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ORIGINAL RESEARCH

Evaluation of Combined Lipiodol and Epirubicin-Loaded Drug-Eluting Bead Transarterial Chemoembolization for Unresectable Hepatocellular Carcinoma

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Purpose: To evaluate the short-term clinical efficacy, side effects and risk factors affecting the clinical effectiveness of the combination of lipidol and epirubicin-loaded drug-eluting bead transarterial chemoembolization (DEB-TACE) in the treatment of hepatocellular carcinoma (HCC).

Methods: A total of 120 patients with HCC who underwent DEB-TACE plus lipiodol treatment from December 2017 to August 2020 were enrolled. Short-term local tumor response was evaluated using mRECIST. Postoperative complications and liver function disorders were analyzed on the basis of clinical parameters.

Results: The median overall survival (OS) was 31.44 months (95% CI: 27.24–35.46 months). According to mRISIST, the disease control rate is 75.8%. The objective response rate was 22.5%. Multivariate analysis showed that tumor size and conversion therapy were the two independent prognostic factors correlated with OS. Postoperatively, liver function showed transient changes and no grade 4 adverse events were observed. Most of the postoperative complications were characterized by post-embolism syndrome.

Conclusion: The combination of lipiodol and DEB-TACE offers effective local control and safety for patients with HCC. Lipiodol used in the DEB-TACE procedure provides several additional benefits for drug-eluting beads embolization. The synergistic effect of these two methods enhances therapeutic efficacy through dual antitumor mechanisms.

Keywords: drug-eluting bead, embolization, hepatocellular carcinoma, lipiodol, transarterial chemoembolization

Introduction

Hepatocellular carcinoma (HCC) remains the third leading cause of cancer-related mortality worldwide, with more than 70% of patients diagnosed in advanced stages and ineligible for curative therapies.[1] Transarterial chemoembolization (TACE) is the standard treatment for unresectable intermediate stage HCC, offering a survival benefit over supportive care with response rates of 35–42%.[2,3] Conventional TACE (C-TACE) combines lipiodol-based cytotoxic drug delivery with arterial embolization, exploiting lipiodol's dual role as a drug carrier and embolic agent. Its intratumoral retention also serves as a radiological marker for the evaluation of treatment response.[4,5] While the treatment landscape for advanced HCC has been revolutionized by combinations based on immune checkpoint inhibitor (IO), locoregional therapies such as transarterial chemoembolization (TACE) play a critical role, either as a primary treatment for intermediate stage disease or in combination with systemic therapies for more advanced cases.[6]

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Drug-eluting bead TACE (DEB-TACE), an advanced TACE technique, employs microspheres to load and gradually release chemotherapeutic agents, theoretically improving tumor targeting while reducing systemic toxicity.[7] However, meta-analyses and randomized trials have yet to demonstrate significant superiority of DEB-TACE over C-TACE in terms of overall survival (OS) or tumor response.[8–10] This highlights the need to optimizing TACE strategies to bridge efficacy gaps.

Despite the established roles of lipiodol in C-TACE and microspheres in DEB-TACE, their combined application (C&D-TACE) remains underexplored. Lipiodol can augment DEB-TACE by improving drug retention, improving embolic effects, and providing real-time imaging guidance during procedures. Such synergy could address limitations of single-agent approaches, such as incomplete embolization or rapid drug clearance.

Furthermore, the evolving treatment paradigm, dominated by IO, underscores the need to reevaluate locoregional approaches. In this context, refining TACE techniques to achieve more robust and predictable tumor necrosis, potentially through combinations like C&D-TACE.[11,12]

This study evaluates the short-term efficacy and safety of combining lipiodol with DEB-TACE in unresectable HCC. We hypothesize that this hybrid approach leverages the complementary benefits of both agents, the embolic and imaging properties of lipiodol combined with the sustained drug release of DEB, to achieve superior local tumor control and reduced systemic toxicity. Our findings not only aim to inform future TACE protocol standardization, but also to provide a robust embolization platform that could be optimally integrated with modern IO-based systemic regimens in the future.

Materials and Methods

Raw Materials

DCB drug-loaded microspheres (British Biocompatibles company) or Callispheres drug-loaded microspheres (China Hengrui company) were applied (70–100μm, 100–300 μm or 300–500 μm) during TACE and epirubicin 50 mg was loaded. Keep this solution in a 20 mL syringe for 20 minutes, shaking every 5 minutes. The epirubicin loaded beads were then added to a nonionic iodinated contrast medium (Hengrui Pharmaceutical Co., Ltd.) and reconstituted 1:1 in saline.

Patients

This was a single-arm retrospective study designed to evaluate the efficacy and safety of the C&D-TACE technique in patients with unresectable HCC. This study retrospectively analyzed HCC patients treated with DEB-TACE plus lipiodol at Zhongshan Hospital Fudan University (Shanghai, China) from December 2017 to August 2020. This study was reviewed and approved by the Ethics Committee of Zhongshan Hospital Fudan University (Approval Number: B2021-595). The ethics committee waived the requirement for written informed consent due to the retrospective nature of the study and the use of anonymized patient data.

All included patients met the following eligibility criteria:

i) Age $\geq$ 18 years and $\leq$ 85 years old; ii) clinically or pathologically diagnosed with primary HCC according to the American Cancer Society liver disease guidelines; iii) Patients with at least one measurable intrahepatic lesion according to mRECIST criteria; iv) life expectancy>3 months.

Exclusion criteria were the following: i) Patients were diagnosed with intrahepatic cholangiocarcinoma, mixed liver cancer, secondary liver cancer, and other nonhepatocellular carcinoma before surgery; ii) contraindications for angiography or visceral catheterization; iii) contraindications for hepatic artery embolism, including arteriovenous fistula, portal vein occlusion, severe coagulation disorder; iv) Extensive peripheral metastases, life expectancy <3 months.

C&D-TACE Treatment

C&D-TACE procedures require transfemoral or radial access with percutaneous arterial cannulation using a modified Seldinger technique. Then, under DSA guidance, a 5F RH catheter (Terumo, Japan) was introduced into the common hepatic artery through a 5F vascular sheath for peritoneal angiography to assess the anatomy of the hepatic artery and tumor staining to confirm tumor blood vessels. The tumor feeding artery was selectively cannulated through a 2.7F microcatheter. The donor artery was first embolized with plain lipiodol. The volume of lipiodol used was determined

based on tumor size and vascularity, typically ranging from 3 to 20 mL. The drug-loaded microspheres were then mixed with epirubicin and placed in a 1 mL syringe. The mixture was manually injected in pulses into the tumor feeding artery at a rate of 1 mL/min under fluoroscopic monitoring until the contrast agent was stable or nearly stable, taking care not to spill material into non-target containers. Angiography was repeated after embolization to assess whether embolization was complete. The endpoint of treatment is stagnation of blood flow in segmental or subsegmental arterial branches.

Follow-Up

Tumor Response

Follow-up was performed every 2 months after initial treatment. Abdominal contrast-enhanced CT or contrast-enhanced magnetic resonance imaging (MRI) was performed according to the mRECIST guidelines.[13] The disease control rate (DCR) was calculated as the sum of complete response (CR), partial response (PR), and stable disease (SD); objective response rate (ORR) was defined as a patient who achieves CR or PR. The evaluation of tumor lesions was performed by two experienced independent abdominal radiologists (more than 5 years of work experience) in collaboration with our department.

Safety was assessed by comparing liver function tests obtained at baseline (preoperative), on day 3 post-procedure, and at 1 month post-procedure. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE; version 4.0) was used to monitor the tolerability of C&D-TACE.

Laboratory Examination

Relevant laboratory parameters, namely alpha-fetoprotein (AFP), albumin, bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and prothrombin time (PT), were also assessed before and after surgery to determine response to treatment. According to various liver function tests, including albumin (ALB), total bilirubin (TBIL), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and prothrombin time (PT), and adverse events such as pain, fever, nausea, and vomiting.

Statistical Analysis

All statistical analyzes were performed with SPSS 23.0 software (SPSS Company, Chicago, Illinois, USA) and the significance level was established as $P < 0.05$. Continuous data are expressed as mean±standard deviation and median and compared using the *t*-test. Qualitative data were expressed as a proportion (%) and compared using the Chi-square test. Survival curve analysis was assessed using the Kaplan-Meier method and differences were evaluated using the Log rank test. Univariate and multivariate analyzes were performed using the Cox proportional hazards regression model.

Result

The drug-loaded microspheres were 70–100μ**m** in 2 cases, 100–300μ**m** in 69 cases, and 300–500μ**m** in 49 cases. The median lipiodol dose was 6.0 mL (range, 3.0–20.0 mL).

Clinical Characteristics of Patients with Liver Cancer

A total of 120 patients (106 men and 14 women; median age, 55.95± 11.67 years) received C&D-TACE treatment. The characteristics of this group of patients are as follows: listed in Table 1. Follow-up was achieved by visit or telephone interview until death or the end of the study (July 31, 2021). The median duration of follow-up was 9.68 months (range,3–48 months). In general, more than 85.8% of the patients had positive hepatitis B virus, 110 (91.7%) were Child-Pugh-A, 10 patients (8.3%) Child-Pugh-B, 19 patients (15.8%) were BCLC stage A, 32 patients (26.7%) were BCLC stage B and 69 patients (57.5%) were BCLC stage C. 54 patients had multiple foci and 66 patients had a single focus.

Treatment Response

Treatment response was evaluated 2 months after C&D-TACE. The results were as follows: complete remission (CR) in 1 case (0.8%); partial remission (PR) in 26 cases (21.7%); the condition was stable (SD) in 64 cases (53.3%); 29 patients (24.2%) had progressive disease (PD). Therefore, the disease control rate (CR + PR + SD) represents 75.8%. The OR rate

Table 1 Clinical Characteristics of the Patients with Hepatocellular Carcinoma (n=120)

Characteristics	Value
Age	55.93±11.67
Sex	
Male	106(88.33%)
Female	14(11.67%)
Etiology	
HBV	103(85.83%)
HCV	17(14.17%)
Maximal tumor diameter	
≤5cm	17(14.17%)
>5cm	103(85.83%)
Multiplicity of tumor	
Single	66(55%)
Multiple	54(45%)
Child-Pugh Grade	
A	110(91.67%)
B	10(8.33%)
Serum AFP	
≤200	54(45%)
>200	66(55%)
Cirrhosis	
Yes	71(59.17%)
No	49(40.83%)
BCLC stage	
A	19(15.83%)
B	32(26.67%)
C	69(57.5%)
ECOG	
0	120(100%)
1	0

Notes: Values are expressed as the mean ± standard deviation or n.

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group.

(CR + PR) was 22.5% (Table 2). At 6 months, 18 (15%) of 120 patients died, leaving 102 survivors. 26 patients died 1 year after C&D-TACE. The median follow-up was 9.68 months (range:3–48 months). The Kaplan-Meier curve of the C&D-TACE recipient OS is shown in Figure 1. The OS time was 31.44 months. (95% confidence interval: 27.24–35.46 months). To address the heterogeneity of the patient cohort, a subgroup analysis was performed based on the stage. The median OS for patients with BCLC stage A /B (n=51) was 38.9 months (95% CI: 33.9–43.8 months), significantly longer than for patients with BCLC stage C(n=69) 23.5 months (95% CI: 27.2–35.6 months).

The representative image therapy of C&D-TACE is shown in Figure 2. HCC lesions were observed in patients with MRI prior to C&D-TACE treatment (Figure 2A) prior to C&D-TACE treatment. Tumor digital subtraction angiography showed that the lesion was visible (DSA) during C&D-TACE treatment (Figure 2D) and lipiodol deposition after C&D-TACE (Figure 2E). Lipiodol deposition within the tumor after 1 week of C&D-TACE treatment with CT (Figure 2B). Tumor activity disappeared significantly after 2 months of C&D-TACE treatment (Figure 2C and F).

During C&D-TACE treatment, lipiodol can make the boundary of tumor lesions more clearly visible (Figure 3A and B), but tumor lesions can still not be observed after DEB-TACE treatment (Figure 3C and D).

Table 2 Tumor Responses at Different Follow-Up Time-Points

Response	Value	Percent (%)
CR	1	0.8%
PR	26	21.7%
SD	64	53.3%
PD	29	24.2%
The disease control rate (CR+PR+SD)	91	75.8%
The OR rate (CR+PR)	27	22.5%

Note: Values are expressed as n.
Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Potential Association Between OS and Clinical Parameters

Univariate analysis showed that for patients with HCC, tumor size (P=0.027), conversion therapy (P=0.039) were significant prognostic factors for OS. Furthermore, multivariate analysis revealed that maximum tumor size >8 cm (hazard ratio [HR] 4.141; 95% CI, 1.162–14.76) and no conversion therapy implemented (HR 0.092; 95% CI, 0.01–0.814) were significant independent prognostic factors for OS (Table 3).

Safety Evaluation

No major complications occurred within 1 month after safe C&D-TACE treatment. Adverse events were: 1 case of peritoneal effusion, 1 case of liver abscess, requiring puncture; Two cases of cholangitis. Most adverse events, especially abdominal pain (46.7%), fever (55.8%), and nausea (15%), were characterized by postembolism syndrome (Table 4). Within 3 days, AST or ALT increased, ALT increased to AE grade 3 in 24 cases, and AST increased to AE grade 3 in 28 cases. Bilirubin in 5 cases was 3–10 times higher than the standard value (AE grade 3). Return to normal within 1 month (Table 5). No grade 4 adverse events were observed.

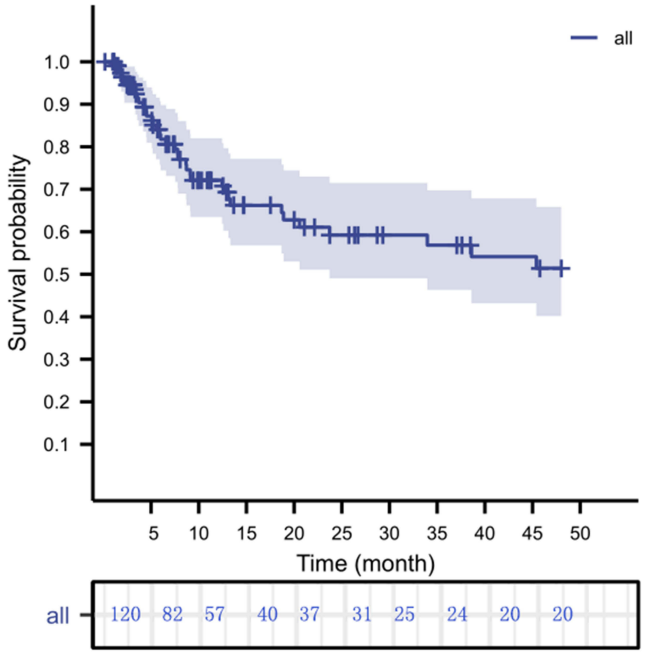

Figure 1 Overall survival of HCC patients treated with C&D-TACE. Kaplan-Meier curve shows the overall survival probability for the entire cohort. The shaded area represents the 95% confidence interval.

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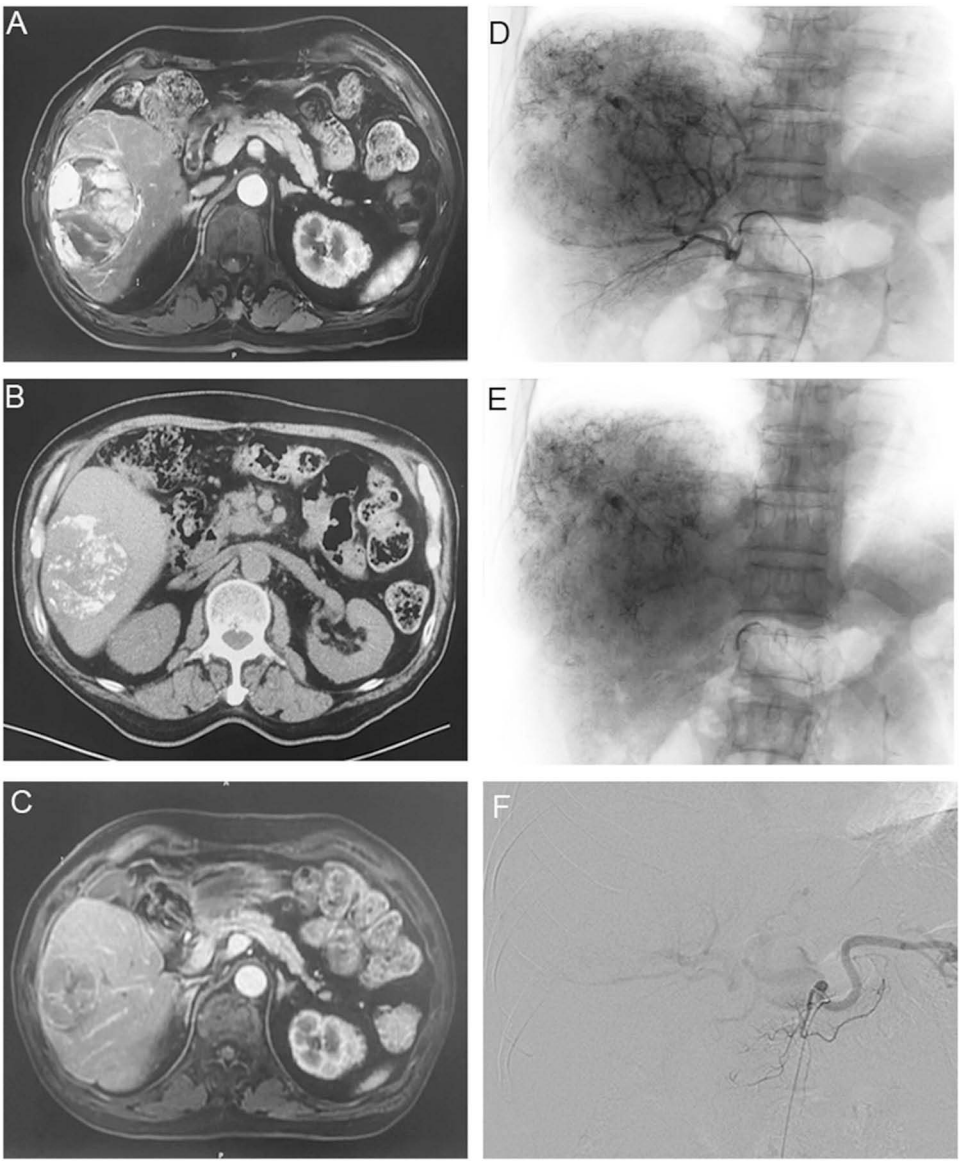

Figure 2 Imaging assessment before and after C&D-TACE in a representative patient. (**A**) Pre-procedural MRI shows the enhancing HCC lesion. (**B**) Non-contrast CT scan one week post-procedure confirms dense lipiodol deposition within the tumor. (**C**) Two-month follow-up contrast-enhanced MRI demonstrates complete response with no residual enhancing tissue. (**D**) Pre-embolization DSA reveals the tumor vasculature and blush. (**E**) The donor artery was embolized with lipiodol and the drug-loaded microspheres were mixed with epirubicin. Lipiodol deposition after C&D-TACE. (**F**) Two-month follow-up DSA confirms sustained complete response.

Discussion

TACE is one of the best treatment options for patients with non-resectable HCC.[14] TACE has been widely used to treat advanced hepatocellular carcinoma.[15,16] C-TACE utilizes lipidol as one of the main materials to embolize tumor feeding vessels, which is used mainly in the eastern era, and with the development of a microcatheter, the precise embolism becomes easier. Therefore, the DEB-TACE based on a drug-eluting bead has rapidly developed. However, in interventional clinical practice, we found that lipiodol and DEB can synergize, a technique we call C&D-TACE. In this study, we retrospectively analyzed the effects and availability of the C&D-TACE strategy when both lipidol and DEB were used in the procedure. The results of this study show that drug-eluting microspheres combined with hyper-liquefied lipiodol have an encouraging effect in patients with liver cancer. The current study using epirubicin-loaded microspheres combined

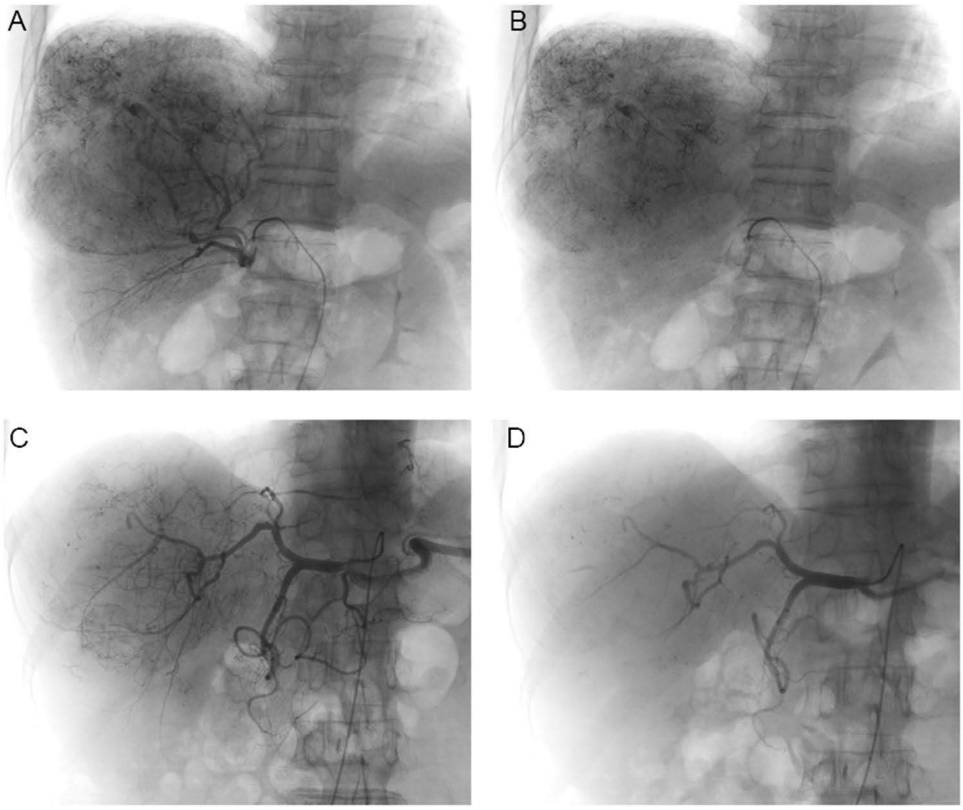

Figure 3 Angiographic comparison of C&D-TACE and DEB-TACE. (**A** and **B**) Representative DSA images during C&D-TACE procedure. (**A**) Pre-embolization image shows hypervascular tumor. (**B**) Post-embolization image shows lipiodol deposition. (**C** and **D**) Representative DSA images during DEB-TACE procedure. (**C**) Pre-embolization image shows tumor blush. (**D**) Tumor lesions can not be observed after DEB-TACE treatment.

with lipiodol in 120 patients with HCC (CR, n=1; PR, n=26; SD, n=64; PD=29) resulted in 75.8% of the disease control rate 2 months after treatment. Long-term follow-up ranged from 3 months to 36 months, with an OS of 31.44 months. (95% CI: 27.24–35.46 months). According to the stratified analysis, OS was related to tumor size (P=0.028) and whether

Table 3 Results of Univariate and Multivariate Cox Regression Analysis for OS in HCC Patients

Characteristics	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	P	HR	95% CI	P
Sex	0.736	0.326–1.661	0.461			
Age(year)	1.005	0.984–1.027	0.639			
HBsAg	2.149	0.814–5.672	0.122			
AFP (ng/mL, ≤200 vs >200)	1.51	0.759–3.003	0.24			
Liver cirrhosis (no vs yes)	0.946	0.483–1.856	0.873			
Tumor number (single vs multiple)	0.754	0.379–1.499	0.42			
Tumor size (cm, ≤8 vs >8)	3.412	1.151–10.116	0.027	4.141	1.162–14.76	0.028
Macrovascular tumor thrombus (no vs yes)	1.742	0.809–3.747	0.156			
BCLC	1.472	0.826–2.624	0.19			
Child-Pugh	2.782	0.806–9.605	0.106			
Conversion therapy	0.117	0.015–0.9	0.039	0.092	0.01–0.814	0.032

Notes: P-value < 0.05 was considered statistically significant. Cox proportional hazards regression mo Conversion therapy refers to the application of modalities such as targeted therapy, immunotherapy, or HAIC to shrink the primary tumor, reduce the extent of tumor thrombus, and decrease the number of satellite lesions, with the ultimate aim of enabling curative resection for patients with HCC.

Abbreviations: OS, overall survival; AFP, α-fetoprotein; TNM, tumor-nodes-metastasis; BCLC, Barcelona Clinic Liver Cancer; HR, hazard ratio; CI, confidential interval.

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Table 4 Post Embolism Syndrome During the Follow-Up

Syndrome	Value	Percent (%)
Fever	67	55.8%
Nausea	18	15%
Pain	56	46.7%

Table 5 Pertinent Laboratory Analytes Were Assessed During the Follow-Up and Corresponding Grade AEs

Laboratory Analytes	Baseline	3d	Grade 1/2	Grade 3/4
ALT	52.39±48.08	146.44±131.417	61/35	24/0
AST	78.84±88.51	142.39±145.11	60/32	28/0
Total bilirubin	15.06±9.6	28.64±19.65	83/32	5/0
Serum albumin (g/L)	38.67±7.216	34.78±5.03	95/25	0/0
PT	12.57±1.17	13.8±1.46	120/0	0/0
WBC (×10 ^{9}/L)	6.21±2.32	8.43±2.32	120/0	0/0

Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; PT, prothrombin time; WBC, white blood cells.

there was conversion therapy (P=0.032). These cumulative data support the use of microspheres in combination with lipiodol as a new treatment approach that provides better outcomes in patients with HCC.

In this study, we summarize the advantages of the combination of lipidol and DEB in the treatment with TACE. On the one hand, C-TACE uses super-liquefied lipiodol as the liquid embolizing agent most widely used,[17,18] which can block the blood supply of the portal vein microbranch and the hepatic sinus to the tumor in the marginal area, and perform dual embolization of the arterial and portal vein.[19] On the other hand, D-TACE uses non-absorbable microspheres as embolic agents and drug loading materials to slowly release cytotoxic drugs to target tumor areas.[20] DEB maintains high concentrations of chemotherapy agents at the tumor site through continuous release, thereby reducing systemic toxicity. Lipidol embolization works by inducing ischemic necrosis through blocking the blood supply of the tumor.[21] Additionally, the unique imaging characteristics of lipidol are pivotal during surgical procedures. In digital subtraction angiography (DSA), lipidol is presented as a high-density image, clearly delineating tumor boundaries and associated blood vessels. This provides real-time navigation for the surgeon, improving the precision of embolization treatment, which helps to precisely target drug microspheres and embolic agents while minimizing damage to surrounding healthy liver tissue. In addition, postoperative imaging follow-up allows for the continuous deposition of lipidol to serve as an objective marker to evaluate the extent of tumor necrosis and the effectiveness of treatment, thus informing adjustments in subsequent therapies. The synergistic effect of these two modalities not only enhances therapeutic efficacy through dual antitumor mechanisms but also optimizes targeting and controllability with imaging guidance, significantly reducing the likelihood of tumor residue or recurrence. Although the single-arm design of our study, the efficacy outcomes of C&D-TACE appear favorable when contextualized with historical data from established modalities. For example, the OS observed in our cohort (OS of 31.44 months) compares encouragingly with those reported in the literature for C-TACE alone (28.6 months).[4] In addition, this combination therapy alleviates the side effects typically associated with traditional systemic chemotherapy, leading to an improved quality of life for patients.

C&D-TACE, as a safe treatment strategy, also provides the possibility of combined systemic therapy. Integration of TACE with immune checkpoint inhibitors (ICIs) and tyrosine kinase inhibitors (TKIs) represents a promising frontier in advanced HCC management, with growing evidence suggesting that such combinations can produce superior results compared to either modality alone. For example, the regimen of TACE with lenvatinib and pembrolizumab has demonstrated significant improvements in progression-free survival versus TACE alone, underscoring the potential of multimodal therapy.[22,23] Mechanically, this synergy may be driven by the release of tumor antigens and the remodeling

of the tumor immune microenvironment—processes that are potentially amplified by C&D-TACE through its enhanced embolic and chemotherapeutic effect. For example, recent studies have proposed the role of PANoptosis (a form of programmed cell death) in modulating treatment response and immune activity in HCC.[24] It may affect the efficacy of TACE by regulating the inflammatory microenvironment and the immune response.

Regarding safety and tolerability, most patients experienced grade 2–3 adverse events as defined by the NCI-CTCAE. However, the majority of adverse events occurred in post-embolization syndrome (abdominal pain (46.3%), pyrexia (56.2%)). Additionally, within 3 days, ALT increased to AE grade 3 in 24 cases, AST increased to AE grade 3 in 28 cases; bilirubin elevation was 3–10 times the standard value in 5 cases (AE grade 3), and they returned to normal within 1 month. The incidence of transient elevations in grade 3 liver enzymes observed in our C&D-TACE cohort is consistent with that reported in the literature for TACE techniques, where elevations of grade 3/4 ALT/AST occur in approximately 15–30% of patients who underwent cTACE or DEB-TACE.[25] Adverse events included ascites, liver abscesses, and cholangitis, which were similar to previous studies.[21,26] Currently, TACE treatment is considered inappropriate for patients with Child-Pugh.[27,28] In this study, we collected 10 Child-Pugh B-grade patients. The above 10 patients did not experience any serious postoperative adverse events after C&D-TACE treatment. Therefore, the combination of lipiodol and drug-loaded microspheres demonstrates a manageable safety profile comparable to that of standard TACE modalities.

The limitations of this study include its single arm, retrospective design, relatively short follow-up, and the lack of a concurrent control group, which excludes definitive efficacy claims. Future randomized trials are needed to conclude the therapeutic potential of the C&D-TACE approach.

Conclusion

In conclusion, our study provides promising evidence for the feasibility, local tumor control, and tolerability of C&D-TACE in patients with HCC. Amid the evolving treatment landscape dominated by systemic therapy, this optimized embolization strategy may be suitable for combination with systemic therapy, which merits definitive evaluation in randomized controlled trials to confirm its potential to improve patient outcomes.

Abbreviations

HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin, TBIL, total bilirubin; PT, prothrombin time; WBC, white blood cells; PLT, platelet; AFP, Alpha fetoprotein, OS, overall survival; TNM, tumor-nodes-metastasis; HR, hazard ratio; CI, confidential interval; DCR, disease control rate; ORR, objective response rate; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease, HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization; C-TACE, Conventional TACE; DEB-TACE, drug-eluting bead TACE; CT, computed tomography; MRI, magnetic resonance imaging.

Ethics Approval and Consent to Participate

Approval of the research protocol by an institutional review board: The protocol for this research project has been approved by the ethics committee of Zhongshan Hospital Fudan University (ethics approval No.: B2021-595) and it conforms to the provisions of the Declaration of Helsinki.

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Disclosure

The authors report that they have no conflicts of interest in this work.

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