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ORIGINAL RESEARCH

Efficacy and Safety of Thermosensitive Hydrogel Combined with Pirarubicin via TACE for Hepatocellular Carcinoma: A Pilot Study

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Aim: This pilot study aims to evaluate the technical feasibility, safety profile, and preliminary efficacy of Tepoxin, a thermosensitive hydrogel, combined with pirarubicin via transarterial chemoembolization (TACE) in patients with unresectable hepatocellular carcinoma (HCC), providing foundational data for future larger-scale trials.

Methods: This is a single-center, retrospective, single-arm pilot study including 7 HCC patients who received Tepoxin combined with pirarubicin TACE between 2023 and 2025. Inclusion criteria were: confirmed HCC by imaging or pathology, Child-Pugh A-B liver function, ECOG performance status ≤ 2, and no severe comorbidities. The procedure involved selective hepatic artery catheterization to deliver pirarubicin-loaded hydrogel for embolization. Primary endpoints were procedure success rate, adverse events, tumor response (evaluated by changes in the maximum tumor diameter and mRECIST criteria for PR/SD/PD), and disease control rate (DCR). Follow-up was conducted for at least 4–6 weeks for preliminary imaging assessment.

Results: All 7 patients completed the procedure without failure or discontinuation. Tumor response was assessable in all patients: 2 achieved partial response (PR), 4 had stable disease (SD), and 1 had progression (PD). The objective response rate (ORR) was 28.6% (2/7), and the disease control rate (DCR) was 85.7% (6/7). Adverse events were mild, including fever, abdominal pain, and nausea/vomiting (grade 1–2), with no severe toxicity (grade ≥3) or treatment interruption. Mild liver function fluctuations were observed in some patients, which recovered to baseline.

Conclusion: Tepoxin combined with pirarubicin TACE is technically feasible and well-tolerated in HCC patients, showing early anti-tumor activity. Larger, well-designed studies are needed to confirm its efficacy and safety.

Keywords: chemoembolization, drug-delivery system, pirarubicin, hepatocellular carcinoma, thermosensitive hydrogel

Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, accounting for 85–90% of all liver cancer cases.[1] According to the GLOBOCAN 2022 database, liver cancer remains a significant global health burden, with approximately 865,000 new cases and 758,000 deaths worldwide in 2022.[2] In China, liver cancer is the fourth most common malignancy and the second leading cause of cancer-related death, with an estimated 367,700 new cases and 316,500 deaths in 2022.[3] HCC is more common in men (male-to-female ratio of 2–3:1), with major risk factors including hepatitis B or C virus infection, cirrhosis, alcohol consumption, and aflatoxin exposure.[4,5] Most patients are diagnosed at intermediate or advanced stages, which limits curative treatment options. The median survival for untreated patients is 3–6 months,[6] and systemic chemotherapy (eg, doxorubicin, epirubicin) has limited efficacy, with an objective response rate of less than 15% and a median survival of under 10 months[7,8] Transarterial chemoembolization (TACE) has proven to extend survival, with a median survival of 16–20 months, and is recommended as first-line treatment for unresectable HCC.[9–11] Traditional TACE using iodized oil combined with chemotherapy drugs has limitations, such as unstable drug release and insufficient local drug concentration, which reduce efficacy and increase complications.[12] Thermosensitive polymer hydrogels, such as Tepoxin, are injectable materials that transform from liquid to gel at body temperature, enabling stable embolization and controlled drug release. Tepoxin, specifically, has been designed for embolization therapy in hypervascular malignant tumors, such as during

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TACE, to improve the delivery and retention of chemotherapeutic agents in liver tumors. Tepoxin provides precise drug delivery with higher local concentration, reduced systemic toxicity, and excellent biocompatibility. Due to its phase transition at body temperature, Tepoxin ensures sustained drug release at the tumor site, which enhances the therapeutic efficacy and minimizes side effects associated with traditional systemic chemotherapy.[13,14] Epirubicin, commonly used in TACE, has lower cardiac toxicity than doxorubicin, but its antitumor activity is limited, and it causes bone marrow suppression.[15–17] Pirarubicin (THP), a semisynthetic derivative of doxorubicin, has stronger antitumor efficacy, faster cellular uptake, and lower toxicity, making it better tolerated by patients.[18,19] Clinical studies suggest pirarubicin achieves higher local response rates and longer progression-free survival in patients requiring multiple TACE sessions.[20]

The application of thermosensitive hydrogels in TACE for HCC is still in the exploratory stage, with limited clinical evidence. Pirarubicin has not yet become a standard drug choice for TACE, although it is widely used in various solid tumor treatments. Given the success of new drug delivery systems like irinotecan-loaded microspheres (DEBIRI) in metastatic colorectal cancer, this study investigates the feasibility and safety of Tepoxin combined with pirarubicin TACE for HCC, aiming to provide preliminary data for larger prospective studies.[21,22]

Materials and Methods

Patient Selection

This is a single-center, retrospective study that included 7 HCC patients who underwent Tepoxin combined with pirarubicin TACE from January 2024 to June 2025. All patients had HCC confirmed by imaging or pathology and met the intermediate or advanced stage criteria of the Barcelona Clinic Liver Cancer (BCLC) staging system.[4] Inclusion criteria: (1) Child-Pugh A–B classification; (2) ECOG performance status ≤2; (3) no prior liver transplantation or curative resection; (4) no severe heart, lung, or kidney dysfunction. Exclusion criteria: (1) severe infection or coagulation disorder; (2) received systemic chemotherapy within 4 weeks before the procedure; (3) history of allergy to anthracyclines; (4) extensive metastasis or diffuse extrahepatic disease.

Treatment Method

All patients underwent TACE under local anesthesia and analgesia. A Seldinger technique was used for femoral artery catheterization, followed by routine hepatic artery angiography to assess blood supply to the tumor. After superselective catheterization into the tumor-feeding artery, pirarubicin-loaded thermosensitive hydrogel was injected. The pirarubicin dose was individualized based on body surface area and liver function (30–50 mg). The hydrogel remains in liquid form at low temperatures and converts to gel when warmed in the body, achieving embolization and sustained drug release. Injection was stopped when blood flow significantly slowed or when the embolization endpoint was reached. Gelatin sponge particles were used, if needed, to enhance embolization. Postoperatively, patients received routine anti-infection, hepatoprotective, and supportive treatments.[14,20]

Monitoring and Follow-Up

Laboratory tests (blood count, liver and kidney function, AFP levels) were performed before the procedure. After 1 week, laboratory parameters were rechecked, and liver function was monitored, with AFP levels dynamically observed. Adverse events and complications were recorded during treatment and follow-up, classified using the Common Terminology Criteria for Adverse Events (CTCAE, v6.0).[23] Imaging (contrast-enhanced CT or MRI) was performed 4–6 weeks after the procedure to assess local efficacy and check for new lesions. Some patients underwent further TACE during follow-up. Imaging was independently reviewed by two qualified radiologists, with disagreements resolved by a senior physician.

Efficacy Evaluation

Efficacy was assessed using the modified Response Evaluation Criteria in Solid Tumors (mRECIST), based on contrast-enhanced CT or MRI to measure arterial-phase enhancement of the tumor. Treatment responses were categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD).[24] Objective response rate (ORR) was defined as the proportion of CR and PR. Disease control rate (DCR) was defined as the proportion of CR, PR, and SD.

Ethical Approval and Informed Consent

This study was approved by the Ethics Committee of the Affiliated Bishan Hospital of Chongqing Medical University (Approval No. cqbky11-20251130-02), with approval granted on November 25, 2025. All patients provided written informed consent for participation. The use of Tepoxin and pirarubicin for TACE in the treatment of HCC is currently in the exploratory stage. This study was conducted in accordance with the principles of the Declaration of Helsinki and relevant medical ethics guidelines. All ethical considerations and the welfare of participants were closely monitored, and the study complied with applicable legal and regulatory requirements.

Results

Patient Characteristics

A total of 7 HCC patients were included in the study, consisting of 5 males and 2 females, with a median age of 58 years (range 49–70 years). Six patients were hepatitis B virus (HBV) positive, and one was negative. Regarding tumor distribution, 3 patients (43%) had a solitary lesion, while 4 (57%) had multiple lesions. The median tumor size was 6.80 cm (range 5.90–10.37 cm) (see Table 1).

Treatment Process and Adverse Events

All 7 patients successfully completed TACE treatment without intraoperative complications. Perioperative adverse events primarily included fever (4 cases), abdominal pain (3 cases), and nausea or vomiting (2 cases), all classified as CTCAE grade 1–2, and relieved by routine symptomatic treatment. No grade ≥3 toxicity, adverse event-related mortality, or treatment interruption was observed (see Table 2).

Imaging Response and Imaging Results

Imaging follow-up (contrast-enhanced CT/MRI) performed 4–6 weeks after the procedure showed assessable efficacy in all 7 patients. Representative CT images showing treatment response are provided in Figure 1. According to the mRECIST criteria, 2 patients achieved PR, 4 had SD, and 1 had PD (ORR: 28.6%; DCR:85.7%). The distribution of tumor size changes is shown in the waterfall plot (see Figure 2), and individual patient data, including pre- and post-treatment diameters, percentage change, and mRECIST response, are summarized in Table 3.

Table 1 Patient Demographics and Baseline Characteristics (n = 7)

Characteristics	n	%
Male/Female	5/2	71/29
Age, years (mean ± SD, range)	58 ± 7.1 (49–70)	
BMI, kg/m^2 (mean ± SD, range)	23.0 ± 1.6 (20.9–25.3)	
Child-Pugh class		
A	5	71
B	2	29
HBV infection		
Positive	6	86
Negative	1	14
No. of lesions		
Single	3	43
Multiple	4	57
Tumor size, cm (mean ± SD, range)	7.70±1.76 (5.90–10.37)	

Table 2 Treatment-Related Adverse Events Graded by CTCAE v5.0

Adverse Event	Any Grade, n (%)	Grade 1–2, n (%)	Grade 3, n (%)
Fever	4 (57.1)	4 (57.1)	0 (0.0)
Abdominal pain	3 (42.9)	3 (42.9)	0 (0.0)
Nausea/vomiting	2 (28.6)	2 (28.6)	0 (0.0)
ALT/AST elevation	2 (28.6)	2 (28.6)	0 (0.0)
Hematologic toxicity	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic failure	0 (0.0)	0 (0.0)	0 (0.0)
Serious complications1	0 (0.0)	–	–

Postoperative Liver Function Changes and AFP Levels

One week post-treatment, most patients showed mild to moderate elevation of transaminases (ALT, AST), which gradually returned to baseline levels within 2 weeks. Specifically, post-treatment (2 weeks) ALT was 48 ± 20 U/L (range 25–80 U/L) and AST was 55 ± 30 U/L (range 30–110 U/L), both values returning close to their pre-treatment levels: ALT (45 ± 18 U/L) and AST (52 ± 29 U/L). These values remained higher than the normal levels, but the elevation was transient and reversible, with no signs of liver failure or cholestasis observed. Total bilirubin and albumin levels showed limited changes, with no signs of liver failure or cholestasis. Individual AFP changes post-treatment were as follows: Patient P1 showed a decrease from 1200 ng/mL to 400 ng/mL (66.7% reduction); Patient P2 from 4280 ng/mL to 1000 ng/mL (76.7% reduction); Patient P3 from 450 ng/mL to 350 ng/mL (22.2% reduction); Patient S1 from 200 ng/mL to 180 ng/mL (10% reduction); Patient S2 from 500 ng/mL to 420 ng/mL (16% reduction); Patient S3 from 1200 ng/mL to 1100 ng/mL (8.3% reduction); and Patient P5 from 1000 ng/mL to 1500 ng/mL (50% increase). Thus, two patients (P1 and P2) experienced a reduction of more than 50% in AFP levels.(see Table 4).

Discussion

This study retrospectively analyzed 7 HCC patients who received Tepoxin combined with pirarubicin TACE. The results showed that this treatment approach was technically feasible and well-tolerated, with no severe perioperative complications and most adverse events being mild to moderate, resolving with routine symptomatic treatment. These findings are consistent with previous literature supporting the safety of chemotherapeutic agent-based embolization approaches. For example, pirarubicin-eluting microsphere TACE has been reported as a feasible and well-tolerated option for unresectable HCC patients, demonstrating manageable adverse events in clinical use.[25] Furthermore, recent reviews on polymeric embolic

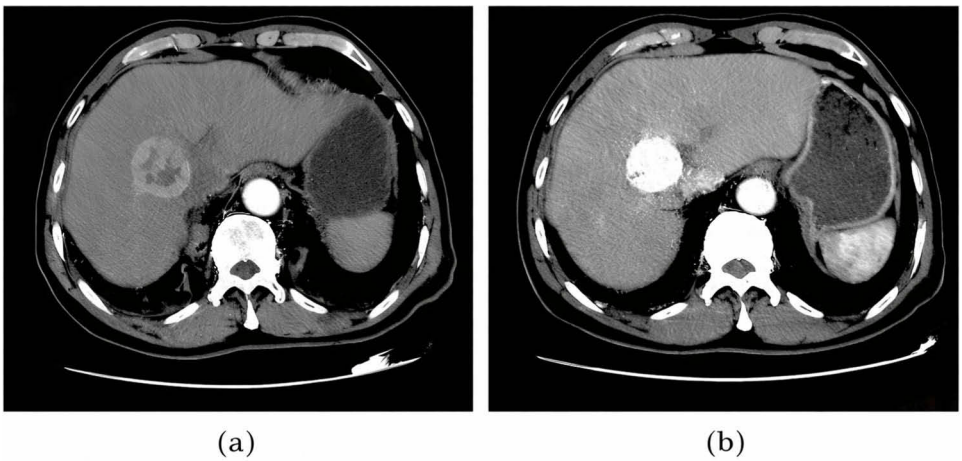

Figure 1 Contrast-enhanced CT images before and after TACE in a patient with HCC. (**a**) Pre-treatment image shows a hypervascular tumor in the right hepatic lobe. (**b**) Follow-up contrast-enhanced CT obtained 4–6 weeks after TACE demonstrates intratumoral deposition of Tepoxin with reduced tumor enhancement, along with mild peritumoral reactive changes consistent with a transient post-embolization reaction; liver size and morphology remain normal with no enlargement.

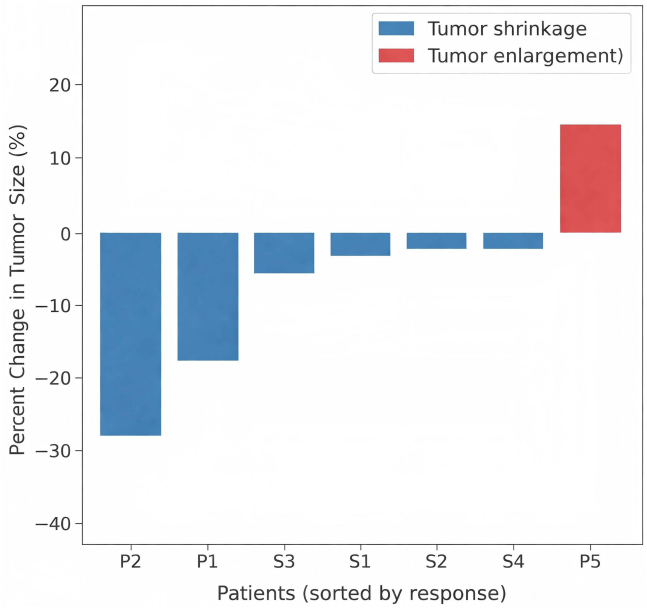

Figure 2 Waterfall plot of percentage change in tumor size after TACE (n = 7). Each bar represents one patient and is arranged from the greatest decrease to the greatest increase in tumor size. Blue bars indicate tumor shrinkage, whereas red bars indicate tumor enlargement.

beads and hydrogels have highlighted their potential to increase local drug delivery while minimizing systemic toxicity, suggesting that thermosensitive embolic materials — including those similar to Tepoxin — are safe and well-tolerated.[26] Compared to traditional chemotherapy agents such as epirubicin, pirarubicin in TACE treatment effectively reduces systemic toxicity while maintaining a high local concentration of the therapeutic agent, thus improving efficacy and reducing systemic side effects. In terms of efficacy, this study observed an ORR of 28.6% and a DCR of 85.7%. These results are similar to those seen in TACE studies using epirubicin or doxorubicin as the main drugs, where the ORR typically ranges from 15% to 25%.[9,27] Although the ORR in this study was relatively low, the higher DCR indicates that the treatment could effectively

Table 3 Tumor Size Changes and mRECIST Response Before and After TACE

Patient	Pre-Treatment Diameter (cm)	Post-Treatment Diameter (cm)	Tumor Size Change (%)	mRECIST Response
P1	10.37	8.50	−18%	PR
P2	5.90	4.50	−24%	PR
S1	6.20	6.00	−3%	SD
S2	8.90	8.70	−2%	SD
S3	6.80	6.50	−4%	SD
S4	9.22	8.90	−4%	SD
P5	6.50	7.50	+15%	PD

Table 4 Changes in Laboratory Parameters Before and After TACE

Parameter	Pre-Treatment	Post-Treatment (1 Week)	Post-Treatment (2 Weeks)	Normal Range (Normal Patients)
ALT (U/L)	45 ± 18 (22–75)	82 ±32 (40–135)	48±20 (25–80)	10–40
AST (U/L)	52 ± 29 (28–110)	96 ±45 (55–180)	55±30 (30–110)	15–40
Total bilirubin (μmol/L)	15 ± 5 (9–22)	24 ± 9 (12–38)	–	5–20
Albumin (g/L)	39 ± 3 (34–45)	37 ± 4 (31–42)	–	35–50
AFP (ng/mL)	1261±1388 (200–4280)	707±492 (180–1500)	–	0–10

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control tumor progression, especially in patients with unresectable HCC, delaying disease deterioration. Specifically, 2 PR patients had a reduction in maximum tumor diameter of approximately 18% and 24%, while the SD patients had tumor size changes ranging from 2% to 4%, suggesting that this treatment can suppress tumor growth to some extent. Furthermore, one PD patient showed a 15% increase in tumor size, indicating that this patient did not respond well to the treatment, and future individualized treatment strategies may be needed to improve efficacy.

In this study, most patients exhibited mild to moderate elevation in liver function markers (such as ALT and AST) post-treatment, which were reversible and returned to baseline levels within a short period. This is consistent with recent studies, which have shown that most liver function abnormalities after TACE are reversible.[28] These changes may be related to localized liver damage due to drug release, but since the drug concentration is high at the tumor site and the thermosensitive hydrogel's controlled release minimizes systemic toxicity, these changes were transient and reversible. Tepoxin, through its phase-transition property, forms a stable gel barrier at the tumor site, which may contribute to controlled drug release and reduced systemic exposure. Furthermore, pirarubicin is characterized by rapid cellular uptake, which may offer an advantage when combined with a slow-release hydrogel, as the drug can be efficiently internalized by tumor cells during the extended release period, potentially enhancing local antitumor efficacy.[18,19] Regarding adverse events, the incidence was mild, mainly involving fever, abdominal pain, nausea, and vomiting, all of which were CTCAE grade 1–2 and were relieved by symptomatic treatment. These symptoms align with the "post-embolization syndrome" commonly observed after TACE treatment.[29] Fever and abdominal pain are the most common symptoms after TACE, usually related to the local delivery of chemotherapy drugs and the irritation caused by embolic agents. Notably, no severe myelosuppression, cardiac toxicity, or other major adverse events were observed in this study, providing further evidence of the safety of Tepoxin combined with pirarubicin TACE.

It should be noted that the combination of Tepoxin and pirarubicin for TACE in HCC is still in the clinical exploration stage. Similar approaches have been explored in other tumor interventional fields, such as DEBIRI in metastatic colorectal cancer, with small pilot studies gradually validating its feasibility and safety.[22] Recent studies have also further evaluated the efficacy and long-term outcomes of drug-eluting bead TACE (DEB-TACE) in various populations. For instance, Zhang et al reported that DEB-TACE in HCC patients with portal vein tumor thrombosis (PVTT) showed good safety and efficacy.[28] Real-world data from Makary et al confirmed stable 5-year follow-up results for DEB-TACE in patients with locally advanced HCC.[30] These findings highlight the importance of exploring new drug delivery systems and drug combinations in small-sample pilot studies, which are crucial for advancing innovation in interventional oncology.

Although this study's results are clinically meaningful, there are several limitations. First, the sample size is small, including only 7 patients, limiting statistical power; therefore, the conclusions should be interpreted with caution. The small sample may introduce potential biases and does not fully reflect the efficacy and safety of this approach across different patient populations. Second, as a single-center retrospective analysis, the lack of a control group limits direct comparison with traditional TACE or other drug delivery systems. Further comparative studies are essential to validate the advantages of this approach. Additionally, the follow-up period was short, reflecting only short-term efficacy and safety, and longer-term survival benefits remain unassessed. Lastly, laboratory parameters were checked only once postoperatively, lacking dynamic monitoring, which may have underestimated some transient adverse events. Future studies should be based on multicenter, large-sample, prospective clinical trials to further validate the efficacy and safety of this approach. Furthermore, as molecular targeted therapies and immune checkpoint inhibitors continue to advance, exploring the combination of TACE with systemic therapies is becoming a trend.[31,32] The Tepoxin combined with pirarubicin TACE regimen may complement targeted or immunotherapies, further improving the long-term survival rate in advanced HCC patients.

Conclusion

In a word, Tepoxin combined with pirarubicin-based TACE appears to be a safe and feasible treatment option for HCC and demonstrated preliminary anti-tumor activity in some patients. As an early exploratory study, it offers initial clinical evidence for the potential use of this approach in HCC. Nevertheless, given the small sample size and short follow-up duration, these findings should be interpreted with caution and further confirmed in large-scale, multicenter, prospective studies.

AI Disclosure

There is no artificial intelligence (AI) tools were used in the preparation of this manuscript.

Abbreviations

TACE, Transcatheter Arterial Chemoembolization; HCC, Hepatocellular Carcinoma; Child-Pugh, Child-Pugh Classification; ECOG, Eastern Cooperative Oncology Group; PR, Partial Response; SD, Stable Disease; PD, Progressive Disease; ORR, Objective Response Rate; DCR, Disease Control Rate; AFP, Alpha-fetoprotein; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; CT, Computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; DEB, Drug-eluting bead; DEBIRI, Drug-eluting bead irinotecan (irinotecan-loaded microspheres); MRI, Magnetic resonance imaging; mRECIST, Modified Response Evaluation Criteria in Solid Tumors; THP, Pirarubicin.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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