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ORIGINAL ARTICLE

Endpoint of embolization: A study of transarterial chemoembolization in patients with large hepatocellular carcinoma

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Summary

Purpose: *To explore the degree of embolization and embolization endpoints in patients with large hepatocellular carcinoma (HCC) treated via transarterial chemoembolization (TACE).*

Methods: *Thirty-two HCC patients treated with TACE from 2015 to 2016 who met the enrollment criteria for this study were retrospectively analyzed. The experimental group was treated via complete embolization, with complete occlusion of the tumor blood supplying artery, while the control group underwent incomplete embolization of any blood supplying arteries, with limited residual visible blood flow detectable via angiography. Postoperative liver and kidney function, complications, prognosis, and survival for patients in these two groups were analyzed.*

Results: *There was no significant difference at baseline patient condition between the two treatment groups before treatment. After treatment, the alanine aminotransferase (ALT), aspartic aminotransferase (AST), and white blood cell (WBC) values in the experimental group were significantly higher than those in the control group (p=0.031, 0.038, and 0.034, respectively). There was also a significant increase in hepatic aseptic necrosis and acute liver function damage in the experimental group relative to the control group (p=0.015 and 0.023, respectively). Compared with the control group, the prognosis and survival of the experimental group was significantly decreased. Univariate and multivariate Cox regression analyses of overall survival revealed that the different treatment group and hepatitis B infection status were the main factors affecting patient prognosis and survival.*

Conclusions: *For patients with large HCC tumors with a limited number of supporting arteries, careful attention should be paid to the use of embolic agents during the TACE procedure. Rather than proceeding to complete embolization of the artery root, embolization can be terminated when the main tumor feeding artery is still faintly visible on an angiogram in a structure reminiscent of a tree with dry branches, thereby reducing adverse outcomes in patients.*

Key words: *hepatocellular carcinoma, transarterial chemoembolization, embolism, angiography, overall survival*

Introduction

Hepatocellular carcinoma (HCC) is the fifth leading cause of cancer in men worldwide, and the second leading cause of cancer-related death [1]. The global incidence of this cancer is still increasing rapidly, with annual HCC incidence and mortality rates being comparable, highlighting the aggressive nature of this disease [2].

The efficacy of treatment for HCC patients is largely dependent on the tumor stage, performance status, and remaining liver function for a given

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patient, requiring a multidisciplinary approach for optimal management [3]. The Barcelona Clinic Liver Cancer Staging System (BCLC) is the most commonly used HCC management guideline [4]. It divides patients into different categories, identifying optimal treatment strategies for patients with a given stage of tumor [5].

Transarterial chemoembolization (TACE) is the standard treatment for BCLC stage B (intermediate) HCC [5]. TACE generally relies on the dissolving of multiple chemotherapeutic agents in lipiodol and then injecting them into the hepatic artery supplying blood to the tumor with the goal of forming a local vascular embolism and achieving a high local chemotherapeutic agent concentration. TACE has been proven to be useful for local tumor control, preventing tumor progression, prolonging patient survival, and alleviating symptoms of disease. Furthermore, there is strong evidence that patients with early and late HCC can also benefit from TACE [6,7].

In addition to the standard TACE approach, additional vascular thrombosis may be required using gelatin sponges or microspheres if necessary [8]. Expert consensus with respect to the use of iodized oil or gelatin sponges as embolic agents varies by region. NCCN guidelines state that the angiographic endpoint of embolization may be chosen by the treating physician [9]. According to the consensus of Chinese TACE experts, a sufficient embolic agent dose should be used provided a patient can tolerate the treatment, particularly during the first intervention. During embolization, the general goal is to achieve complete embolization of tumor-supporting vessels as much as possible in order to induce tumor retro-vascularization [10].

There is a lack of standardization with respect to the embolic agents used during conventional TACE operations. Nakao et al have proposed that when the amount of iodized oil and tumor cross-path ratio is less than or equal to 1.5, this approach can achieve a good curative effect [11]. Some Japanese authors have proposed that iodized oil only be used at 0.25 mg/cm^2 of tumor area in order to achieve complete tumor necrosis [12]. However, those studies included patients with a tumor diameter <10 cm. In clinical practice, it is often found that the amount of conventional iodized oil used is often insufficient to completely infiltrate the tumor, leading to a poor therapeutic effect. Due to individual differences in tumor size, location, blood supply, and invasion status, patient outcomes after TACE can be heterogeneous despite similar initial presentation.

For patients with large HCC tumors, in clinical practice, we have discovered that angiography can be used to determine the extent of tumor embolization. In this study, we assessed the extent to which angiographic staining of the tumor blood supplying artery is visible following embolization and if it correlates with patient outcomes and disease progression.

Methods

Patients

This study was approved by the Ethics Committee of the institutional review board, Shandong Cancer Hospital, and all patients provided signed informed consent. We retrospectively studied HCC patients treated between January 2015 and December 2016 that had not received prior treatment. The end of the follow-up period was June 30, 2018. HCC was diagnosed according to the latest current clinical guidelines [3]. Specifically, two dynamic contrast-enhanced imaging modalities were used to identify typical features of HCC, or one imaging study was used to identify these typical features together with elevated serum alpha fetoprotein (AFP) levels over 400 ng/dL, or HCC was confirmed via cytologic/histologic examination. The maximal diameter of the tumor was measured based on cross-sectional imaging conducted via computed tomography (CT).

Patients who met the following criteria were included in this study: (1) between 18 and 75 years of age, with no sex limitation; (2) had not received other cancer treatments, and were unable to receive surgery or refused surgery; (3) solitary tumor of 8-12 cm in diameter, with angiographic confirmation that all arteries supplying blood to the tumor originated from the same superior artery; (4) there were no obvious signs of portal vein invasion, or intrahepatic or extrahepatic metastasis; (5) Child-Pugh A/B scores for liver function; (6) an Eastern Cooperative Oncology Group (ECOG) performance status < 2; (7) no evidence of serious cardiorespiratory and renal dysfunction.

TACE procedure

The TACE procedures were conducted under expert guidance [13]. The tumor staining was observed by angiography after intubation into the hepatic artery. The catheter was super-selectively inserted into the tumor-feeding artery, and intravascular infusion of oxaliplatin (100-200 mg) was performed. Epirubicin (20-30 mg) mixed with 10-20 mL iodized oil was then used to conduct embolization of tumor blood supplying arteries. The injection was stopped when we observed static blood flow in the target artery. Gelatinous sponge granules were selected based on re-examination. The experimental group consisted of patients with complete embolization to the root of the main artery supplying blood to the tumor as determined by digital subtraction angiography (DSA) with no visible tumor vascular staining. The control group, in contrast, consisted of patients in who the trunk and primary branches of the tumor supplying artery were faintly visible after embolization, resembling a bare tree with thin branches.

Treatment assessment and follow-up

After chemoembolization, patients were monitored closely for post-embolization syndrome (pain, nausea, and/or fever) or other adverse effects, such as puncture bleeding, decreased white blood cells, transient abnormal liver function, renal impairment, dysuria, other common complications, liver abscess, hepatic rupture, hepatonecrosis, acute upper gastrointestinal bleeding, and other rare complications. The primary outcome measurement was overall survival (OS) from the date of treatment. A multivariate Cox proportional hazards regression analysis was performed to assess the prognostic risk factors associated with OS.

Statistics

Continuous variables are presented as means±SD and categorical variables as numbers and percentages. Differences between the two groups were compared with the t-test for continuous variables and x^2 test for categorical variables. Kaplan-Meier method with log-rank test was used to estimate OS of these two groups of patients. Univariate and multivariate analyses were performed to test the effect of different biochemical indicators and treatments on survival. Statistical significance was defined as a two-sided p value of less than 0.05. Statistical analyses were performed with SPSS v24.0 (IBM Corporation., Armonk, NY, USA).

Table 1. Baseline characteristics of the 32 patients with huge HCC

Characteristics	*Experimental group (N=16)*	*Control group (N=16)*	*Probability value*
Sex (Male/Female)	14/2	13/3	0.640
Age, years (Mean±SD)	58.88±12.74	54.06±10.52	0.253
Diameter of tumor (cm)	10.27(8.50-12.00)	10.58(8.60-12.00)	0.449
Site (Left/Right hepatic lobe)	1/15	1/15	1.000
Pseudocapsule, n (%)	6 (37.50)	7 (43.75)	0.729
Hepatitis B, n (%)	12 (75.00)	15 (93.75)	0.156
Cirrhosis, n (%)	5 (31.25)	9 (56.25)	0.164
Child-Pugh classification			0.705
A, n (%)	11 (68.75)	12 (75.00)	
B, n (%)	5 (31.25)	4 (25.00)	
AFP (μg/L)			1.000
≤400	3	3	
>400	13	13	
ALT (U/L)			0.376
≤150	16	15	
>150	0	1	
AST (U/L)			0.879
≤120	15	13	
>120	1	3	
GGT (U/L)			0.110
≤180	10	7	
>180	6	9	
ALB (g/L)			0.162
≥30	14	16	
<30	2	0	
Scr (μmol/L)			0.434
≤156	16	16	
>156	0	0	
WBC ($\times 10^9$/L)			0.698
≥12.5	1	2	
<12.5	15	14	
HGB (g/L)			0.650
≤105	4	3	
>105	12	13	
PLT ($\times 10^9$/L)			0.060
≤100	0	1	
>100	16	15	

Results

Patient characteristics

The baseline characteristics of enrolled patients are summarized in Table 1. In total, 16 patients from the experimental group and the control group were selected for our study. The clinical characteristics of these patients including sex, age, diameter of tumor, tumor site, pseudocapsule, hepatitis B status, cirrhosis, Child-Pugh classification, AFP, ALT, AST, GGT, ALB, Scr, WBC, HGB, and PLT were collected before treatment. No significant differences in these baseline parameters were evident between the two groups.

Effect on liver and kidney function and blood routine tests

After the two groups of patients underwent treatment, differences in treatment outcomes were assessed via comparing the changes in postoperative AFP, ALT, AST, GGT, ALB, Scr, WBC, HGB, and PLT. The AFP level of the experimental group was significantly decreased relative to controls (p=0.033), while the average ALT and AST levels

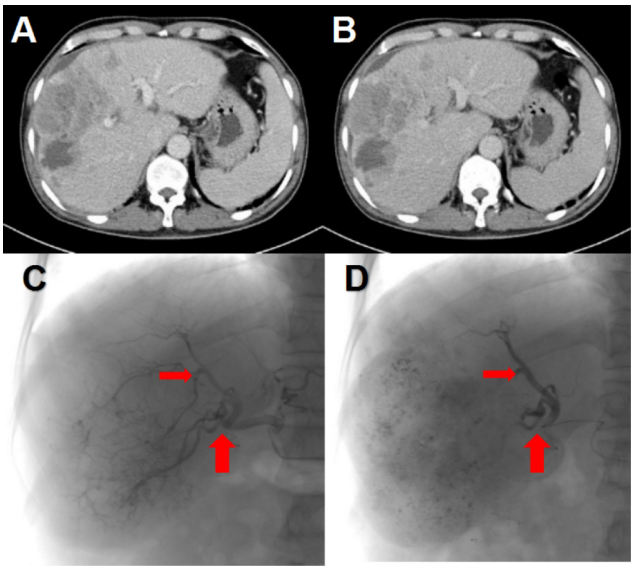

Figure 1. (A and B) Patient A was diagnosed with HCC on the basis of contrast CT. **(C)** Tumor staining and tumor blood supply artery were seen before interventional embolization (arrows). **(D)** After interventional embolization, tumor embolization was observed without any staining, and the blood supply artery was embolized to the vascular root (arrows).

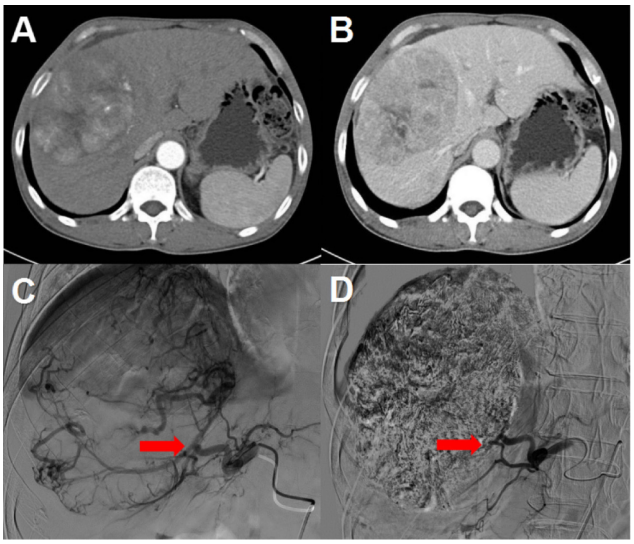

Figure 2. (A and B) Patient B was diagnosed with HCC on the basis of contrast CT. **(C)** Tumor staining and tumor blood supply artery were seen before interventional embolization (arrows). **(D)** After interventional embolization, tumor embolization was observed without any staining, and the blood supply artery was embolized to the vascular root (arrows).

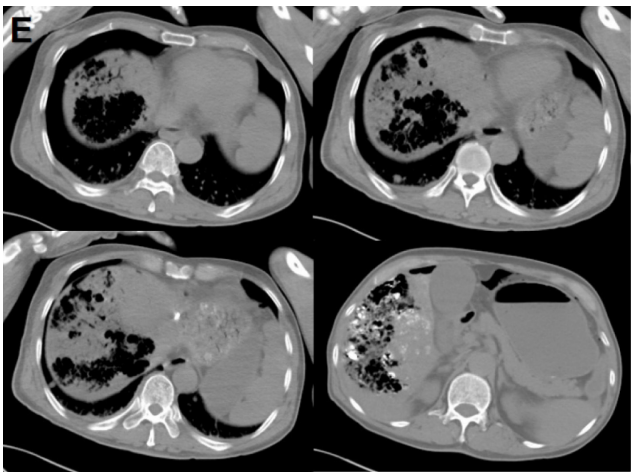

Figure 3. (E) CT examination 3 days after treatment revealed extensive necrosis and cavitation in the liver of patient A.

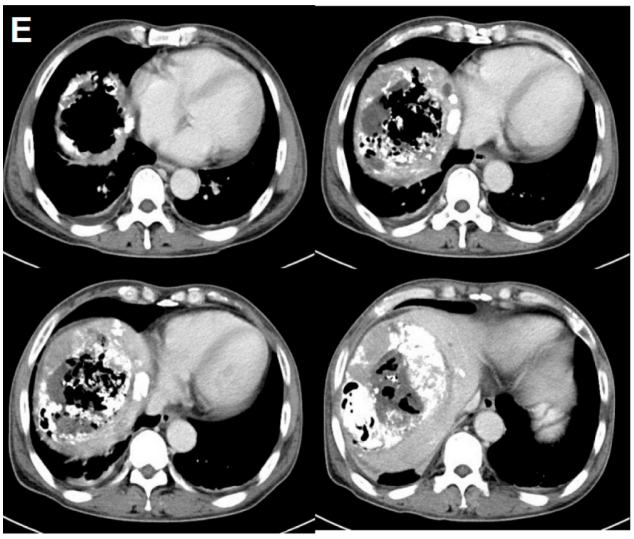

Figure 4. (E) CT examination after treatment revealed extensive necrosis and cavitation in the liver of patient B.

of the experimental group (446.65±603.98 and 477.36±584.13, respectively) were significantly higher than those of the control group (86.56±30.91 and 141.06±107.10, respectively) (p=0.031 and 0.038, respectively). The average WBC levels of patients in the experimental group was 12.05±4.97, which was significantly higher than those of the control group patients (8.56±3.87; p=0.034). No significant differences were detected for other indicators including GGT, ALB, Scr, HGB, and PLT.

Complications

There were no statistically significant differences between groups in postembolic syndromes, including fever, pain, nausea, or vomiting. There were no statistically significant differences in the incidence of serious complications such as liver abscess, liver failure, liver rupture, or liver hemorrhage. In contrast, the incidence of hepatic aseptic necrosis and acute liver function damage in the experimental group were significantly higher than that in the control group (p=0.015 and 0.023, respectively). After embolization in the experimental group the tumor blood supplying arteries exhibited complete embolization without any angiographic tumor staining (Figures 1 and 2). The experimental group showed clear signs of rapid-onset necrosis (Figures 3 and 4). In contrast, in the control group, after operation, the tumor and supplying artery were still faintly detectable via angiography, resembling a bare tree with thin branches akin to a tree in the winter (Figure 5). The therapeutic outcomes in these patients were better (Figure 6).

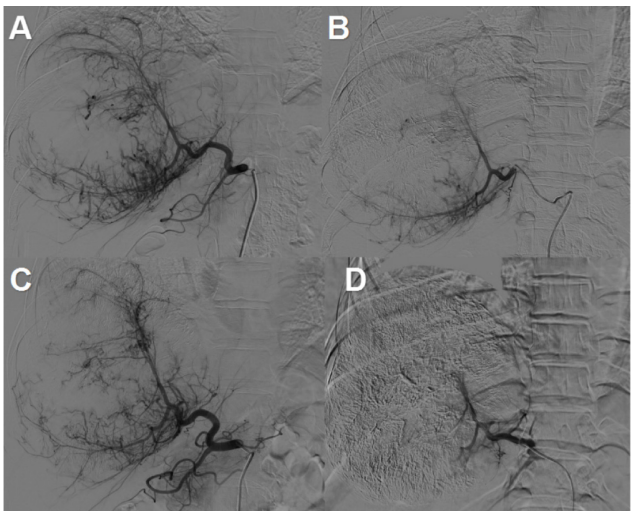

Figure 5. (A) Angiography of the patient C before the first TACE. **(B)** After the first TACE, the arterial trunk was still visible. **(C)** Three weeks later, the tumor was still slightly stained before the second TACE. **(D)** After the second TACE, the tumor embolization was complete, but the main artery was still visible.

Intraoperative medication

There was an increased use of gelatin sponges in the experimental group relative to the control group (p=0.034). There was no significant difference between the two groups with respect to the use of intraoperative chemotherapy drugs and iodized oil.

Survival analysis

We next conducted a survival analysis of these two groups of patients. A statistical analysis of OS

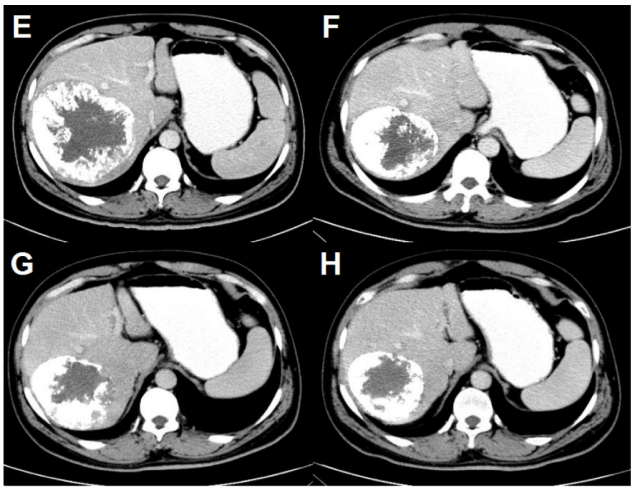

Figure 6. (E-H) After the second TACE, CT reexamination showed that the tumor gradually decreased, and AFP, the tumor marker of the patient, returned to normal.

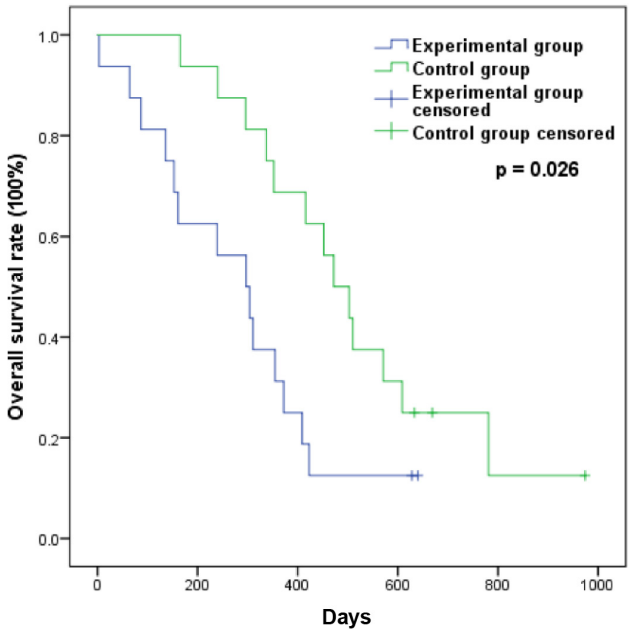

Figure 7. OS curve after treatment in both groups. This graph shows the cumulative survival of patients with HCC. Data were analyzed with the Kaplan-Meier method between groups (p=0.026).

Table 2. Univariate and multivariate Cox regression analysis for the prediction of overall survival

Parameter	*Univariate Cox Regression*		*Multivariate Cox Regression*	
	p value	*Hazard ratio (95% CI)*	*p value*	*Hazard ratio (95% CI)*
Group	0.046	0.456 (0.210-0.987)	0.019	0.336 (0.135-0.838)
Sex	0.778	0.857 (0.295-2.494)		
Age	0.731	1.007 (0.968-1.047)		
Diameter of tumor	0.614	0.910 (0.632-1.311)		
Site	0.038	0.193 (0.041-0.915)		
Pseudocapsule	0.961	1.020 (0.471-2.207)		
Hepatitis B	0.016	0.271 (0.093-0.787)	0.029	0.281 (0.090-0.877)
Cirrhosis	0.378	0.707 (0.327-1.529)		
Child-Pugh classification	0.313	0.638 (0.266-1.528)		
AFP	0.326	1.631 (0.614-4.334)		
ALT	0.051	1.009 (1.000-1.019)		
AST	0.637	1.001 (0.997-1.006)		
GGT	0.344	1.001 (0.999-1.003)		
TB	0.263	1.030 (0.978-1.085)		
ALB	0.654	1.018 (0.940-1.103)		
Scr	0.476	0.986 (0.950-1.024)		
WBC	0.499	0.954 (0.833-1.093)		
HGB	0.173	1.007 (0.997-1.018)		
PLT	0.038	1.008 (1.000-1.015)		
Oxaliplatin	0.950	1.000 (0.995-1.005)		
Epirubicin	0.740	0.996 (0.972-1.021)		
Iodipin	0.077	0.920 (0.839-1.009)		
Gelatin sponge	0.278	1.523 (0.712-3.261)		

revealed significant differences, with a log-rank test yielding a p value of 0.041 (Figure 7). Specifically, we found that the survival time of the control incomplete embolization group was significantly longer than that of complete embolization experimental group.

We subsequently established ideal prognostic cut-off values by fitting a Cox proportional hazard model to the survival status and the survival time of patients, and testing the influence of individual variables most significant log-rank tests as recently described. Using the ideal cutoff values determined via this approach, we then conducted a Kaplan-Meier analysis which revealed that long-term survival rates were significantly reduced in patients whose the degree of embolization, tumor site, hepatitis B status, and PLT levels were higher than their ideal cut off levels (p=0.046, 0.038, 0.016, and 0.038, respectively). Importantly, these prognostic risk factors between groups were independent of tumor diameter, site, pseudocapsule, cirrhosis, Child-Pugh classification, AFP, ALT, GGT, ALB, Scr, WBC, HGB, PLT, or other factors (Table 2).

Discussion

Our study showed that incomplete embolization (control group) had less influence on liver function, a lower rate of serious complications, and better long-term survival outcomes than did complete embolization (experimental group) for patients with solitary large HCC tumors measuring 8-12 cm in diameter. Excessive embolization can thus evidently lead to severe complications including hepatic aseptic necrosis after TACE in these patients, and this necrosis can in turn serve as a risk factor for hepatic failure or liver rupture, which can result in a significant decrease in survival time and a poorer prognosis.

For unresectable primary and metastatic hepatic tumors, TACE is recognized as the preferred palliative treatment option by doctors due to its wide indication, good tolerance, and enhanced local focal therapeutic efficacy [14]. Multiple complications can occur after TACE treatment of hepatic tumors, including liver rupture, liver abscess, femoral artery pseudoaneurysm, cholecystitis, biloma, pulmonary embolism, and rare complica-

tions including cerebral lipiodol embolism, tumor lysis syndrome, partial intestinal obstruction, and gallbladder perforation [15,16]. Liver necrosis is a rare complication in these cases. During an 8-year study period, Huang et al [17] found that the incidence of liver necrosis after TACE for malignant hepatic tumors was just 0.27% in 1374 patients who underwent 2581 TACE procedures in Taiwan. A similar incidence rate (0.28%) was observed in 351 Korean patients with liver cancer who received a single or multiple TACE procedures [18].

Compared with previous studies, we found that hepatic necrosis in the experimental group was primarily aseptic in nature, likely due to the complete embolization of these large HCC tumors, not only suppressing the tumor blood supply but also inducing the necrosis of a large number of normal hepatocytes in the surrounding tissue due to ischemia and hypoxia [19]. Patients with these outcomes were treated not only with iodized oil during the operation, but also with gelatinous sponge granules aimed at enhancing the degree of vascular embolism. Unlike liver abscesses, no infectious bacteria were detected in aspirate tests of these patients, which were instead composed mostly of necrotic components [20]. This aseptic necrosis develops rapidly and can result in severe necrosis in a very short period of time of both tumor lesions and normal liver tissue. In these cases, treatment can lead to liver abscess, and as such intubation and drainage should be given as soon as conditions permit, and antibiotics should be used when necessary to prevent infection [21,22].

The incidence of hepatic necrosis in this study was significantly higher in the experimental group relative to the control group, and this was directly related to the degree of embolism. The following factors were evident when comparing our two different groups: 1) All tumors had a diameter ranging from 8 to 12 (average: 10.42±1.12); 2) Angiographic examination of all patients detected a limited number of arteries supplying blood to the tumor, all of which originated from the same superior artery; 3) After embolization, in the experimental group the tumor blood supplying arteries exhibited complete embolization without any angiographic tumor staining; (4) The experimental group showed clear signs of rapid-onset necrosis. In contrast, in the control group, after operation the tumor and supplying artery were still faintly detectable via angiography, resembling a bare tree with thin branches akin to a "tree in the winter". Therapeutic outcomes in these patients were better, with a reduced degree of hepatic ischemia and hypoxia, thereby reducing the probability of necrosis and hepatic failure [23]. Liver necrosis in response to excessive embolization also significantly impacted the liver and kidney function and long-term survival of the patients.

In current clinical practice, the most commonly used embolic materials include ethyl iodide oil, gelatin sponges, and embolization microspheres [24]. Ethiodized oil was first used as a therapeutic agent in 1901. Recognition and application of ethiodized oil as a tumor-seeking drug-delivery vehicle facilitating the intracellular entry of chemotherapeutic agents prompted its widespread use in transarterial hemoembolization beginning in the 1980s, and demanded a formal understanding and scientific foundation for ideal chemotherapy mixture preparation methodologies to provide maximal therapeutic benefit [25]. Recently, embolization materials other than iodized oil with smooth hydrophilic surfaces and minimal aggregation tendencies have been used in clinical studies, including gelatin sponge particles with diameters of 1 mm which are often used as a supplementary embolic agent after iodized oil injection during conventional TACE [26]. Multiple studies have confirmed that TACE conducted using microspheres or microparticles has advantages in terms of safety and efficiency relative to TACE performed using iodized oil [27,28].

Intraoperative patients are often treated with gelatinized sponge granules to enhance the degree of vascular embolism [29]. These gelatin sponge particles have the following advantages over iodized oil: 1) By simultaneously embolizing the tumor blood supplying artery, they can effectively extend the tumor ischemia time, contain the collateral artery, generate similar in diameter and gelatin sponge particles in arterial thrombosis weaver, which makes hepatic artery blood difficult to flow again in a short period of time; 2) these gelatin sponge particles synergize with iodized oil, and when embolization is nearly complete iodized oil can generally not continue through the blood vessel into the tumor, whereas gelatin sponge particles can be used to enhance peripheral embolization owing to their ability to traffic within the tumor and the surrounding blood vessels during embolization [30].

Although various embolic agents have shown excellent benefits when used to TACE treatment of HCC, their excessive use can lead to adverse outcomes. Insufficient embolization may not be sufficient for the treatment of target tumors [31]. However, excessive embolization may increase hepatic toxicity and vascular growth factor expression [32]. In clinical practice, determining the degree of tumor embolism depends on the chosen embolization endpoint. DSA-guided therapy for tumor intervention relies on an endpoint of angiographic embolization, with studies suggesting the degree

of embolism can be divided into four levels [33]. Level I indicates a tumor with standard staining and largely unchanged blood flow suggesting poor embolization, while level IV indicates a tumor that has undergone total embolization with no blood flow detectable by DSA. Given that this latter approach completely blocks blood flow, level IV embolization inevitably maximizes ischemic tissue hypoxia. Our results suggest that patients with level II or III embolization have better overall survival, consistent with other results. Although our study is retrospective in nature and includes a limited number of cases, it may provide useful guidance for future clinical practice and suggests important avenues for future research.

Conclusions

Through a retrospective analysis of available case data, we have determined that for patients with large HCC tumors supported by multiple blood supplying arteries, complete embolization should not be performed during embolization treatment. Instead, embolization should be conducted to the point that on angiographic visualization the tumor blood supply is faintly visible and resembles a tree with dry branches, indicating a limited residual blood flow. This approach allows for the simultaneous embolization of the small tumor blood supplying arteries while significantly reducing the occurrence of serious postoperative complications, preserving the patency of the hepatic segment or hepatic artery so as to facilitate subsequent re-embolization treatments.

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Conflict of interests

The authors declare no conflict of interests.

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