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Efficacy analysis of drug-eluting beads transcatheter arterial chemoembolization combining systemic chemotherapy and immune checkpoint inhibitors in unresectable intrahepatic cholangiocarcinoma: a multicenter retrospective cohort study based on propensity score matching

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Abstract

Objective To investigate the efficacy and safety of drug-eluting beads transcatheter arterial chemoembolization(DEB-TACE) combined with systemic chemotherapy and immune checkpoint inhibitors in the treatment of unresectable intrahepatic cholangiocarcinoma.

Methods This study used retrospective cohort analysis to collect the clinical data of 209 patients with unresectable intrahepatic cholangiocarcinoma treated in Linyi Cancer Hospital, Affiliated Zhongshan Hospital of Dalian University, Affiliated Central Hospital of Dalian University of Technology from January 2020 to January 2024. The patients were divided into observation group and control group based on their treatment plans. The observation group was treated with DEB-TACE combined with systemic chemotherapy and immune checkpoint inhibitor, and the control group was treated with simple systemic chemotherapy and immune checkpoint inhibitor. Based on propensity score matching analysis, the clinical treatment efficacy, survival prognosis, and incidence of adverse reactions of two groups of patients were evaluated.

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Results 82 patients in the observation group received DEB-TACE combined with systemic chemotherapy and immune checkpoint inhibitors, The control group of 127 patients were treated with systemic chemotherapy and immune checkpoint inhibitors. After a propensity score matching analysis to control for the consistency of patient age, sex, tumor size, tumor number, Child grade, ECOG score, and tumor stage. Propensity score matching analysis created 71 pairs of patients in 2 groups. The objective response rate (ORR, 76.06%) and disease control rate (DCR, 97.18%) in the observed group were significantly higher than that in the control group (52.11%, 85.92%), Progression-free survival (PFS, 10 months) and overall survival (OS, 17 months) were higher than the control group (8 months, 11 months). The Cox proportional hazards model analysis revealed that, Child grade and treatment modality were independent predictors of PFS and OS in patients. The adverse effects during treatment were similar in the two groups, with no statistical difference.

Conclusions Compared with systemic therapy alone (systemic chemotherapy + immune checkpoint inhibitor), combined DEB-TACE improves the tumor control rate of patients with unresectable intrahepatic cholangiocarcinoma, extends the survival time and without increasing treatment-related adverse effects, which is a safe and feasible treatment modality.

Keywords Intrahepatic cholangiocarcinoma, Transcatheter arterial chemoembolization, Drug-eluting beads, Systemic therapy, Immune checkpoint inhibitor, Propensity score matching

Background

Intrahepatic cholangiocarcinoma (ICC) is a common primary liver malignancy in clinical practice, except for hepatocellular carcinoma. Its early symptoms are often atypical, and by the time medical attention is sought, the disease typically has progressed to its middle to late stages. Approximately 80% of patients miss out on opportunities for radical treatments like surgical removal and liver transplantation [1, 2]. Systemic chemotherapy is the main treatment for unresectable ICC patients, and combined with immune checkpoint inhibitors further improves treatment efficacy. However, there are still some patients who terminate anti-tumor treatment due to treatment side effects or treatment resistance, and their survival prognosis is not ideal, with a survival period of no more than 3 months [3–5]. Comprehensive therapy is still considered as the key to improve the survival prognosis of patients with intrahepatic cholangiocarcinoma [6, 7]. These treatments include cytotoxic therapy, targeted therapy and immunotherapy [8]. Transcatheter arterial chemoembolization (TACE) is an effective treatment for non-surgical treatment of liver cancer. With the improvement of embolization materials, Drug-eluting beads transcatheter arterial chemoembolization(DEB-TACE) has shown a broad application prospect in ICC [9–11]. Therefore, the combination of both may be more advantageous than the current chemotherapy and immune checkpoint inhibitors alone for advanced ICC. However, there are few reports on the combined use of DEB-TACE and systemic therapy for ICC both domestically and internationally. This study aims to conduct a preliminary study and explore the safety and efficacy of drug-eluting beads transcatheter arterial chemoembolization and systemic therapy in the treatment of unresectable intrahepatic cholangiocarcinoma, which is reported as follows.

Methods

Case selection

This study used a retrospective cohort analysis to collect clinical data of 209 patients with unresectable intrahepatic cholangiocarcinoma admitted to Linyi Cancer Hospital, Affiliated Zhongshan Hospital of Dalian University, Affiliated Central Hospital of Dalian University of Technology from January 2020 to January 2024. Among them, 82 patients received DEB-TACE combined with systemic chemotherapy and immune checkpoint inhibitors, and 127 patients received systemic chemotherapy and immune checkpoint inhibitors alone. Inclusion criteria: ① Age range of 18 to 80 years old (including 18 and 80 years old), regardless of gender; ② Pathological diagnosis confirmed by histological or cytological examination, meeting the diagnostic criteria for intrahepatic cholangiocarcinoma on the basis of clinical features, imaging, and tumor markers; ③ ECOG score ≤ 2 points, Child A/B level (5–7 points); ④ Clinical and follow-up data are complete. Exclusion criteria: ① Hepatocellular carcinoma or mixed hepatocellular carcinoma; ② Unable to effectively control extrahepatic metastases: lung metastasis combined with pulmonary dysfunction, bone metastasis cancer combined with uncontrollable bone pain or inability to take care of oneself, brain metastasis cancer combined with uncontrollable intracranial hypertension, etc.;③ Previously received anti-tumor treatments such as TACE, radiotherapy, and chemotherapy; ④ Lack of clinical and follow-up data.

Basic information

Basic clinical information of the patients was extracted, including gender, age, ECOG score, Child grade, tumor size, tumor number, tumor stage, presence of extrahepatic metastasis, tumor control, patient survival time, treatment side effects, etc.

Treatment methods

After the patient is admitted, general examinations and relevant examinations before treatment should be completed, and a comprehensive evaluation should be conducted to rule out treatment-related contraindications. The comprehensive treatment team for liver and gallbladder tumors discussed the patient's condition, stage, and basic physical condition, and combined with the wishes and economic situation of the patient and their family, ultimately determined the treatment plan (DEB-TACE combined with systemic therapy or systemic therapy).

DEB-TACE: the right femoral artery was punctured by Seldinger method, the RH liver tube routine abdominal artery, common hepatic artery angiography, according to the tumor site, size, and the complete tumor staining, auxiliary diaphragmatic artery, superior mesenteric artery, left gastric artery, right renal artery, angiography, to identify all the feeding artery of the tumor. After the microcatheter was selected to the tumor feeding artery, the pre-configured drug loaded microsphere (microsphere diameter: 100～300 μ m, loaded drug: epirubicin 60～80 mg) was slowly injected until embolization was stopped when the contrast flow rate stopped. After 5 min, embolization occurred until the tumor staining completely disappeared. If the tumor is still stained, embolization was added. DEB-TACE was performed once every 6 weeks for 1 to 2 times.

Systemic therapy: primary systemic regimen was gemcitabine combined with oxaliplatin and PD1-inhibitor. Gemcitabine was administered intravenously at a dose of 1000 mg/m^2 on days 1 and 8, and oxaliplatin was administered intravenously at a dose of 85 mg/m^2 on days 1, and PD1-inhibitor [Carelizumab (200 mg) or Sintilimab (200 mg) or Tirelizumab (200 mg) or Treprizumab (240 mg)] was administered intravenously on days 1. These cycles were repeated every 21 days. In the observation group, administration of systemic therapy was first within 2–3 weeks after the initiated DEB-TACE.

Postoperative follow-up

The first evaluating was administered at 2 cycles of treatment after, during which, the abdominal contrast-enhanced computed tomography (CT), or magnetic resonance (MRI) was carried out for assessment of tumor response. After the first follow-up, subsequent visit was conducted every 2–3 months. During the follow-up process, when there is intolerable toxicity, disease progression and other conditions, the follow-up treatment was discussed according to the needs of our comprehensive hepatobiliary tumor treatment team and the patient.

Efficacy evaluation

According to the modified efficacy evaluation criteria for solid tumors (m RECIST), tumor response was evaluated by two radiologists with 10 years of work experience: efficacy was determined as complete response (CR), partial response (PR), stable disease (SD), and disease progression (PD). Objective response rate (ORR) = (CR + PR) /total cases × 100%, disease control rate (objective response rate, DCR) = (CR + PR + SD) /total cases × 100%. Progression-free survival (PFS) was defined as the time from treatment initiation to PD or death, and the time from treatment initiation to last follow-up; overall survival (OS) was defined as the time from treatment initiation to death or last follow-up. Adverse reactions: Adverse reactions: According to the Common Terminology Criteria for Adverse Events (CTCAE) 5.0 of the National Cancer Institute (NCI) in the United States, the criteria are classified as grades 0–4.

Statistical analysis

IBM SPSS software (version 21.0) and the R software (Version 4.1.1) were used for statistical analysis of the detected data. The quantitative data(age) did not follow a normal distribution, which were expressed as Median (Quartile Range); and Wilvoxon rank sum test was used for comparison. The Categorical variables(gender, ECOG score, child grading, tumor characteristics, extrahepatic metastases, tumor control rate, treatment side effects, etc.) were expressed as frequency and percentage; a comparison was carried out by using the chi-square test. Propensity score matching was used to minimise selection bias, the PSM ratio was set to a 1:1 ratio. Age, sex, Child-pugh grade, ECOG score, extrahepatic metastasis, tumor size, tumor number, tumor Staging were included in the matching model. The Kaplan–Meier approach was used to calculate OS and PFS, plot survival curves, while differences in survival were assessed using the log-rank sum test. The univariate and multivariate analyses on prognosis of patients were conducted by Cox regression model. All statistical tests were two-sided, and a $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

From January 2020 to January 2024, a total of 301 patients with ICC were admitted to Linyi Cancer Hospital, Affiliated Zhongshan Hospital of Dalian University and Affiliated Central Hospital of Dalian University of Technology. After excluding resectable ICC ($n = 59$), combined

hepatocellular-cholangiocarcinoma (cHCC-CCA, $n=7$), incomplete follow-up data ($n=9$), uncontrolled distant metastases ($n=6$), and previous anti-tumor treatment ($n=11$), 209 patients were included in the data analysis (Fig. 1). Among 209 patients, 82 (observation group) received DEB-TACE combined with systemic treatment, while 127 (control group) received simple systemic treatment. We conducted a 1:1 propensity score matching between the two groups. After PSM, a control group of 71 cases and an observation group of 71 cases were

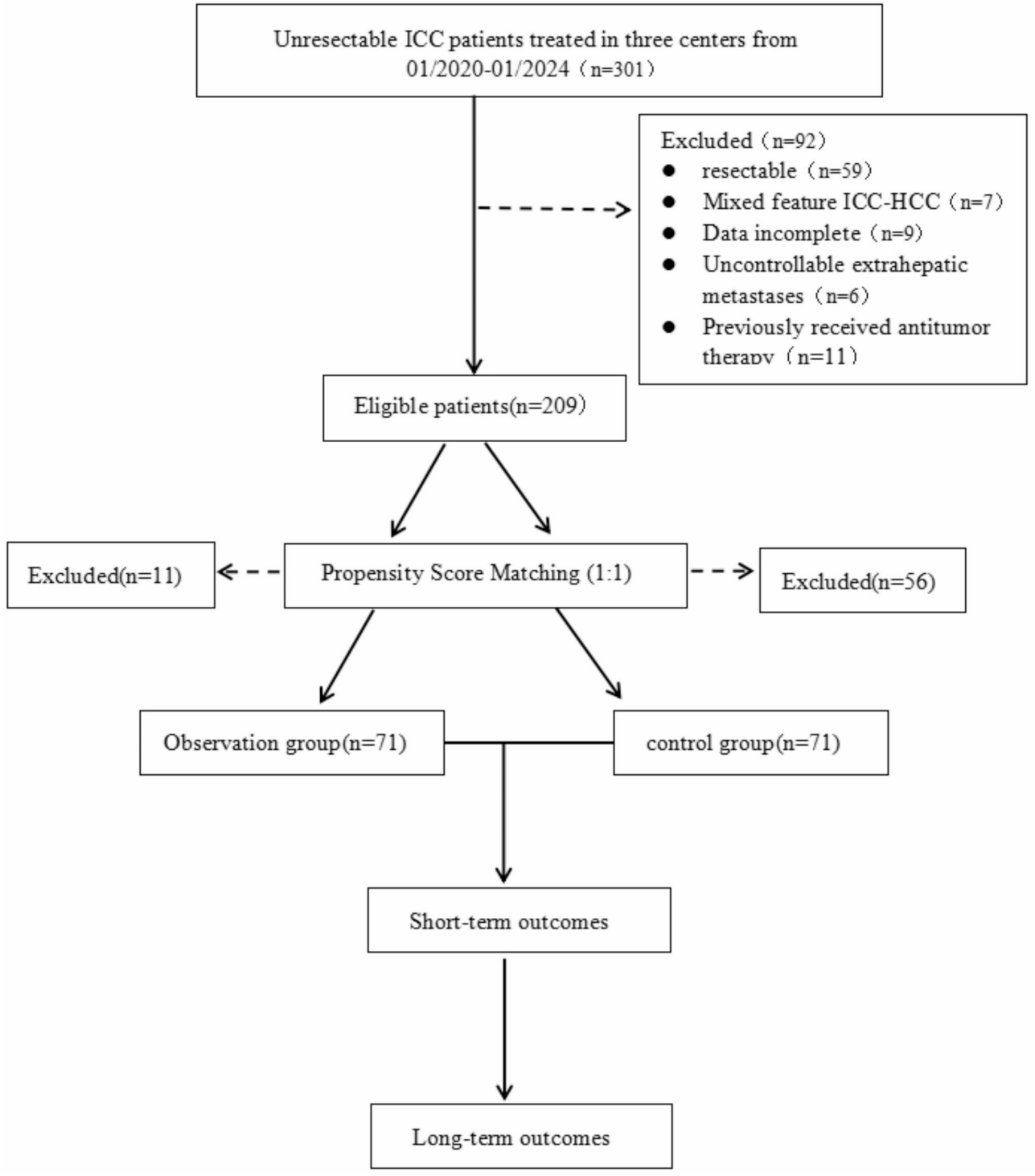

Fig. 1 Flowchart of this study. 209 patients who underwent in three centers from January 2020 to January 2021 were collected and divided into control and observation groups. After propensity-score matching, shortand long-term outcomes were compared

included in this study. Prior to matching, there were statistically significant differences in some baseline features between the two groups, particularly in terms of tumor characteristics, including ECOG score ($P = 0.018$), extrahepatic metastasis ($P = 0.013$), tumor size ($P = 0.002$), and tumor staging ($P = 0.040$). As shown in Table 1, there was no statistically significant difference in the covariates between the two groups after PSM ($P > 0.05$), and the SMD values of each factor were all < 0.2, indicating an improvement in balance.

Tumor response evaluation

Before PSM, In the observation group, 82 patients, ORR 74.39% (61 / 82,CR 1, PR 60), DCR 96.34% (79 / 82,SD 18); In the control group, 127 patients, ORR 36.22% (46 / 127,PR 46) and DCR 89.76% (114 / 27,SD 68). The ORR was significantly higher than the control group ($P < 0.001$), and the DCR of the observation group was not different from the control group ($P = 0.081$). After PSM, In the observation group, 71 patients, ORR was 76.06% (54 / 71,CR 1, PR 53), DCR 97.18% (69 / 71,SD 15), in the control group, 71 patients ORR was 52.11% (37 / 71,PR 37), DCR 85.92% (61 / 71,SD 24), both the ORR and DCR were significantly higher than the control group ($P = 0.004$; $P = 0.025$)(Table 2).

Survival analysis

Follow-up to June 1,2024 was 4 to 31 months, median follow-up of 12 months, mean (13.55 ± 5.05) months. 89.02% (73 / 82) of patients in the observation treatment group died and 88.19% (112 / 127) of patients in the control group died. Before PSM, the median PFS in the observation group was 10 months(95%*CI*: 9.29–10.71), and the median PFS in the control group was 9 months (95%*CI*: 8.40–9.60), and The two groups were tested by Log Rank (Mantel Cox) with a $\chi 2 = 3.885$ and $P = 0.059$. The survival curves are shown in Fig. 2a, and the difference in results between the two groups is statistically insignificant. After PSM, the median PFS in the observation group was 10 months(95%*CI*: 9.36–10.64), and the median PFS in the control group was 8 months (95%*CI*: 7.16–8.84). The two groups were subjected to Log Rank (Mantel Cox) test with $\chi 2 = 21.991$ and $P<0.001$. The survival curves are shown in Fig. 2b, and the difference between the two groups is statistically significant. Before PSM, the median OS in the observation group was 17 months (95%*CI*:

Table 1 Baseline characteristics of patients in the two groups before and after PSM

Characteristics	Before PSM				After PSM			
	Observation group($n = 82$)	Control group($n = 127$)	SMD	*P*	Observation group($n = 71$)	Control group($n = 71$)	SMD	*P*
Median (IRQ)	60(37~79)	59(35~78)	0.039	0.969	60(37~79)	60(35~77)	0.059	0.731
Sex				0.974				0.723
Male	56	87	0.180		48	46	0.010	
Female	26	40	0.180		23	25	0.010	
Child-Pugh Grade				0.406				0.797
A5	49	71	0.101		42	41	0.029	
A6	22	44	0.242		19	22	0.038	
B7	11	12	0.192		10	8	0.015	
ECOG Score				0.018				0.699
0	32	30	0.389		28	24	0.036	
1	43	91	0.443		37	42	0.019	
2	7	6	0.196		6	5	0.006	
Extrahepatic metastasis				0.013				0.835
Yes	65	80	0.236		56	57	0.033	
No	17	47	0.236		15	14	0.033	
Tumor size, cm				0.002				0.392
≤ 5	28	71	0.104		26	31	0.051	
>5	54	56	0.104		45	40	0.051	
Tumor number				0.990				0.730
1~3	49	76	0.072		43	45	0.046	
>3	33	51	0.072		28	26	0.046	
Tumor Staging				0.040				0.604
II	5	17	0.283		4	7	0.068	
III	12	30	0.453		11	12	0.023	
IV	65	80	0.604		56	52	0.017	

PSM: Propensity Score Matching; IQR: InterQuartile Range; ECOG: Eastern Cooperative Oncology Group; SMD: Standardized Mean Difference. SMD<0.1 considered as well balanced among baseline variables

Table 2 Summary of response rates before and after PSM

All response, *n* (%)	Before PSM			After PSM		
	Observation group(*n* = 82)	Control group(*n* = 127)	*P*	Observation group(*n* = 71)	Control group(*n* = 71)	*P*
CR	1(1.22)	0(0)		1(1.41)	0(0)	
PR	60(73.17)	46(36.32)		53(74.65)	37(52.11)	
SD	18(21.95)	68(53.54)		15(21.12)	24(33.81)	
PD	3(3.66)	13(10.24)		2(2.82)	10(14.08)	
ORR	61(74.39)	46(36.32)	<0.001	54(76.06)	37(52.11)	0.002
DCR	79(96.34)	114(89.76)	0.081	69(97.18)	61(85.92)	0.015

CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progression Disease; ORR: Objective Response Rate; DCR: Disease Control Rate; PSM: Propensity Score Matching

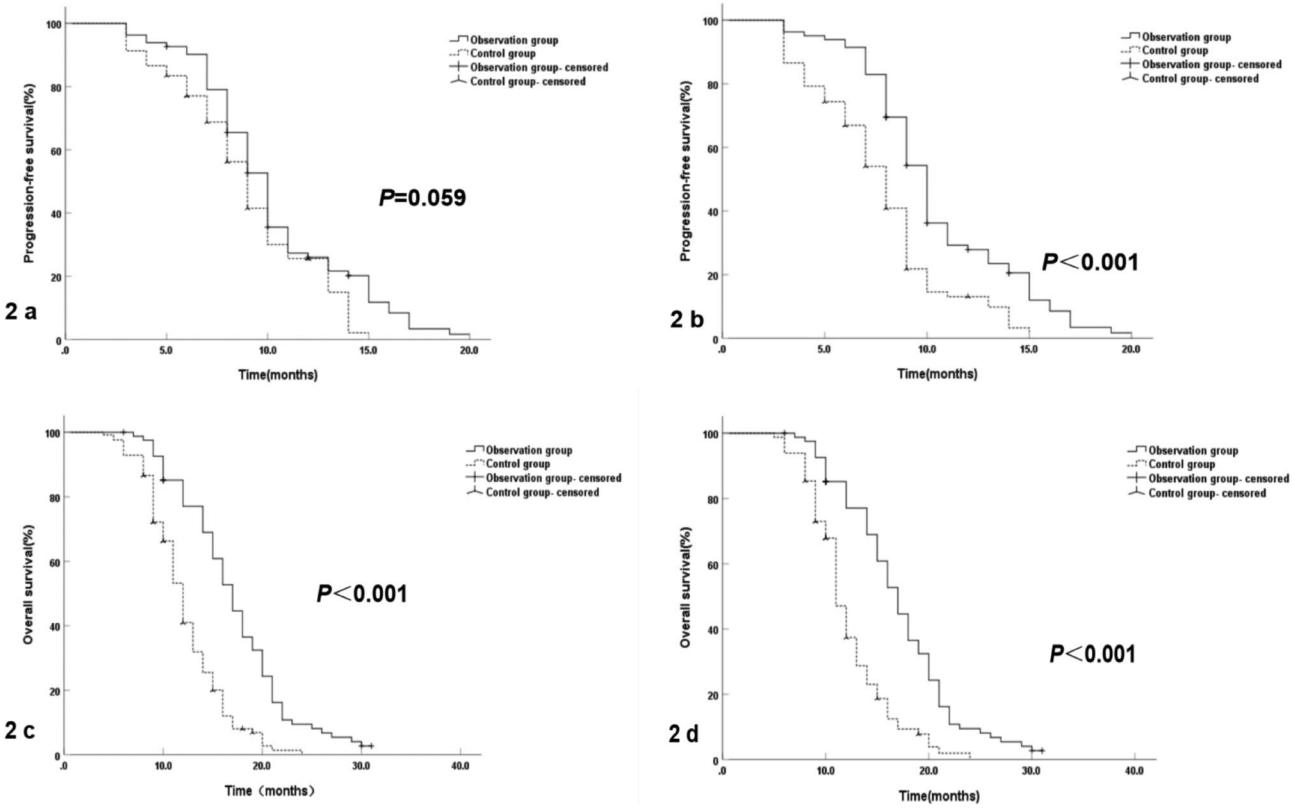

Fig. 2 Kaplan-Meier analyses of progression-free survival and overall survival in the two groups before PSM and after PSM

15.61 ~ 18.39), and the median OS was 12 months(95%*CI*: 11.30–12.70). The two groups were subjected to Log Rank (Mantel Cox) test with $\chi 2 = 42.085$ and $P<0.001$. The survival curves are shown in Fig. 2c, and the difference in results between the two groups is statistically significant. After PSM, the median OS of patients in the observation group was 17 months, 95%*CI*: 15.61 ~ 18.39, and the median OS of the control group was 11 months, 95%*CI*: 10.26 ~ 11.73. The two groups were subjected to Log Rank (Mantel Cox) test with $\chi 2 = 34.826$ and $P<0.001$. The survival curves are shown in Fig. 2d, and the difference in results between the two groups is statistically significant. Figure 3 for typical cases.

Prognostic factors analyses

Univariate analysis showed that Child grade, tumor size, tumor number and treatment mode were factors affecting the PFS of patients ($P<0.05$); statistically significant differences in univariate analysis were included in multivariate analysis showed that Child grade and treatment mode were independent influencing factors affecting the PFS of patients ($P<0.05$). Univariate analysis showed that Child grade, tumor size, tumor number and treatment mode were factors affecting the OS of patients ($P<0.05$); statistically significant differences in univariate analysis were included in multivariate analysis showed that Child grade and treatment mode were independent influencing factors affecting the OS of patients ($P<0.05$). Results of

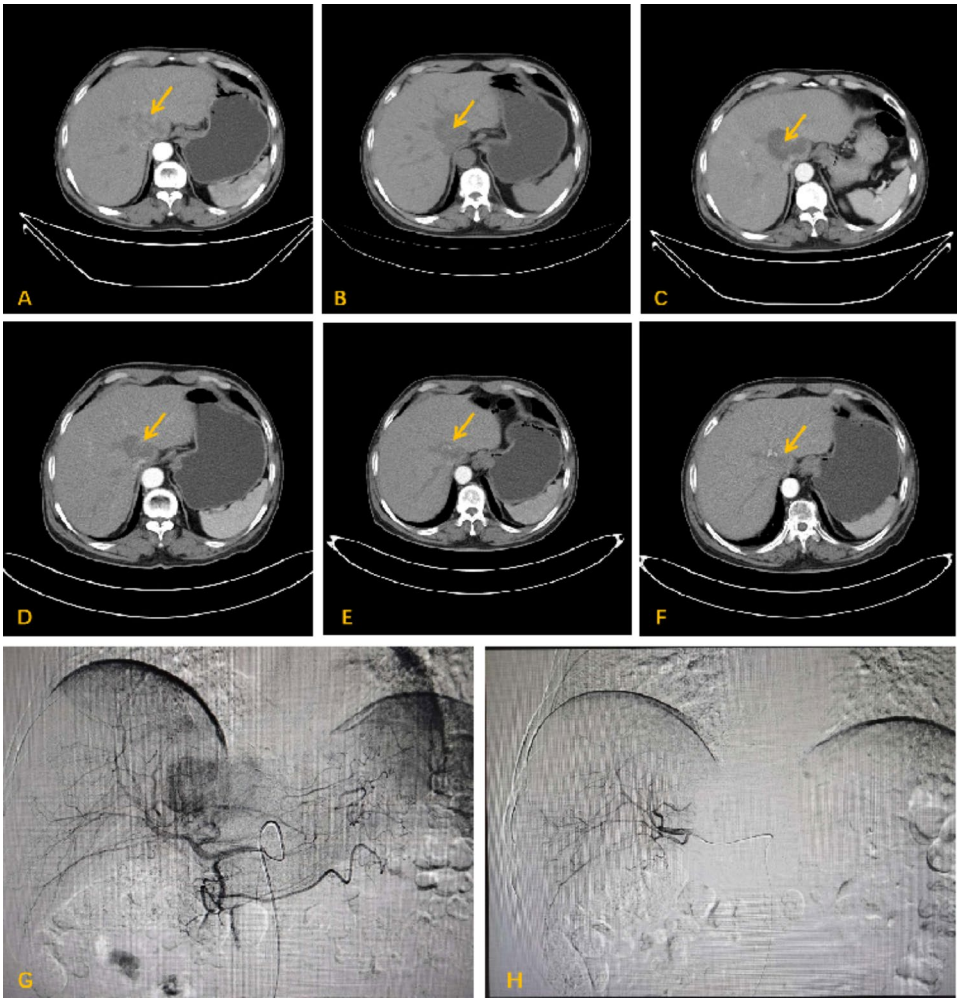

Fig. 3 **A**: Enhanced CT images before interventional treatment. **B**: Plain CT scan showed signifcant low-density changes of the tumor 5 days after treatment. **C**: Enhanced CT showed signifcant low-density changes of the tumor 1.5 months after treatment, without any enhancement. **D**: Enhanced CT showed that the lesion was signifcantly reduced, and no signifcant enhancement was found 3 months after treatment. **E**:6 months after treatment, the features of the lesion were further reduced compared to group D, without signifcant changes. **F**: 12 months after treatment, the features of the lesion were basically the same as those in E, without signifcant changes. **G**: Digital subtraction angiography during the interventional procedure, suggesting that the lesion in the liver was stained and supplied by the right hepatic artery branch. **H**: Image after interventional embolization, showing complete disappearance of tumor staining

the univariate and multivariate analyses after matching are shown in Table 3.

Safety

After PSM, the DEB-TACE related adverse reactions in the observation group patients included fever, pain, nausea and vomiting, liver function damage, etc., all of which were ≤grade 2 and lasted for 5–7 days. After symptomatic treatment by internal medicine, all of them were relieved. There were no serious complications such as liver abscess, gastrointestinal perforation, liver and kidney failure. The adverse reactions that occurred during the systemic treatment of the two groups of patients, except for a few that were grade 3, were all grade 2 or below. After symptomatic treatment such as leukocyte elevation, antiemetic, gastric protection, and anti allergy, they improved. There was no statistically significant difference in the incidence of various adverse reactions between the two groups of patients during systemic treatment ($P>0.05$)(Table 4).

Discussion

ICC is a primary liver cancer originating from the epithelium of the secondary bile duct and its branches, accounting for 5%~10%, and is prone to extrahepatic metastasis, leading to low surgical resection rate [12, 13]. According to statistics, even if ICC obtains radical resection, the 5-year survival rate after surgery is only 20–40% [14, 15]. Patients with unresectable ICC often choose palliative radiotherapy and chemotherapy, mainly to delay tumor

Table 3 Prognostic factors associated with PFS and OS after PSM

Variables	Progression-free survival						Overall survival					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95%CI	*P*	HR	95%CI	*P*	HR	95%CI	*P*	HR	95%CI	*P*
Age (years) ≤60/>60	0.608	0.358~1.339	0.576				0.643	0.513~1.302	0.321			
Sex Female/Male	0.603	0.432~1.328	0.469				0.753	0.733~1.049	0.343			
Child-Pugh Grade A/B	0.364	0.211~0.672	0.012	0.489	0.291~0.813	0.026	0.672	0.581~0.952	0.017	0.703	0.523~0.955	0.026
ECOG Score 0/1–2	1.001	0.732~2.279	0.367				1.070	0.701~1.742	0.902			
Extrahepatic metastasis Yes/No	1.806	0.927~2.692	0.557				1.376	0.775~3.557	0.223			
Tumor size(cm) ≤5/>5	0.571	0.372~0.816	0.021	0.713	0.404~3.732	0.794	0.613	0.391~0.944	0.026	0.771	0.350~4.247	0.926
Tumor number 1~3/>3	0.857	0.661~0.979	0.037	0.715	0.661~2.031	0.150	0.701	0.502~0.816	0.041	0.779	0.408~3.179	0.706
Tumor Staging II-III/IV	0.676	0.559~1.443	0.370				0.852	0.569~1.402	0.277			
Treatment method (combined/not combined)	0.355	0.152~0.643	0.011	0.386	0.163~0.657	0.010	0.657	0.441~0.981	0.031	0.364	0.271~0.619	0.015

PFS: Progression-Free Survival; OS: Overall Survival; HR: Hazard Ratio; CI: Confidence Interva; PSM: Propensity Score Matching

Table 4 Incidence of adverse reactions of two groups during the treatment with systemic therapy

Adverse Reaction	Observation Group (*N* = 71)			Control Group (*N* = 71)			χ2	*P*
	Grades I~II (case)	Grades III~IV (case)	Incidence (%)	Grades I~II (case)	Grades III~IV (case)	Incidence (%)		
Bone marrow suppression	21	5	36.62	22	6	39.44	0.116	0.729
Nausea and vomiting	26	8	47.89	24	5	40.85	0.713	0.398
Rash	7	0	9.86	8	0	11.27	0.075	0.785
Reactive cutaneouscapillary endothelial proliferation	8	0	11.27	10	0	14.08	0.255	0.614
Hypothyroidism	5	0	7.04	6	0	8.45	0.099	0.754
Immunotherapy related pneumonia	3	0	4.23	3	0	4.23	0.000	1.000
Immunotherapy related hepatitis	4	0	5.63	3	0	4.23	0.150	0.698
Arthrodynia	4	0	5.63	5	0	7.04	0.119	0.731

progression and have poor overall survival prognosis. Studies have shown that immune checkpoint inhibitors combined with radiotherapy and chemotherapy are an effective treatment for biliary malignancies [16–18]. In a study of a GEMOX (gemcitabine plus oxaliplatin) regimen combined with camrelizumab for advanced bile duct malignancy, the combination resulted in an 89% DCR and a PFS rate of 50% at 6 months [19]. The mid-term results of KEYNOTE-966 Phase III clinical trial showed that compared with chemotherapy alone, chemotherapy combined with pembrolizumab can reduce the risk of death in advanced biliary malignancies by 17%, but the median OS was only prolonged by 1.8 months [20]. Systemic chemotherapy combined with immune checkpoint inhibitors is a promising treatment option for biliary malignancies, but the survival benefits seem to be limited. As a palliative treatment, most patients will experience intolerable toxicity or disease progression during continuous systemic therapy, ultimately leading to treatment termination. Therefore, it is urgent to explore and solve a new and effective treatment plan for ICC, especially for unresectable ICC.

TACE is considered an effective local treatment for unresectable hepatocellular carcinoma, but the blood supply vessels are the basis for TACE treatment of liver tumors. ICC is often considered the main reason for poor TACE efficacy due to its thin blood vessels and lack of blood supply to tumors [21]. In addition, iodinated oil has always been the main embolic agent for TACE. As a permanent embolic agent, iodinated oil requires superselective tumor vessel embolization to further reduce liver damage and ectopic embolism. When DSA imaging shows a lack of blood supply, iodinated oil often deposits poorly, which affects the efficacy of TACE in treating ICC [22, 23]. With the continuous development of embolization materials and technologies, TACE therapy is gradually entering the era of microsphere embolization. As a new type of embolization material, drug-eluting beads have the dual effects of embolization of tumor arteries and slow release of chemotherapy drugs, and have shown good application prospects in the treatment of liver cancer with poor blood supply [24, 25]. In the previous study, our team applied domestic drug-loaded microspheres TACE to treat the liver metastasis of colorectal cancer to achieve satisfactory treatment results, and significantly prolonged the survival of patients [26]. Luo et al. treated 37 patients with unresectable ICC using DEB-TACE, with an ORR of 67.6% and a median OS of 376 days [27]. In a prospective study comparing DEB-TACE with c-TACE in the treatment of ICC, Wang et al. found that the ORR of patients in the DEB-TACE group was 70%, significantly better than the 20% in the c-TACE group. PFS was prolonged by 5 months, and OS was prolonged by 2.5 months [28]. These studies suggest that drug loaded microspheres may be more suitable for TACE treatment of intrahepatic cholangiocarcinoma. The high conformability of drug loaded microspheres can better embolize the donor blood vessels, while synergistically enhancing the chemoembolization effect with slowly releasing chemotherapy drugs. Zhou et al. conducted a retrospective analysis of 88 patients with unresectable ICC treated with DEB-TACE, and the study suggests that combined systemic therapy is a protective factor for improving prognosis [29]. The DEB-TACE procedure cannot achieve complete tumor embolization and necrosis, and it still cannot overcome the problem of tumor recurrence and progression. Therefore, for unresectable ICC patients, combining TACE with systemic treatment can complement each other's advantages, address the shortcomings of monotherapy, and may further improve the overall treatment effect.

In this study, the combined use of DEB-TACE and systemic therapy, or the application of systemic therapy alone, in unresectable ICC patients demonstrated that the observation group exhibited higher ORR and DCR than the control group. The observation group of patients demonstrated significant low-density necrosis of liver tumors 5–7 days post-intervention, with some showing honeycomb-like changes, indicating that despite the lack of blood supply and fine tumor vessels in ICC,

DEB-TACE effectively embolizes the feeding arteries of the tumor, rapidly reducing tumor burden. Subsequent chemotherapy and immune checkpoint inhibitor treatments sustained this favorable state of tumor necrosis, therefore led to reduced recurrence risk and favorable survival profile in ICC patients. Follow-up observations indicated that the observation group patients achieved a median PFS of 10 months and a median OS of 17 months, significantly longer than those in the control group. The Cox multivariate prognostic analysis revealed that combined DEB-TACE treatment serves as a protective factor for patient survival outcomes (PFS and OS), further indicating that in unresectable ICC patients, the addition of DEB-TACE to systemic chemotherapy and immune checkpoint inhibitor treatments can further extend progression-free and overall survival, significantly improving patient prognosis. Furthermore, the prognosis of patients is unaffected by the size and number of tumors, particularly for multiple liver tumors. During DEB-TACE, a hybrid approach of superselective catheterization to the feeding artery embolization and regional tumor-specific embolization is employed. Regional tumor-specific embolization aligns more closely with the fundamental principles of radical treatment for malignant tumors. ICC patients, free of adverse conditions like hepatitis and cirrhosis, exhibit greater tolerance to DEB-TACE treatment. Regarding multiple tumors, it might indicate various cellular origins and molecular evolutions, which made them difficult to treat. While by using DEB-TACE, multiple tumors were easier to embolism, which led to favorable prognosis in ICC patients. Studies have shown that DEB-TACE is more suitable for the treatment of multiple ICC, which is consistent with the results of this study [28]. Certainly, the prognostic factor analysis in this study also suggested that liver function is a protective factor for the survival prognosis of ICC patients, which is similar to TACE treatment in HCC [30, 31], In the treatment of liver tumors, the maintenance of good liver function is an important basis for antitumor and improved prognosis.

In this study, the common adverse reactions after DEB-TACE treatment were fever, pain, nausea and vomiting, all grade 2, lasting 5 d to 7 d, and relieved after symptomatic treatment, which was consistent with the reports related to adverse reactions of DEB-TACE [32, 33]. Liver abscess is considered as one of the most serious complications of TACE treatment, and too small microparticle size and excessive embolization are considered as the main cause of liver abscess after TACE [34]. In this study, drug-eluting beads ranging from 100 to 300 μm were employed, with no liver abscesses observed throughout 35 TACE sessions, confirming the safety of this embolization approach for treating ICC. The primary systemic therapy-related adverse reactions in this study included bone marrow suppression, gastrointestinal issues, rash, liver dysfunction, and treatment-associated pneumonia. Immune-related skin reactions are a common adverse effect of ICI therapy, occurring in approximately 30–45%.> Grade 2 skin reactions are uncommon [35, 36]. In this study, the primary skin adverse reactions were rash and capillary hyperplasia, occurring in about 23.24% of the patients, a rate lower than that reported in the literature. Additionally, we observed other adverse reactions to ICI therapy including treatment-related pneumonia, hepatitis, and hypothyroidism, all below Grade 3, with no severe immunological side effects. Recent literature has noted fatal adverse reactions associated with immune checkpoint inhibitor therapy, such as fatal myocarditis and hepatotoxicity, which have been reported to result from combined treatments [37]. Although no fatal adverse reactions occurred in this study, it is still believed that monitoring and management of immune-related adverse reactions must be enhanced in future treatments.

As we all known, the prognosis for patients with unresectable advanced biliary tract carcinoma is poor. Although this study showed that the efficacy of interventional therapy combined with systemic therapy is superior to standard first-line therapy, these results were still unsatisfactory compared to hepatocellular carcinoma. Individualized precision treatment based on genetic testing and molecular targeted detection is in full swing. According to statistics, up to 40% of BTC patients have at least one target gene that can be utilized or potentially explored, which demonstrates the great potential of precision treatment [38]. However, these drugs may still be lacking at present, and local combined with systemic treatment is still the main treatment for unresectable ICC.Our previous studies have found that m-TACE can enhance the positive anti-tumor ability of patients with malignant liver tumors, and these changes in the micro environment include the increase of NK cells and CD4+/CD8 + ratios and the decrease of Treg cells and IL-17 A level [39, 40]. Changes in the immune microenvironment bring additional anti-tumor benefits to the patient, and if combined with other treatment methods, an anti-tumor"superposition phenomenon"may occur. Of course, this is still a speculation, and deeper mechanistic studies are needed to confirm this speculation. It is also interesting to provide a theoretical basis for combined targeted and immunotherapy after intervention, as this research may subvert conventional treatment methods and thinking patterns.

The present study has several limitations that need to be addressed. First, the retrospective and non-randomized nature of this study makes it subject to certain selection bias. Second, participants who underwent treatment in this study may be preliminary selected by us, this limited the external validity of our results. Third, meaningful subgroup analyses could not be conducted because of the

sample size. Fourth, the doctors who perform DEB-TACE were not completely unified, a denser embolization could be achieved by a more distal and superselective intubation to improve the embolization effect, but we could not analyze their correlation. In short, Future large-scale prospective clinical studies are required to validate the efficacy and safety of this approach. Additionally, the mechanism of action for this combined approach requires further in-depth investigation.

In conclusion, in this propensity-score matching analysis, we have found that drug-eluting beads transcatheter arterial chemoembolization and systemic therapy, are safe and effective for treating unresectable ICC, offering a favorable treatment option for the comprehensive management of advanced ICC in clinical practice.

Abbreviations

CR	Complete response
CT	Computed tomography
DCR	Disease control rate
DEB-TACE	Drug-eluting beads Transcatheter arterial chemoembolization
ECOG	Eastern cooperative oncology group
ICC	Intrahepatic cholangiocarcinoma
mRECIST	Modified response evaluation criteria in solid tumors
MRI	Magnetic resonance imaging
ORR	Objective response rate
OS	Overall survival
PD	Progression disease
PFS	Progression-free survival
PR	Partial response
PSM	Propensity score matching
SD	Stable disease
SMD	Standardized mean difference
TACE	Transcatheter arterial chemoembolization

Author contributions

L.S.,Z.G.S.,Y.G.J and W.D. conceived and designed the project. W.Q.D, Y.S.H and L.L. collected the data. L.S.and Y.S.H. analyzed and interpreted the data. L.S.,W.Q.D and W.D. drafted the manuscript. All authors read and approved the final manuscript.

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Data availability

The original contributions presented in the study are included inthe article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Declarations

Ethics statement

This study adhered to the principles outlined in the Declaration of Helsinki and met all relevant requirements in China. Approval for the study was obtained from The Ethics Committee of Linyi Cancer Hospital, The Ethics Committee of Affiliated Zhongshan Hospital of Dalian University, The Ethics Committee of Affiliated Central Hospital of Dalian University of Technology. Due to the retrospective cohort study design, a waiver of documentation of consent was used; the waiver for consent was granted by The Ethics Committee of Linyi Cancer Hospital, The Ethics Committee of Affiliated Zhongshan Hospital of Dalian University, The Ethics Committee of Affiliated Central Hospital of Dalian University of Technology.

Competing interests

The authors declare no competing interests.

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