracil (GS) chemotherapy. The median overall survival (OS) was 13.4 months and 15.1 months ($p = 0.046$), respectively, and GS was adopted as the standard treatment for patients with advanced BTC

(*8*). Moreover, a Japanese phase III study confirmed that the triple therapy of gemcitabine combined with cisplatin and teysuno (S-1) was superior to GC and was adopted as the standard treatment regimen for patients with advanced BTC (*9*). A post hoc analysis of a prospective, randomized clinical study on advanced biliary cancer named ABC-01, ABC-02, and ABC-03 revealed that patients with advanced ICC had better OS compared to other patients with extrahepatic biliary cancer (*5,10,11*). However, no large-scale prospective trials comparing local chemotherapy (TACE) with systemic chemotherapy have been conducted for patients with advanced ICC.

In recent years, the rapid advancement of immunotherapy and targeted therapy has substantially altered the overall scenario of BTC treatment. In a phase III study, namely TOPAZ-1, it was proven that durvalumab in combination with GC provided sustained and stable OS advantages. This treatment regimen marked the entry of systemic treatment for BTC into the immunotherapy era and was the first and sole global phase III clinical study to attain comprehensive survival benefits in terms of OS and progression-free survival (PFS) (*12*). In another global phase III study, KEYNOTE-966, it was revealed that, in comparison with GC monotherapy, pembrolizumab combined with GC significantly enhanced the OS of patients, and the difference was statistically significant. This discovery implies that this treatment regimen is anticipated to become a novel treatment alternative for previously untreated patients with metastatic or unresectable BTC (*13*).

In the present study, the objective was to compare the efficacy and survival advantages of patients with unresectable ICC who underwent local chemotherapy or systemic chemotherapy. The aim is to determine the optimal treatment regimen for patients with advanced ICC under various circumstances.

2. Materials and Methods

2.1. Study design and patients

A retrospective analysis was carried out on the prognosis of 124 patients with ICC who were diagnosed and TACE or systemic chemotherapy at the First Affiliated Hospital of Chongqing Medical University and the First Affiliated Hospital of Army Medical University from January 2014 to January 2024. The study protocol was approved by the Clinical Research Ethics Committee of Chongqing Medical University (K2023-451-02) and followed the Declaration of Helsinki. Informed consents were obtained from all patients.

All patients were newly diagnosed ICC cases without any other concomitant tumors and had not received any prior anti - tumor treatment. Additionally, all patients were aged between 18 and 80 years and had an Eastern Cooperative Oncology Group (ECOG) performance status ranging from 0 to 2. Patients with a history of prior chemotherapy or radiotherapy were excluded. Those with severe pulmonary or cardiac diseases were also excluded. Pregnant or lactating women were excluded too. Baseline characteristic data of the research subjects were collected, including patients' survival status, age, gender, tumor location and size, lymph node invasion status, vascular invasion status, metastasis sites, alterations in serological indicators, follow-up imaging data, and the selection of different chemotherapy regimens (Table 1).

2.2. Procedures

Regarding the treatment options for patients with inoperable tumors in this study, each center made decisions through multidisciplinary consultation and deliberation. The treatment modalities included systemic chemotherapy or local chemotherapy. Systemic chemotherapy regimens primarily involved intravenous infusion of chemotherapy drugs (single or combined treatment based on gemcitabine, oxaliplatin, tegafur), combined with targeted therapy and immunotherapy. TACE entailed first injecting chemotherapy drugs and iodized oil, followed by using drug - eluting beads for embolization to maintain a high concentration of chemotherapy drugs in the tumor area until complete stasis of the tumor's blood supply vessels was attained. Subsequently, targeted therapy and immunotherapy were combined. The patients in this study were initially staged, and the evidence of extra-hepatic lesions was verified through enhanced CT and enhanced MRI imaging. Then,

Table 1. Baseline characteristics of the patients' clinical pathology

Characteristics	*n* = 124	Percentage (%)
Gender		
Male	71	57.3
Female	53	42.7
Median age (range)	58	(35-80)
Treatment method		
Systemic treatment	88	71.0
TACE	36	29.0
Tumor characteristics		
Median size (range)	7.0	2.3-15.4
Multiple lesions	100	80.6
Long-distance transfer	59	47.6
Lymph node	95	76.6
Vascular invasion	89	71.8
Clinical picture		
Abdominal pain	54	43.5
Liver cirrhosis	66	53.2
Jaundice	21	16.9
Hepatitis B	44	35.5
CA19-9	84	67.7
AFP	14	11.3
Imaging		
CT	124	100
MRI	124	100

Abbreviations: TACE: Transarterial Chemoembolization; CA19-9: Carbohydrate Antigen19-9; AFP: Alpha-Fetal Protein; CT: Computed Tomography; MRI: Magnetic Resonance Imaging.

a biopsy was performed for pathological confirmation.

2.3. Follow-up

The median follow-up time was 11 months. After the treatment commenced, the changes in the lesions were monitored through imaging (enhanced CT and enhanced MRI) every 6-8 weeks. For patients with measurable target lesions, the tumor was evaluated in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. When the disease progressed, the treatment plan was adjusted according to specific circumstances.

2.4. Outcomes

In treatment modalities entailing the continuous administration of local chemotherapy or systemic chemotherapy, continuous surveillance of the patient's condition is conducted until the following scenarios transpire: progression of intrahepatic lesions, extrahepatic progression, severe treatment-associated toxicity and complications, successful conversion followed by surgical resection, or patient demise. The primary endpoint of this research is overall survival (OS), while the secondary endpoints are progress free survival (PFS) and adverse events (AEs). OS is delineated as the duration commencing from the date of diagnosis until death due to any cause. PFS is defined as the period from the date of diagnosis until tumor progression or death from any cause.

2.5. Statistical analysis

Survival analyses were carried out for patients in the local chemotherapy group and the systemic chemotherapy group according to different treatment regimens. SPSS version 26.0 was used for statistical analysis. Categorical data were expressed as numbers (%), and group comparisons were performed using x^2 test or the Fisher exact probability method. Normally distributed measurement data was evaluated using the Kolmogorov-Smirnov test. Normally distributed measurement data were presented as mean ± SD (x ± s) and analyzed using the *t* test for two independent samples. Non-normally distributed measurement data were presented as the median (Q1, Q3) and compared using the rank sum test. Survival curves were plotted *via* the Kaplan-Meier method, and the statistical disparities in survival outcomes were computed. The log-rank test was employed to assess the differences between survival curves. $p < 0.05$ was statistically significant.

3. Results

3.1. Baseline characteristics

Following the exclusion of patients who did not receive any treatment (n = 53) and those who solely received radiofrequency ablation treatment (n = 9), a total of 124 patients were ultimately incorporated into the survival analysis (Figure 1). In Table 1, the median age of the included patients was 58 years (35-80 years). There were 71 males (57.3%) and 53 females (42.7%). The median size of the tumors detected *via* imaging was 7.0 cm (2.3-15.4 cm). According to the Eastern Cooperative Oncology Group Performance Status (ECOG), all patients had scores ranging from 0 to 2. The most prevalent clinical manifestations were as follows: abdominal pain was observed in 54 patients (43.5%); multiple tumor foci were present in 100 patients (80.6%); extrahepatic distant metastasis was detected in 59 patients (47.6%); vascular invasion was identified in 89 patients (71.8%); lymph node invasion was found in 95 patients (76.6%); liver cirrhosis was diagnosed in 66 patients (53.2%); and hepatitis B was confirmed in 44 patients (35.5%).

3.2. Chemotherapy regimen

Among patients undergoing total body chemotherapy, 45 patients were administered a first line chemotherapy regimen centered around gemcitabine. Specifically, 21 patients (47%) received a combination of gemcitabine and cisplatin, 9 patients (20%) received a combination of gemcitabine and albumin-bound paclitaxel, 9 patients (20%) received a combination of gemcitabine and oxaliplatin, 5 patients (11%) received a combination of gemcitabine and tegafur-uracil, and 1 patient (2%) received gemcitabine monotherapy. In addition, 15 patients were treated with a chemotherapy regimen based on oxaliplatin. Twelve patients were subjected to a systemic treatment regimen based on S-1, and 22 patients received other systemic chemotherapy regimens (Table 2).

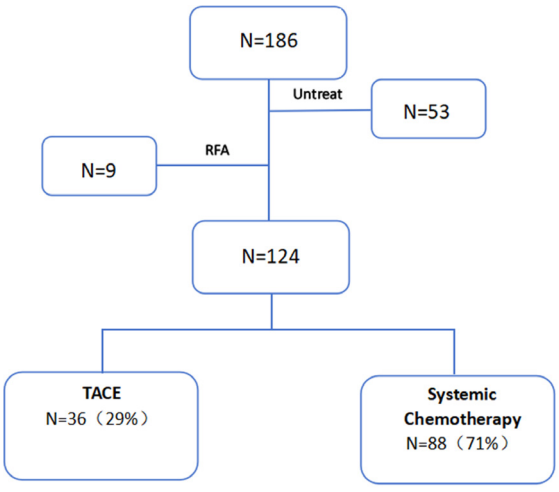

Figure 1. Grouping according to different chemotherapy modalities.

We further classified the diverse chemotherapy regimens into subgroups for survival comparison. Through comparative analysis, it was found when comparing gemcitabine plus albumin paclitaxel chemotherapy regimen with TACE, the median survival time was 9 months (7-17 months) as opposed to 11 months (2-66 months); $p = 0.05$. The survival advantage of TACE regimen was more prominent than that of gemcitabine plus albumin paclitaxel chemotherapy. Moreover, it was noted that the median overall survival (mOS) of the gemcitabine combined with cisplatin regimen was 12 months (2-48 months), indicating better survival outcomes compared to other regimens.

Table 2. Whole-body chemotherapy regimen

Chemotherapy regimen	*n* (%)
Gemcitabine-based	45 (100)
GP	21 (47)
AG	9 (20)
GEMOX	9 (20)
GS	5 (11)
Gemcitabine	1 (2)
Oxaliplatin-based	15 (100)
SOX	3 (20)
XELOX	3 (20)
GEMOX	9 (60)
S-1-based	12 (100)
S-1	4 (33)
SOX	3 (25)
GS	5 (42)
Other systemic drugs	22 (100)

Abbreviations: GP: Gemcitabine combined with Cisplatin; AG: Gemcitabine combined with albumin paclitaxel; GEMOX: Gemcitabine combined with Oxaliplatin; GS: Gemcitabine combined with Tarceva; SOX: Oxaliplatin combined with tegafur-oguacitinib; XELOX: Oxaliplatin combined with Capecitabine; S-1: Tegafur; Other systemic drugs: irinotecan, capecitabine, calcium folinate, *etc.*

3.3. Therapeutic effect of all patients

The clinical characteristics of the 124 ICC patients who underwent systemic chemotherapy or local chemotherapy in this study are presented in Table 3. Among them, 88 patients (71%) opted for systemic chemotherapy, whereas 36 patients (29%) selected TACE. Regarding patients receiving systemic chemotherapy, 39 (44.3%) were intolerant to the combined targeted and immunotherapy and only received systemic chemotherapy with chemotherapeutic agents. Forty nine (55.7%) chose systemic chemotherapy combined with targeted and immunotherapy, and the treatment regimens were all determined based on the results of genetic testing.

In this study, 99 (79.8%) patients succumbed to ICC. The mOS of all patients in this study was 11 months (1-66 months). The mOS and Median mPFS in the systemic chemotherapy group were 10 months (range, 2-53 months) and 6 months (range, 2-49 months), respectively. The mOS and mPFS of the TACE group were 11 months (1-66 months) and 6 months (1-57 months), respectively.

3.4. Systemic/local chemotherapy combined with targeted therapy had better survival performance than chemotherapy alone

In the survival analysis comparing patients undergoing TACE combined with targeted therapy and those receiving chemotherapy alone (Figure 2a), the mOS was 19 months (7-66 months) for the former group and 6 months (2-15 months) for the latter group, $p < 0.05$. Patients receiving TACE combined with targeted therapy exhibited superior survival performance. In the survival analysis comparing patients receiving TACE combined with targeted therapy and those undergoing systemic chemotherapy combined with targeted therapy

Table 3. Tumor characteristics and performance status score

	TACE (*n* = 36)	Systemic treatment (*n* = 88)	*p*
Median tumor size (range)	7.8 (2.8-15.0)	7.8 (2.8-15.0)	0.34
Number of tumors			< 0.05
single	19 (52.8%)	19 (52.8%)	
multiple	17 (47.2%)	17 (47.2%)	
Lymph node metastasis			< 0.05
No	16 (44.4%)	16 (44.4%)	
Local	7 (19.4)	7 (19.4)	
Multiple	13 (36.1%)	13 (36.1%)	
Extrahepatic metastasis	22 (61.1%)	22 (61.1%)	0.03
Vascular involvement	24 (66.7%)	24 (66.7%)	0.56
CA19-9	16 (44.4%)	16 (44.4%)	< 0.05
Liver cirrhosis	12 (33.3%)	12 (33.3%)	< 0.05
Median treatment cycle	2 (1-5)	2 (1-5)	0.19
Combined targeted immunotherapy	23 (63.9%)	23 (63.9%)	0.52
ECOG			0.11
0	22 (61.1%)	22 (61.1%)	
1	12 (33.3%)	12 (33.3%)	
2	2 (5.6%)	2 (5.6%)	

Abbreviations: TACE: Transarterial Chemoembolization; CA19-9: Carbohydrate Antigen19-9; ECOG: Eastern Cooperative Oncology Group Performance Status Score.

(Figure 2b), the mOS was 19 months (7-66 months) and 16 months (4-53 months) respectively, $p = 0.39$. There was no significant difference in survival between the two groups. When a survival analysis was carried out for patients receiving only TACE and those receiving systemic chemotherapy combined with targeted therapy (Figure 2c), the mOS was 5 months (1-11 months) for the former group and 16 months (4-53 months) for the latter group, $p < 0.05$. The survival benefit of systemic chemotherapy combined with targeted therapy was significantly greater than that of receiving only TACE. In the survival analysis comparing patients receiving only TACE and those receiving only chemotherapy (Figure 2d), the mOS was 5 months (1-11 months) and 6 months (2-15 months) respectively, $p = 0.68$. There was no significant difference in survival between the two groups. In the survival analysis comparing patients receiving only TACE and those receiving TACE combined with targeted therapy (Figure 2e), the mOS was 5 months (1-11 months) for the former group and 19 months (7 -

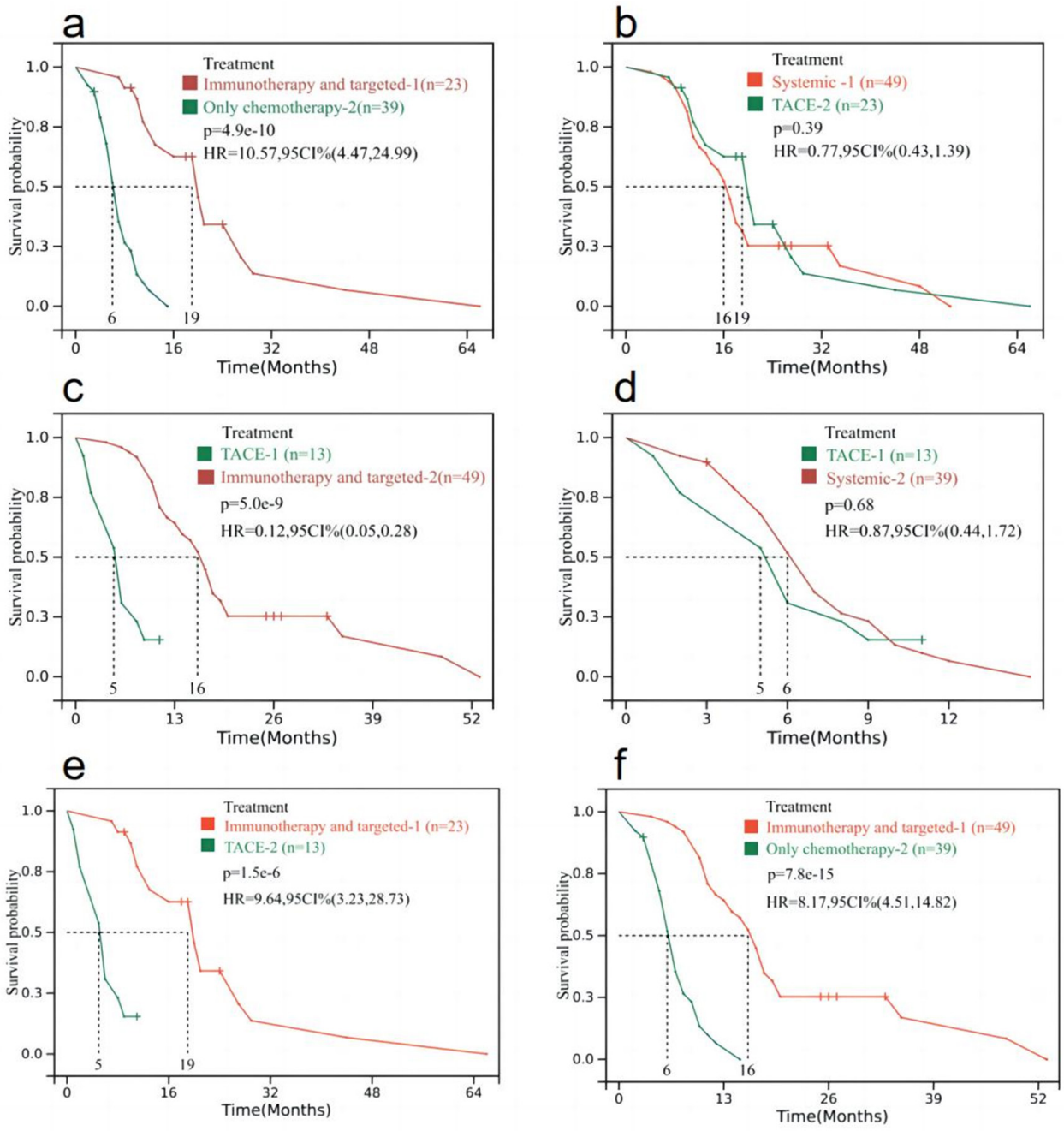

Figure 2. Survival curves of the TACE and systemic chemotherapy subgroups. a: 1 is the TACE combined with targeted immunotherapy; 2 is chemotherapy alone, $p < 0.05$; **b**: 1 is systemic chemotherapy combined with targeted immunotherapy; 2 is TACE combined with targeted immunotherapy, $p = 0.39$; **c**: 1 is the sole TACE regimen; 2 is systemic chemotherapy combined with targeted immunotherapy, $p < 0.05$; **d**: 1 is the sole TACE regimen; 2 is chemotherapy alone, $p = 0.68$; **e**: 1 is the TACE combined with targeted immunotherapy; 2 is the sole TACE regimen, $p < 0.05$; **f**: 1 is systemic chemotherapy combined with targeted immunotherapy; 2 is chemotherapy alone, $p < 0.05$.

66 months) for the latter group, $p < 0.05$. The survival benefit of TACE combined with targeted therapy was significantly greater than that of receiving only TACE. When a survival analysis was conducted for patients receiving only chemotherapy and those receiving chemotherapy combined with targeted therapy (Figure 2f), the mOS was 6 months (2-15 months) for the former group and 16 months (4-53 months) for the latter group; $p < 0.05$. The survival benefit of patients receiving systemic chemotherapy combined with targeted therapy was significantly greater than that of patients receiving only chemotherapy.

3.5. Confined lesions in the liver and large tumor (> 6 cm) have a better survival benefit from systemic chemotherapy

In the survival analysis incorporating liver and extrahepatic organ metastases of tumors, among patients undergoing systemic chemotherapy (Figure 3a), the mOS of patients with liver-only lesions was 11 months (4-35 months) compared with 8 months (2-48 months) for patients with other types of lesions. $p < 0.05$. Lesions restricted to the liver conferred a more favorable survival benefit compared to those in extrahepatic organs. When examining the tumor location in patients receiving TACE (Figure 3b), the mOS of patients with lesions restricted to the liver was 8 months (1-44 months), as opposed to 13 months (2-66 months); $p = 0.75$. Among patients receiving local chemotherapy, there was no significant disparity in survival benefit between those with lesions restricted to the liver and those with extrahepatic organ metastases.

Upon re-incorporating the maximum tumor diameter into the survival analysis, among patients who underwent systemic chemotherapy, with the maximum tumor diameter demarcated at 6 cm, it was discovered that patients with a maximum tumor diameter exceeding 6 cm exhibited more favorable survival benefits compared to those with a maximum tumor diameter less than 6 cm (Figure 4). The mOS was 12 months (2-53 months) as opposed to 8 months (2-18 months); $p < 0.05$. Nevertheless, no survival disparities were detected

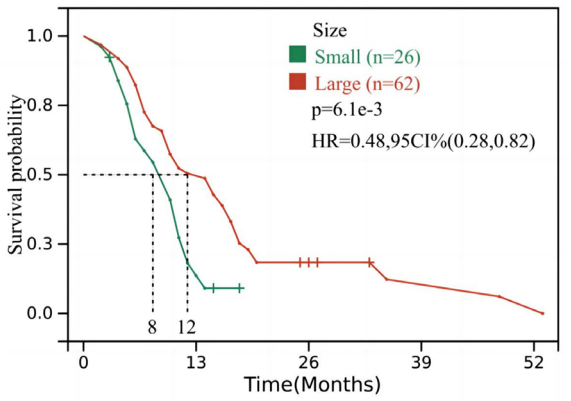

Figure 4. Survival curve of the maximum tumor diameter after systemic chemotherapy.

Table 4. Baseline characteristics of patients based on the maximum diameter of the tumor

Tumor diameter (cm)	< 6 cm (n = 26)	> 6 cm (n = 62)	p
Lymph	24 (92.3%)	51 (82.3%)	0.38
Extrahepatic	6 (23.1%)	25 (40.3%)	0.19
Vascular involvement	19 (73.1%)	46 (74.2%)	1.00
Number of lesions			0.98
1	2 (7.7%)	3 (4.8%)	
≥ 2	24 (92.3%)	59 (95.2%)	
Targeted immunotherapy	14 (53.8%)	35 (56.5%)	1.00
Median treatment cycle	4.0 (2.0-6.0)	3.0 (1.8-6.0)	0.69
ECOG			0.18
0	9 (34.6%)	31 (50.0%)	
1	9 (34.6%)	22 (35.4%)	
2	8 (30.7%)	9 (14.5%)	

Abbreviations: ECOG: Eastern Cooperative Oncology Group Performance Status Score.

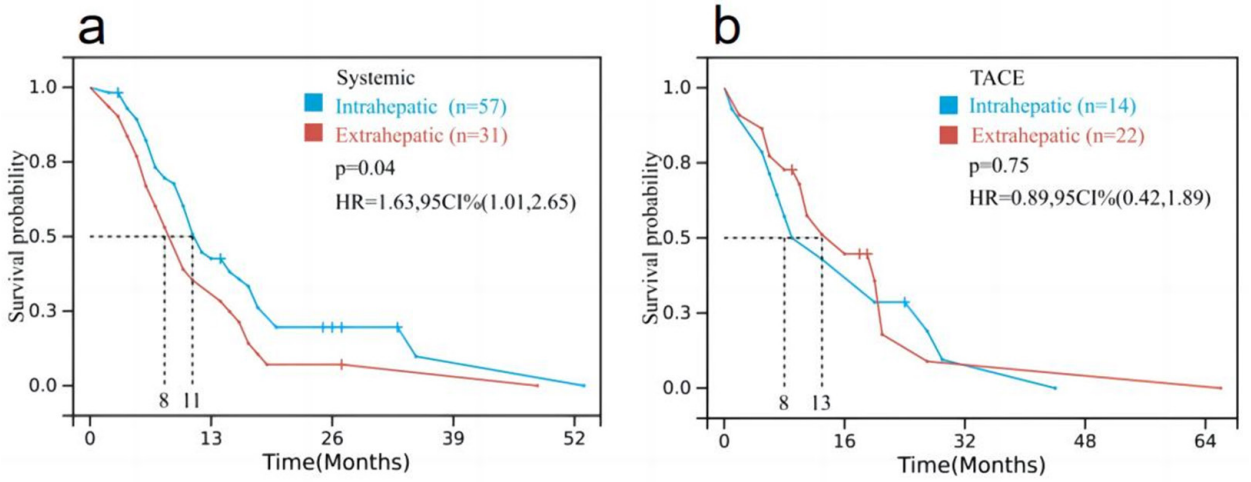

Figure 3. Survival curve of tumor metastasis sites. a: For patients undergoing systemic chemotherapy; **b**: For patients receiving TACE treatment.

among patients with varying tumor diameters in the TACE group. Table 4 show cases the subsequent analysis of the tumor characteristics of patients who received systemic chemotherapy, with a maximum tumor diameter of 6 cm serving as the standard.

3.6. Treatment-related adverse events (TRAE)

An analysis of treatment-related adverse events (TRAE) was conducted on all patients who received treatment (Table 5). Among the 124 patients included in this study, 47 (37.9%) experienced treatment-related adverse events. Among these 47 patients, 38 (43.2%) had grade 1-2 events, and 9 (10.2%) had grade 3 or above adverse events. The grade 3 adverse events primarily manifested as lymphocyte reduction in 6 (4.8%) patients, neutrophil reduction in 6 (4.8%) patients, and platelet reduction in 8 (6.5%) patients. This may be associated with the bone marrow suppression induced by chemotherapy drugs. There were 12 (9.7%) patients with immune-related adverse events (irAEs), mainly presenting as immune-related pneumonia after treatment. In addition, the majority of patients (77, 62.1%) experienced weight loss after treatment, all of which were grade 1-2 adverse events. Among the patients who received TACE, the main manifestation was liver function impairment after embolization, all of which were grade 1-2 adverse events. Alanine aminotransferase increased in 14 (38.9%) patients; aspartate aminotransferase increased in 14 (38.9%) patients. All the related adverse events were resolved after treatment discontinuation and symptomatic treatment.

4. Discussion

In the past three years, the core frontier of ICC research has centered on chemotherapy combined with targeted immunotherapy and stratified treatment based on tumor characteristics (*e.g.*, tumor size, metastasis site, and the influence of physical condition on treatment selection) (*14*). By analyzing subgroups of patients undergoing systemic chemotherapy or TACE, it was found that both local chemotherapy combined with targeted immunotherapy and systemic chemotherapy combined with targeted immunotherapy resulted in more favorable long-term survival and PFS outcomes compared to patients who received only chemotherapy drugs or only TACE. This phenomenon might be ascribed to the support of targeted combined immunotherapy. As confirmed in the "TOPAZ-1" study, durvalumab plus GC had superior OS compared with placebo, with a mOS of 12.9 months (11.6-14.1 months) *vs.* 11.3 months (10.1-12.5 months) ($p < 0.05$). In the KEYNOTE-966 study, pembrolizumab combined with GC had a better overall survival compared with placebo in patients with advanced biliary tract cancer, with a mOS of 12.7 months (11.5-13.6 months) and 10.9 months (9.9-11.6 months), respectively ($p < 0.05$) (*12,13*). In our study, patients who received systemic chemotherapy combined with targeted immunotherapy had a better survival than those who received chemotherapy alone, 16 months (4-53 months) *vs.* 6 months (2-15 months) ($p < 0.05$). Systemic chemotherapy combined with targeted immunotherapy also has better survival performance.

Although there are currently no specific targeted

Table 5. Analysis of treatment-related adverse events

Events *n* (%)	TACE *n* = 36		Systemic *n* = 88	
	Grade 1–2	Grade 3 or higher	Grade 1–2	Grade 3 or higher
Lymphocytes	5 (13.9)	0 (0)	20 (22.7)	5 (5.7)
Neutrophils	6 (16.7)	1 (2.8)	21 (23.9)	5 (5.7)
PLT	8 (22.2)	1 (2.8)	23 (26.1)	7 (8.0)
Anemia	4 (11.1)	1 (2.8)	12 (13.6)	2 (2.3)
ALB	5 (13.9)	1 (2.8)	19 (21.6)	3 (3.4)
ALT	12 (33.3)	0 (0)	10 (11.4)	0 (0)
AST	12 (33.3)	0 (0)	10 (11.4)	0 (0)
TBIL	10 (27.8)	0 (0)	9 (10.2)	0 (0)
Hypertension	10 (27.8)	0 (0)	14 (15.9)	0 (0)
High blood sugar	9 (25.0)	0 (0)	12 (13.6)	0 (0)
Anorexia	5 (13.9)	0 (0)	17 (19.3)	0 (0)
Nausea	6 (16.7)	0 (0)	10 (11.4)	0 (0)
Diarrhea	7 (19.4)	0 (0)	11 (12.5)	0 (0)
Oral ulcer	7 (19.4)	0 (0)	9 (10.2)	0 (0)
URTI	3 (8.3)	1 (2.8)	8 (9.1)	3 (3.4)
Cough	4 (11.1)	0 (0)	9 (10.2)	0 (0)
Fatigue	6 (16.7)	0 (0)	21 (23.9)	0 (0)
Weight loss	8 (22.2)	0 (0)	69 (78.4)	0 (0)
Rash	7 (19.4)	0 (0)	13 (14.8)	0 (0)
Abdominal pain	8 (22.2)	0 (0)	6 (6.8)	0 (0)

Abbreviations: TACE: Transarterial Chemoembolization; PLT: platelet; ALB: albumin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TBIL: Total bilirubin; URTI: upper respiratory tract infection.

drugs for ICC, up to 40% of patients with biliary system malignant tumors possess potential targetable genetic variations, amplifications, and fusions, including FGFR2 fusion/rearrangement, IDH mutation, NTRK fusion, HER2 amplification/expression, BRAF mutation, RET fusion, *etc.* (*14-17*). Through genetic testing, some patients can derive benefits from targeted drugs *via* the discovery of variant genes. However, this study did not conduct in-depth gene analysis, which hindered us from determining the treatment options for patients with different molecular subtypes. Additionally, although immunotherapy provides limited long - term survival benefits for ICC patients, the combination of chemotherapy and targeted drug treatment can enhance OS.

Within the framework of systemic chemotherapy, patients with lesions restricted to the liver demonstrate higher treatment efficacy and longer survival durations in comparison to those with extrahepatic and lymph node metastases. This implies that early-stage patients can reap greater benefits from systemic chemotherapy and presents a potential for conversion therapy. In the process of clinical treatment decision-making, the scope of metastasis should be ascertained prior to commencing systemic chemotherapy. For patients with solely intrahepatic lesions, systemic chemotherapy can be given priority; for those with extrahepatic metastases, local control measures ought to be integrated.

Notably, during the course of whole-body chemotherapy, through the analysis of tumor sizes, it was observed that tumors with a diameter larger than 6 cm exhibited a more favorable treatment response in comparison to smaller tumors. Regarding large-diameter tumors that were responsive to chemotherapy, an earlier shrinkage effect might be more pronounced. However, in the survival analysis of local chemotherapy, no significant treatment disparities were detected, which warrants further investigation. In a subgroup analysis of a phase 3 study, "LEAP-012", of unresectable, nonmetastatic hepatocellular carcinoma, there was a trend toward better survival among patients with a larger tumor burden (number of tumors plus a maximum tumor diameter of more than 6cm) (*18*). For patients with a substantial tumor burden, liver dysfunction may ensue following the progression of TACE, leading to the forfeiture of the opportunity for subsequent treatment (*19,20*). For these patients, it may be more imperative to integrate systemic treatment in advance rather than awaiting the point at which TACE fails to yield benefits before commencing systemic treatment (*21,22*).

In the analysis of adverse events associated with tumor treatment, the primary adverse events in the TACE group were grade 1-2 liver function impairment, and there were no events above grade 3. The main adverse events in the systemic chemotherapy group were bone marrow suppression and weight loss. These conclusions can directly guide clinical pre-treatment. Before TACE, it is necessary to routinely safeguard liver function; before systemic chemotherapy, it is essential to prevent bone marrow suppression and enhance nutritional support, enabling patients to achieve the optimal therapeutic effect and a longer survival time (*23-25*).

Although there have been significant technological advancements and multimodal treatment approaches in clinical practice, the prognosis of ICC remains poor. Local combined with systemic treatment for patients with advanced ICC has gradually shown its effectiveness. Additionally, adjuvant and neoadjuvant chemotherapy, as well as multimodal treatment strategies based on molecular profiling for targeted therapy and immunotherapy, can be applied (*26,27*). These approaches can be discussed in surgical centers and multidisciplinary tumor committees (MDTs) to formulate the best treatment plan for ICC patients (*28*). Moreover, molecular analysis should be conducted for ICC, as approximately 25% of cases have genetic alterations that can be targeted for treatment, providing better evidence support for subsequent research and laying the foundation for subsequent "precision treatment" studies (*29,30*).

This study is a retrospective study with certain limitations, including selection bias. When conducting subgroup analysis for patients who received local chemotherapy, the sample size was relatively small. Moreover, not all patients underwent surgical staging, and there may be potential differences in staging among different treatment groups. However, to minimize this possibility, during the subsequent continuous treatment and follow-up of the patients, we used imaging monitoring to ensure the changes and authenticity of the patient's lesions. Despite these limitations, this study aims to find the best treatment plan for patients with advanced ICC who are not eligible for surgical resection.

In summary, the treatment methods for ICC are constantly being innovated. In this retrospective study, patients who received local chemotherapy, chemotherapy combined with targeted and immunotherapy, and those with lesions confined to the liver all exhibited better survival rates. Additionally, it was observed that when the tumor diameter was at the 6-cm boundary, systemic chemotherapy yielded better results in patients with tumors larger than 6 cm. The results of this study still need to be confirmed in more prospective studies.

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