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Original article

Exploratory study of microparticle transcatheter arterial chemoembolization combined with resection for huge hepatocellular carcinoma

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ABSTRACT

Objective: To investigate the safety and clinical efficacy of microparticle transcatheter arterial chemoembolization (mTACE) combined with surgical resection for the treatment of huge hepatocellular carcinoma (hHCC; ≥ 10 cm).
Methods: A retrospective descriptive study was conducted to gather the clinical data of nine patients with hHCCs treated with mTACE combined with resection in Beijing Tsinghua Changgung Hospital from December 2016 to July 2020. The outcome were as follows: (1) the excellent effect and adverse reactions of mTACE and (2) the efficacy and safety of perioperative resection. Count data were expressed as absolute numbers and percentages. The measurement data of the normal distribution is represented by X ± S, and the measurement data of the skewed distribution are represented by M (range). A paired t-test was used to compare the data of the same patient. p values <0.05 are considered statistically significant.
Results: (1) Regarding the efficacy and safety of mTACE, all nine hHCCs were treated with mTACE one time. The tumor necrosis rate after particle TACE was (77.6 ± 15.7)% (51.7%–100%); according to the modified response evaluation criteria in solid tumors, the objective response was partial response in eight patients and complete response in one patient. The alpha fetoprotein (AFP) level was abnormal in six cases (>20 ng/mL), of which three cases exceeded the maximum value (>30,000 ng/mL) pre-mTACE. In six patients with abnormal AFP levels, the AFP level decreased in five patients, with a median percentage of 74.5% (35.2%–96.0%). The PIVKA-II level in nine patients was > 40 mAU/mL before mTACE and decreased to varying degrees after mTACE. The median percentage of decline was 76.0% (4.5%–99.8%). The maximum diameter of the tumor decreased from (13.9 ± 1.9) cm (11.0–16.4 cm) to (12.8 ± 1.9) cm (10.4–15.6 cm) (P = 0.001) before surgical resection. Prior to the surgical resection, the tumor volume decreased from (897 ± 244) mL (436–1250 mL) to (750 ± 291) mL (260–1130 mL) (P = 0.001), and the residual liver volume/standard liver volume increased from (42.8 ± 12.8)% (25.8%–61.3%) to (50.2 ± 14.9)% (28.8%–67.4%) (P = 0.008). All patients had embolism syndrome such as fever and abdominal pain in varying degrees, and no serious complications such as liver abscess, liver and kidney failure, or ectopic embolism were noted. (2) For perioperative efficacy and safety, all lesions were successfully resected in (31 ± 11) days (14–48 days) after mTACE. The operation time was (395 ± 79) min (296–540 min), and the amount of intraoperative bleeding was (433 ± 158) mL (200–600 mL). Complications such as biliary fistula, abdominal bleeding, liver and kidney failure, or abdominal infection were not found. The postoperative hospital stay was (13 ± 4) days (9–19 days). No tumor invasion was found at the cutting edge, and hepatic vein invasion was observed in one case. (3) The follow-up ended in November 2021, with a median follow-up of 34 months (16–46 months). Recurrence or distant metastasis occurred in four patients, of which two patients died. The survival times were 18 and 31 months, respectively. The other two patients were followed up for 34 and 41 months. The remaining five patients were followed up for 16–46 months without antitumor treatment or disease progression.
Conclusions: mTACE combined with tumor resection is feasible for the treatment of patients with hHCC, which needs to be further confirmed by prospective studies.

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1. Introduction

Hepatocellular carcinoma (HCC) ≥ 10 cm in diameter is called a huge HCC (hHCC). Compared with small HCC, the risk of vascular invasion and extrahepatic metastasis is significantly increased in hHCC, and patient survival is significantly reduced [1–4]. Conventional transcatheter arterial chemoembolization (cTACE) using lipiodol as an embolization agent has a poor curative effect for the treatment of hHCC, with a five-year survival of only 7.0%–23.1% and a median survival of 6.5–23.0 months [5–7]. The tumor recurrence rate within one year after surgical resection is as high as 62.2%–77.2%, which is considered the main reason for the difficulty in improving the long-term efficacy of cTACE for the treatment of hHCC [8,9]. To further reduce the recurrence rate of tumors after surgical resection and improve the long-term survival rate of patients, cTACE, as a commonly used preoperative neoadjuvant method, has become a hotspot in clinical research [10–16]. Although the efficacy and safety of cTACE are still controversial, it has been shown that the degree of tumor necrosis after TACE is an important factor affecting the prognosis of surgical resection [17–19]. For the treatment of large HCCs with TACE, our team used gelatin sponge microparticles (GSMs) as an absorbable embolization agent and observed significant tumor necrosis after TACE [20,21]. In addition, our previously published data showed that regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and the ratio of $CD4^+/CD8^+$ in peripheral blood were significantly decreased after microparticle TACE (mTACE), confirming that it has a positive regulatory effect on immune function [22,23]. Based on our previous results, we hypothesized that preoperative mTACE combined with surgical resection could significantly improve the immune function of patients with hHCC, possibly breaking the bottleneck of high postoperative recurrence rate for the treatment of hHCC by surgical resection alone, which is a worthy research topic for exploration.

This study retrospectively analyzed the clinical data of nine patients with massive liver cancer treated with mTACE combined with surgical resection at the Hepatopancreatobiliary Center of Tsinghua Affiliated University Beijing Tsinghua Changgung Hospital from December 2016 to July 2020, to explore the safety and effectiveness of this new mode for the treatment of hHCC and provide a basis for the subsequent design of prospective randomized controlled trials.

2. Methods

2.1. General information

A retrospective descriptive study was conducted from December 2016 to July 2020 in the Hepatopancreatbiliary Center of Beijing Tsinghua Changgung Hospital. Ethical approval was obtained from the Ethics Committee of Tsinghua Affiliated University Beijing Tsinghua Changgung Hospital (20200-0-02). Nine patients with hHCC were enrolled in this study, including seven men and two women, aged (50 ± 14) years (29–71 years). The Child Pugh score is A, and the tumor diameter was (13.9 ± 1.9) cm (11.0–16.4 cm). All enroled patients suffered from chronic viral hepatitis B. Moreover, informed consent was obtained from both the patients and their families.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) The lesions were evaluated to be resectable by two deputy senior physicians or above of the Department of Hepatobiliary Surgery; (2) the maximum diameter of the tumors was > 10 cm, the number of tumors was < 3, and all lesions were located ipsilateral to the liver lobe; (3) no vascular invasion or distant metastasis was found; (4) no other antitumor therapy has been previously received; (5) HCC was confirmed by pathological examination; (6) the Child Pugh score was A, and the liver reserve function was normal; and (7) clinical data were complete.

Exclusion criteria were as follows: (1) patients without surgical resection after receiving mTACE, (2) patients with an ECOG physical strength score > 2, (3) patients with vascular invasion and distant metastasis, and (4) patients with missing clinical data and lost follow-up.

2.3. Treatment methods

2.3.1. Microparticle TACE

Nine patients selected microparticle as embolization agents (GSM, specification, 100 mg; Alicon Biomedical Science and Technology Co., Zhejiang, China.). The details of the diameter and dose of chemotherapy drugs (Pirarubicin for injection; specification, 10 mg; Shenzhen Wanle Pharmaceutical Co., Shenzhen, China.) are shown in Table 1. The criteria for terminating mTACE were complete occlusion of the tumor-supplying artery. Symptomatic treatments, such as liver protection, fluid rehydration, antiemetic and analgesic administration, and acid inhibition, were routinely performed 4–7 days after mTACE operation.

2.3.2. Partial hepatectomy

Surgical procedures were planned by considering preoperative imaging and liver reserve function tests. Complete tumor resection is ensured on the premise of a reserved adequate liver volume. Attention should be paid to protecting the integrity of the vascular structure of the remaining liver and to ensure that the liver is fully hemostatic. The operation was performed after the abdominal drainage tube was placed under the diaphragm and the liver. Symptomatic treatments, such as liver protection, fluid rehydration, antiemetic and analgesic administration, and acid inhibition were routinely performed, and the abdominal drainage tube was maintained for 4–10 days.

3. Main outcome measures

3.1. Microparticle TACE

The main outcome measures of mTACE were tumor necrosis rate, tumor diameter, tumor volume, indocyanine green retention rate at 15 min (ICG-R15), standardized remnant liver volume ratio (residual liver volume/standard liver volume ratio [RLV/SLV]), tumor markers, routine blood examination, liver and kidney function, and adverse reactions after embolization. Liver function indexes included aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBIL), and albumin (ALB). The tumor necrosis rate was calculated using the GE Healthcare Centricity Radiology ra600 (version 8.0) (Manufactured by GE Healthcare Integrated IT Solutions, Illinois, USA.). After enhanced CT scanning, the area of fluid density in the tumor was identified as the necrotic area, and the enhanced part was defined as the residual focus of the tumor. The above areas were outlined, and the volume ratio was calculated as the necrosis rate.

3.2. Hepatectomy

The surgical method, operative time, operative blood loss, postoperative complications, postoperative pathology, and postoperative hospital stay were evaluated.

3.3. Objective evaluation of tumor response

The modified response evaluation criteria in solid tumors [24] was used to evaluate the reaction of liver tumors together with the change in AFP value, using the following indicators: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and tumor objective response rate (ORR).

3.4. Follow-up

Patients were followed up through outpatient visits and via telephone; the follow-up items included follow-up time, survival status,

Table 1
Baseline and mTACE treatment data.

	Gender	Age	Child Pugh class	Hepatitis	AFP (ng/mL)	PIVIK (mAU/mL)	Largest tumor diameter (in cm)	Number of lesions	Tumor capsular	Vascular invasion	Particle diameter (in μm)	Drugs and dose	Tumor necrosis rate after mTACE	Response of mTACE
Case 1	Male	45	A	HBV	1822.7	799.9	11.0	2	–	–	350	Pirarubicin 30 mg	70.6%	PR
Case 2	Male	62	A	HBV	5344.6	11537.2	16.4	1	–	–	150 + 350	Pirarubicin 30 mg	72.9%	PR
Case 3	Female	29	A	HBV	> 30,000	17118.8	15.7	2	+	–	350 + 560	Pirarubicin 30 mg	89.2%	PR
Case 4	Female	34	A	HBV	> 30,000	5582.3	14.7	2	+	–	350 + 560+710	Pirarubicin 30 mg	59.2%	PR
Case 5	Male	42	A	HBV	1.5	> 30,000	13.2	1	+	–	350	Pirarubicin 30 mg	92.3%	PR
Case 6	Male	63	A	HBV	2.8	151.0	12.8	1	+	–	350 + 560	Pirarubicin 30 mg	51.7%	PR
Case 7	Male	60	A	HBV	242.8	17491.7	14.0	2	+	–	150 + 350	Pirarubicin 30 mg	100%	CR
Case 8	Male	45	A	HBV	> 30,000	> 30,000	12.6	2	+	–	350 + 710	Pirarubicin 30 mg	82.3%	PR
Case 9	Male	71	A	HBV	5.5	> 30,000	14.7	1	+	–	150	Pirarubicin 30 mg	80.6%	PR

tumor recurrence, metastasis, and treatment plan; and the follow-up end point was November 2021.

3.5. Statistical analysis

The SPSS19.0 statistical software was used for the analysis. The measurement data of the skewed distribution are expressed as the median value M (range), and the counting data are expressed as absolute logarithms.

4. Result

4.1. mTACE

4.1.1. Safety

Nine patients with hHCCs were treated with particle TACE once. All patients had different degrees of fever, epigastric pain, ALT and AST level elevation, and high embolism syndrome. The abdominal pain was relieved on the second day, and fever was completely alleviated after 7–21 days. The AST and ALT levels increased transiently 4 days after mTACE, which were managed with liver protection treatment and returned to the operation level 10 days postoperatively (Figs. 1 and 2). The TBIL level increased transiently 4 and 10 days postoperatively, but the difference was not statistically significant ($P > 0.05$) (Fig. 3). The ALB level transiently decreased 4 and 10 days postoperatively, and the difference was statistically significant ($P < 0.05$), which recovered to the preoperative level ($P > 0.05$) (Fig. 4). None of the patients had serious complications, such as liver and kidney failure, ectopic embolism, cholesteatoma, or liver abscess.

4.1.2. Efficacy

Nine patients underwent surgical resection at (31 ± 11) days (14–48 days) after mTACE (Fig. 5). Among them, eight patients achieved PR, and one patient achieved CR after mTACE (Table 1). The AFP level was > 20 ng/mL in six cases, of which three cases exceeded 30,000 ng/mL, and AFP degression was observed in five patients after mTACE, with a median percentage of 74.5% (35.2%–96.0%). The PIVKA-II was > 40 mAU/mL in nine cases before surgery, which all decreased after surgery, with a median percentage of 76.0% (4.5%–99.8%), as shown in Table 2.

The tumor necrosis rate of the nine patients was (77.6 ± 15.7)% (51.7%–100%). After mTACE, the maximum tumor diameter decreased from (13.9 ± 1.9) cm (11.0–16.4 cm) to (12.8 ± 1.9) cm (10.4–15.6 cm) ($P = 0.001$). The tumor volume decreased from (897 ± 244) mL (436–1250 mL) to (750 ± 291) mL (260–1130 mL) ($P = 0.001$). No significant difference in the ICG-R15 value was observed ((4.4 ± 2.0)% vs. (5.2 ± 2.8)%, $P = 0.078$). The RLV/SLV increased from (42.8 ± 12.8)% (25.8%–61.3%) to (50.2 ± 14.9)% (28.8%–67.4%) ($P = 0.008$).

4.1.3. Surgical resection

All patients underwent successful surgical resection, six underwent right hemihepatectomy, one underwent left hemihepatectomy, one underwent middle lobe hepatectomy, and one underwent right posterior lobe hepatectomy. The median operation time was (395 ± 79) min (296–540 min), and the median amount of intraoperative bleeding was (433 ± 158) mL (200–600 mL). Death 30 days after the operation and complications, such as biliary fistula, abdominal bleeding, liver and kidney failure, or abdominal infection, were not observed, as shown in Table 3.

4.1.4. Efficacy and follow-up

Postoperative pathology showed that seven cases were moderately differentiated HCC, and two cases were moderately to poorly differentiated HCC. Postoperative stay was (13 ± 4) days (9–19 days). The median follow-up time was 34 months (16–46 months). Until November 2021, two patients had intrahepatic recurrence and two patients had lung metastasis. One case of intrahepatic recurrence occurred 25 months postoperatively. After receiving targeted therapy, the patient died of tumor progression 31

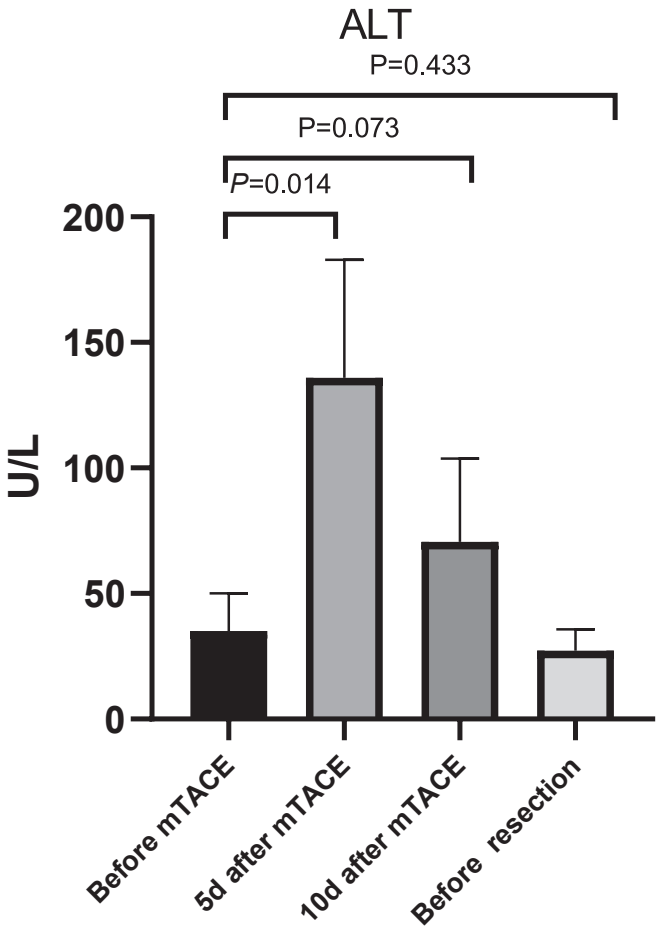

Fig. 1. Changes of ALT levels before and after mTACE.

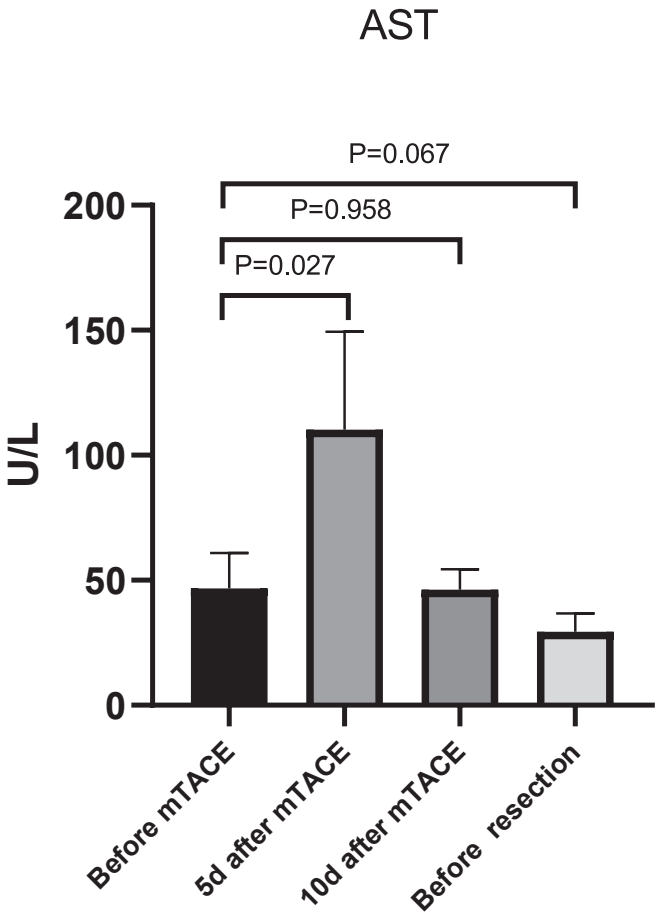

Fig. 2. Changes of AST levels before and after mTACE.

months after the operation; another case appeared 15 months after the operation. After radiofrequency ablation, targeted therapy, and immunotherapy, the patient remained in complete remission at the end of follow-up. Of the two patients with lung metastasis, one occurred 12 months after the operation and died of tumor progression 18 months after targeted treatment. In another patient, lung metastasis appeared 10 months after the operation. After targeted treatment, the patient's condition was stable. The other five patients were followed up for 16–46 months. No other antitumor treatment was performed after the operation, and disease progression has not been recorded to date (see Table 4).

5. Discussion

5.1. Feasibility of mTACE for the treatment of hHCC

Varela et al. [25] first reported the application of drug-eluting bead (DEB)-TACE for the treatment of HCC in 2007. In 2013, our team was the first to report the application of GSM-TACE alone for the treatment of HCC, which achieved good safety and efficacy [26]. Since microparticles embolize the tumor supplying artery more thoroughly, mTACE treatment for HCC, especially hHCC, is characterized by more significant tumor necrosis after TACE. Moreover, there is no space-occupying effect similar to that in cTACE due to a large amount of lipiodol deposition in the tumor; therefore, tumor volume reduction after mTACE is more significant [20,27]. The pathological characteristics of HCC after mTACE are significantly different from those of traditional lipiodol TACE; however, clinical studies of mTACE combined with surgical resection for the treatment of hHCC are rarely reported. Kurniawan et al. [28] published a case report showing the efficacy of mTACE combined with surgical resection for the treatment of hHCC. Our previous research results showed that the CR, PR, and OR rates were 61.3%, 29%, and 90.3%, respectively, six months after mTACE treatment for hHCC [26]. Moreover, good efficacy and safety of mTACE for the treatment of patients with HCC with different stages of BCLC have been reported [20–22]. These are important clinical research bases for exploring a new mode of mTACE in combination with surgical resection for hHCC.

5.2. Safety and efficacy of mTACE combined with surgical resection for the treatment of hHCC

5.2.1. Safety

Transient epigastric pain is relatively common after mTACE, which may be related to transient ischemia of visceral organs caused by complete embolization of the tumor supplying artery, and can be relieved on the second day of symptomatic treatment. The AST and ALT levels transiently increased 4 days after mTACE, which were managed with liver protection and returned to the operative level 10 days postoperatively. The TBIL transiently increased 4 and 10 days postoperatively, but the difference was not statistically significant ($P > 0.05$). The ALB level transiently decreased 4 and 10 days postoperatively and recovered to the preoperative level before operation. Fever is the primary clinical manifestation of embolism syndrome, resulting from aseptic inflammation caused by tumor necrosis, and is characterized by an elevated ratio of white blood cells to neutrophils. Antibiotics are not required for routine treatment, but should be added if the patient has a history of biliary surgery, as intestinal bacteria may migrate through the biliary system to the necrotic tumor tissue and develop bacterial infection. In addition, if the tumor is large and the artery is rich in blood supply, large microparticles (>300 μm) should be selected; otherwise, the liquefactive necrosis of the tumor may increase the chance of

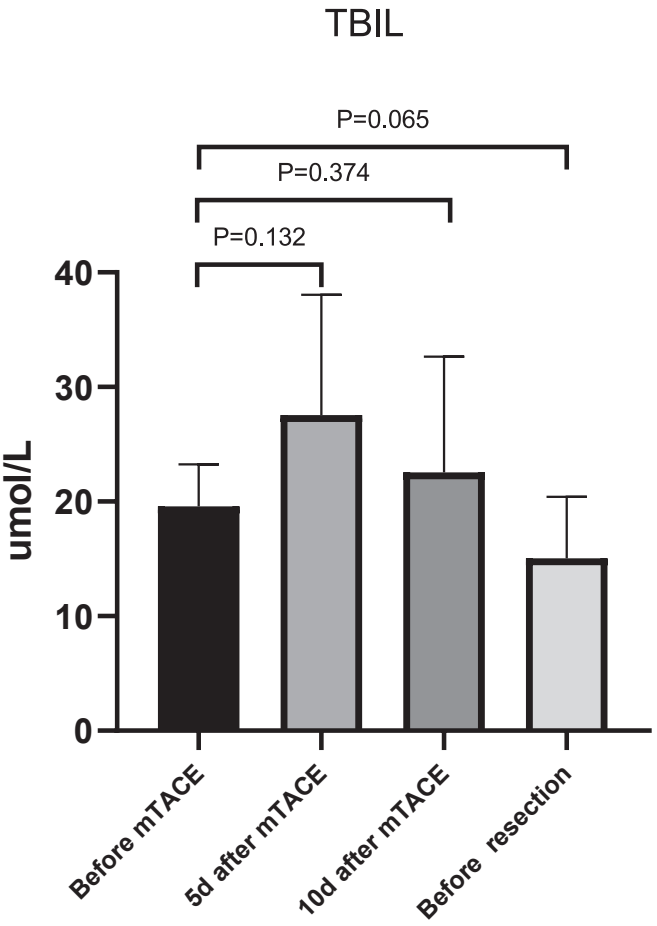

Fig. 3. Changes of TBIL levels before and after mTACE.

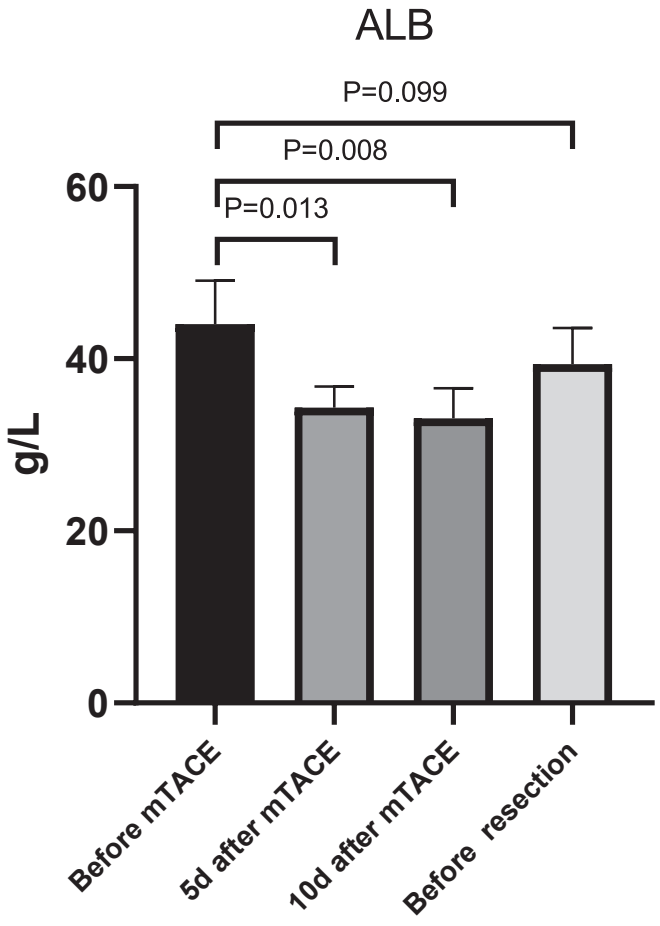

Fig. 4. Changes of ALB levels before and after mTACE.

infection in necrotic tumor tissue [29]. Therefore, the degree of tumor necrosis is correlated with the size of the microparticles. The selection of the appropriate size of microparticles and striking a balance between increasing the rate of tumor necrosis and reducing the rate of infection in necrotic tumor tissue need to be summarized in clinical practice, and the optimal treatment regimen of mTACE should be determined through prospective, multicenter studies. In this study, to reduce the risk of postoperative necrotic tumor infection during mTACE, only one of the nine patients was treated with 150 μm microparticles alone.

Some scholars oppose cTACE treatment before the surgical resection of HCC, believing that lipiodol TACE may increase the risk of adhesion between liver or tumor tissues and surrounding organs, and the application of high-dose chemotherapy drugs can also induce drug-induced liver injury, which prolongs the operation time and increases perioperative mortality [14–16]. Six patients in this group underwent surgical resection at an interval of (31 ± 11) days after mTACE. No adhesion between the liver or tumor and the surrounding tissues was observed during the operation. The intraoperative blood loss was approximately (433 ± 158) mL, and postoperative biliary fistula, infection, bleeding, liver failure, or other serious complications were not observed. The mean length of hospital stay was (13 ± 4) days. In conclusion, preliminary clinical results indicate that mTACE combined with surgical resection is safe for the treatment of hHCC.

5.2.2. Efficacy

The degree of tumor necrosis after TACE has been shown to be an important factor influencing the efficacy. Kim et al. [17] found that the median survival times of patients who received CR or PR efficacy after the first cTACE, those who received CR or PR efficacy after multiple cTACE, and those who failed to achieve CR or PR efficacy were 52.6, 27.0, and 10.8 months, respectively ($P < 0.001$). Further stratified analysis showed that the median survival of patients receiving CR after the first cTACE and those receiving CR after two or more rounds of cTACE was 70.2 and 40.6 months, respectively ($P < 0.001$), confirming that patients receiving CR after the first cTACE with better tumor ORR had better long-term efficacy. Haywood et al. [18] reported that patients with CR or PR after the first cTACE or DEB-TACE had a longer median survival than in those with SD or PD (20.8 vs. 14.9 months, $P = 0.011$). The median survival in CR, PR, SD, and PD groups was 21.4, 20.8, 16.8, and 7.73 months, respectively ($P = 0.003$). Majno et al. [19] showed that the 5-year survival rate of patients with complete tumor necrosis after cTACE was much higher than in those with incomplete tumor necrosis (87% vs. 47%, $P = 0.03$). These results confirmed a significant correlation between the degree of tumor necrosis after the first TACE treatment and long-term efficacy. In this study, all patients received one dose of mTACE, and the efficacy evaluation showed that the tumor necrosis rate was (77.6 ± 15.7)%, and the ORR was 100%. After combined surgical resection, five patients survived without tumors until now. Significant tumor necrosis after mTACE was one of the reasons for the efficacy of this study.

Further, we observed interesting clinical phenomena. The RLV/SLV values of seven patients before surgical resection were significantly higher than in those before mTACE. This clinical phenomenon is similar to the conclusion that internal irradiation treatment of HCC can help increase residual liver volume [30]. These results suggest that mTACE may not only cause significant tumor necrosis, but also promote residual liver volume hyperplasia.

Our previous study confirmed that with significant liver tumor necrosis, the frequency of immunosuppressive cells such as Tregs and MDSCs in the peripheral blood of patients was significantly reduced after mTACE, whereas the ratio of CD4/CD8 was significantly increased [22,

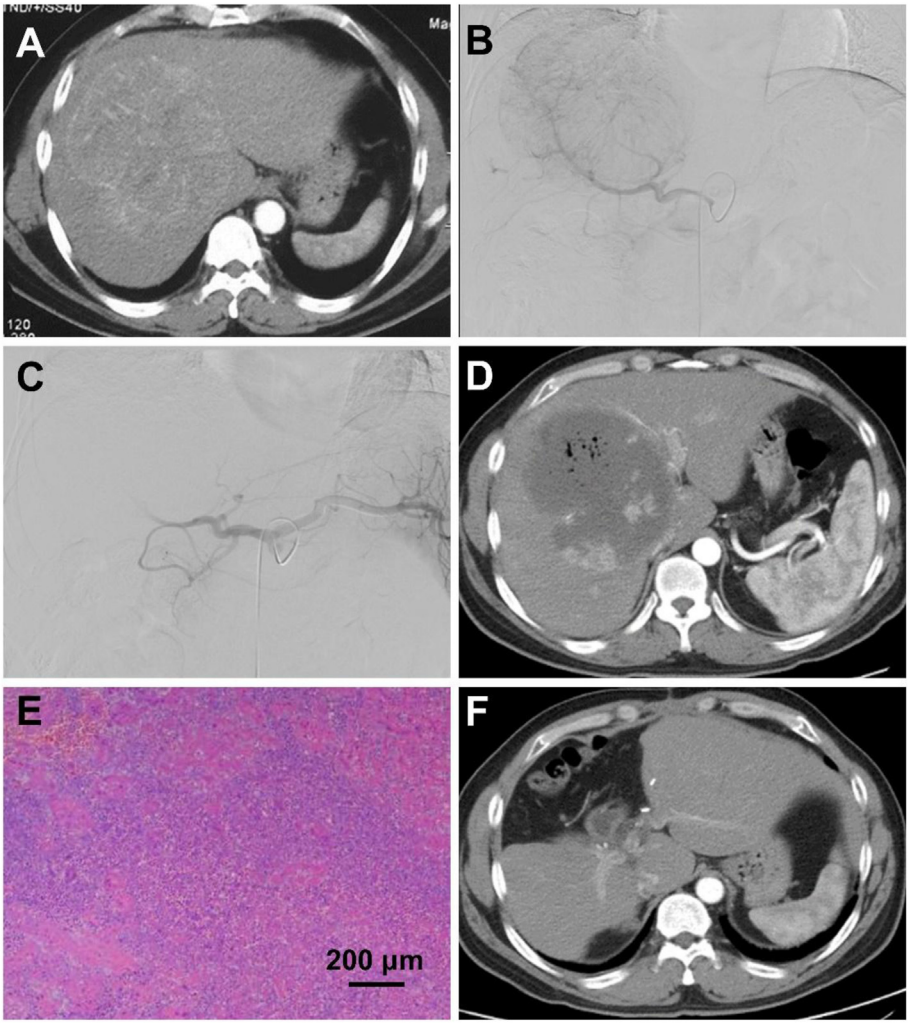

Fig. 5. An example of preoperative and postoperative images of a 42-year-old male patient. A. Preoperative enhanced CT of the upper abdomen shows a massive tumor in the right lobe of the liver; **B.** Before mTACE, obvious tumor vascular staining was seen on angiography; **C.** The tumor staining disappeared after mTACE; **D.** One month after mTACE, enhanced CT of the upper abdomen showed that most of the tumor was liquefied and necrotic, and the necrotic rate was about 92.3%; **E.** Postoperative pathology showed moderately differentiated hepatocellular carcinoma with massive necrosis; **F.** Forty months after surgical resection, there was no tumor recurrence in the liver by enhanced CT of upper abdomen.

Table 2
Changes of tumor and markers, tumor maximum diameter, tumor volume, and RLV/SLV indices in 9 patients before microparticle TACE treatment and surgical resection.

	Percentage change in tumor markers before and after mTACE (%)		Change of tumor maximum diameter (in cm)	Change of tumor volume (in mL)	Change of ICG-R15 (%)	Change of SLV/FLR (%)
	AFP (ng/mL) before mTACE/after mTACE	PIVKA (mAU/mL) before mTACE/after mTACE	Before mTACE/before surgical resection	Before mTACE/before surgical resection	Before mTACE/before surgical resection	Before mTACE/before surgical resection
Case1	35.2	76.0	11.0/10.4	436/260	4.0/4.6	25.8/32.0
Case2	74.5	78.3	16.4/15.6	1250/1130	2.7/3.6	33.6/42.1
Case3	> 80.0	97.7	15.7/15.4	1167/1089	3.0/2.7	45.0/63.9
Case4	—	4.5	14.7/14.1	983/912	1.7/1.8	46.4/56.8
Case5	—	> 95.6	13.2/12.3	1008/947	5.0/6.7	61.3/60.5
Case6	—	68.0	12.8/11.3	751/640	8.0/9.1	29.1/28.8
Case7	96.0	99.8	14.0/12.7	845/658	5.7/8.7	33.9/38.3
Case8	> 48.0	> 56.8	12.6/10.4	755/463	3.2/2.1	54.5/67.4
Case9	—	> 35.5	14.7/13.1	876/649	6.0/7.2	56.3/62.1

23], confirming that mTACE can positively regulate the antitumor immune response. Pinato et al. also confirmed that compared with direct surgical resection, TACE, as a preoperative neoadjuvant method, can significantly reduce the number of $CD4^{+}/FOXP3^{+}$ cells in tumor tissues and significantly prolong the postoperative recurrence-free survival time of patients with HCC [31]. In this study, the patients were followed up for 34 months. Recurrence or distant metastasis occurred in four patients: two patients died at 18 and 31 months, and the other two patients were alive after 34 and 41 months. The remaining five patients were followed up for 16–46 months without antitumor therapy and survived without disease progression to date. Preliminary results showed that mTACE combined with surgical resection had the advantage of prolonging the overall survival time.

This is a small-sample exploratory clinical study of mTACE combined with surgical resection for the treatment of hHCC, which preliminarily confirmed the satisfactory safety and efficacy of this new mode of treatment, laying a research foundation for subsequent large-sample, prospective, randomized controlled clinical studies.

Table 3
Observation indices, postoperative pathology, and postoperative hospital stay during surgical resection of 9 cases.

	Time between microparticle TACE and surgical resection (in d)	Surgical method	Operating time (in min)	Bleeding volume (in mL)	Blood transfusion volume (in mL)	Pathological diagnosis	Vascular invasion	Surgical margin	Postoperative hospital stay (in d)
Case 1	48	Right hemihepatectomy	348	200	0	Moderately differentiated hepatocellular carcinoma	–	–	18
Case 2	36	Right hemihepatectomy	296	600	0	Moderate to poorly differentiated hepatocellular carcinoma	–	–	12
Case 3	14	Right hemihepatectomy	419	400	400	Moderately differentiated hepatocellular carcinoma	–	–	10
Case 4	16	Right hemihepatectomy	299	200	0	Moderately differentiated hepatocellular carcinoma	–	–	19
Case 5	35	Mesohepatectomy	540	600	800	Moderately differentiated hepatocellular carcinoma	–	–	14
Case 6	30	Right hemihepatectomy	423	600	0	Moderately differentiated hepatocellular carcinoma	–	–	9
Case 7	41	Right hemihepatectomy	428	400	0	Moderately differentiated hepatocellular carcinoma	–	–	9
Case 8	33	Right posterior lobectomy	450	500	0	Moderately differentiated hepatocellular carcinoma	–	–	10
Case 9	22	Left hemihepatectomy	353	400	0	Moderate to poorly differentiated hepatocellular carcinoma	+	–	12

Table 4
Following-up data of 9 cases (end up to November 2021).

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Recurrence/extrahepatic metastasis	–	Pulmonary metastasis	Intrahepatic recurrence	Intrahepatic recurrence	–	–	Pulmonary metastasis	–	–
Treatment after tumor progression	–	TKI drugs	TKI drugs	Radiofrequency ablation + TKI drugs + ICI drugs	–	–	TKI drugs	–	–
TTP (month)	–	12	25	15	–	–	10	–	–
Follow-up time	46	18	31	41	34	34	34	26	16
Survival situation	Survive	Death	Death	Survive	Survive	Survive	Survive	Survive	Survive

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Declaration of competing interest

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.

References

[1] Liu PH, Su CW, Hsu CY, et al. Solitary large hepatocellular carcinoma: staging and treatment strategy[J]. PLos One 2016;11(5):e0155588. https://doi.org/10.1371/journal.pone.0155588.
[2] Chang YJ, Chung KP, Chang YJ, et al. Long-term survival of patients undergoing liver resection for very large hepatocellular carcinomas[J]. Br J Surg 2016;103(11):1513–20. https://doi.org/10.1002/bjs.10196.
[3] Fang Q, Xie QS, Chen JM, et al. Long-term outcomes after hepatectomy of huge hepatocellular carcinoma: a single-center experience in China[J]. Hepatobiliary Pancreat Dis Int 2019;18(6):532–7. https://doi.org/10.1016/j.hbpd.2019.09.001.
[4] Wakayama K, Kamiyama T, Yokoo H, et al. Huge hepatocellular carcinoma greater than 10 cm in diameter worsens prognosis by causing distant recurrence after curative resection[J]. J Surg Oncol 2017;115(3):324–9. https://doi.org/10.1002/jso.24501.
[5] Xue T, Le F, Chen R, Xie X, et al. Transarterial chemoembolization for huge hepatocellular carcinoma with diameter over ten centimeters: a large cohort study [J]. Med Oncol 2015;32(3):64. https://doi.org/10.1007/s12032-015-0504-3.
[6] Dong J, Zhai X, Chen Z, et al. Treatment of huge hepatocellular carcinoma using cinobufacini injection in transarterial chemoembolization: a retrospective study[J]. Evid Based Complement Alternat Med 2016:2754542. https://doi.org/10.1155/2016/2754542.
[7] Miyayama S, Kikuchi Y, Yoshida M, et al. Outcomes of conventional transarterial chemoembolization for hepatocellular carcinoma ≥10 cm[J]. Hepatol Res 2019;49(7):787–98. https://doi.org/10.1111/hepr.13335.
[8] Bhanu JS, Venkitaraman B, Palaniappan R, et al. Prognostic factors and survival outcomes of surgical resection of huge hepatocellular carcinomas [J]. J Gastrointest Cancer 2020;51(1):250–3. https://doi.org/10.1007/s12029-019-00240-x.
[9] Hwang S, Lee YJ, Kim KH, et al. Long-term outcome after resection of huge hepatocellular carcinoma ≥ 10 cm: single-institution experience with 471 patients[J]. World J Surg 2015;39(10):2519–28. https://doi.org/10.1007/s00268-015-3129-y.
[10] Li C, Wang MD, Lu L, et al. Preoperative transcatheter arterial chemoembolization for surgical resection of hugehepatocellular carcinoma (≥ 10 cm):a multicenter propensity matching analysis[J]. Hepatol Int 2019;13(6):736–47. https://doi.org/10.1007/s12072-019-09981-0.
[11] Nishikawa H, Arimoto A, Wakasa T, et al. Effect of transcatheter arterial chemoembolization prior to surgical resection for hepatocellular carcinoma[J]. Int J Oncol 2013;42(1):151–60. https://doi.org/10.3892/ijo.2012.1711.
[12] Yamashita Y, Takeishi K, Tsuijita E, et al. Beneficial effects of preoperative lipiodolization for resectable large hepatocellular carcinoma (≥ 5 cm in diameter) [J]. J Surg Oncol 2012;106(4):498–503. https://doi.org/10.1002/jso.23098.
[13] Zhou WP, Lai EC, Li AJ, et al. A prospective, randomized, controlled trial of preoperative transarterial chemoembolization for resectable large hepatocellular carcinoma[J]. Ann Surg 2009;249(2):195–202. https://doi.org/10.1097/SLA.0b013e3181961c16.
[14] Luo YQ, Wang Y, Chen H, et al. Influence of preoperative transcatheter arterial chemoembolization on liver resection in patients with resectable hepatocellular carcinoma. Hepatobiliary Pancreat Dis Int 2002;1(4):523–6.
[15] Choi GH, Kim DH, Kang CM, et al. Is preoperative transarterial chemoembolization needed for a resectable hepatocellular carcinoma?[J]. World J Surg 2007;31(12):2370–7. https://doi.org/10.1007/s00268-007-9245-6.
[16] Kim IS, Lim YS, Lee HC, et al. Preoperative transarterial chemoembolization for resectable hepatocellular carcinoma adversely affects post-operative patient outcome[J]. Aliment Pharmacol Ther 2008;27(4):338–45. https://doi.org/10.1111/j.1365-2036.2007.03580.x.
[17] Kim BK, Kim SU, Kim KA, et al. Complete response at first chemoembolization is still the most robust predictor for favorable outcome in hepatocellular carcinoma [J]. J Hepatol 2015;62(6):1304–10. https://doi.org/10.1016/j.jhep.2015.01.022.
[18] Haywood N, Gennaro K, Obert J, et al. Does the degree of hepatocellular carcinoma tumor necrosis following transarterial chemoembolization impact patient survival? [J]. J Oncol 2016:4692139. https://doi.org/10.1155/2016/4692139.
[19] Majno PE, Adam R, Bismuth H, et al. Influence of preoperative transarterial lipiodol chemoembolization on resection and transplantation for hepatocellular carcinoma in patients with cirrhosis[J]. Ann Surg 1997;226(6):688–701. https://doi.org/10.1097/00000658-199712000-00006.
[20] Zhou J, Liu Y, Ren Z, et al. Transarterial chemoembolization with gelatin sponge microparticles for barcelona clinic liver cancer Stage C and large hepatocellular carcinoma: initial clinical experience[J]. J Cancer Res Ther 2017;13(5):767–72. https://doi.org/10.4103/jcrt.JCRT_297_17.

[21] Liu Y, Zhang Y, Bautista D, et al. Trans-arterial p53-gene-embolization with gelatin sponge microparticles for hepatocellular carcinoma with BCLC stage B: single-center experience[J]. Cell Biochem Biophys 2015;71(1):99–104. https://doi.org/10.1007/s12013-014-0167-2.

[22] Yue YX, Ren ZZ, Liu Y, et al. Effect of gelatin sponge particle TACE on myeloid derived inhibitory cells in peripheral blood of Barcelona stage B hepatocellular carcinoma[J]. Chin J Interventional Imaging Ther 2019;16(5):280–4. https://doi.org/10.13929/j.1672-8475.201901018.

[23] Ren Zhizhong, Zhang Yuewei, Yue Yuanxun, et al. Changes in the peripheral blood treg cell proportion in hepatocellular carcinoma patients after transarterial chemoembolization with microparticles[J]. Front Immunol 2021;12:624789. https://doi.org/10.3389/fimmu.2021.624789.

[24] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1) [J]. Eur J Cancer 2009;45(2):228–47. https://doi.org/10.1016/j.ejca.2008.10.026.

[25] Varela M, Real MI, Burrel M, et al. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics[J]. J Hepatol 2007;46(3):474–81. https://doi.org/10.1016/j.jhep.2006.10.020.

[26] Zhang YW, Liu Y. Effect of transcatheter arterial chemoembolization with gelatin sponge particles on primary liver cancer[J]. Chin J Hepatol 2013;21(8):637–8. https://doi.org/10.3760/cma.j.issn.1007-3418.2013.08.017.

[27] Zhang ZS, Li HZ, Ma C, et al. Conventional versus drug-eluting beads chemoembolization for infiltrative hepatocellular carcinoma: a comparison of efficacy and safety[J]. BMC Cancer 2019;19(1):1162. https://doi.org/10.1186/s12885-019-6386-6.

[28] Kurniawan J, Sulaiman AS, Matondang SBRE, et al. Complete remission after sequential therapy of drug eluting beads transarterial chemoembolization and liver resection in large solitary nodule hepatocellular carcinoma[J]. Case Reports Hepatol 2017:3682614. https://doi.org/10.1155/2017/3682614.

[29] Zhang GS, Zhang YW, Liu Ying. New gelatin sponge particles TACE in the treatment of liver abscess after primary liver cancer and literature review[J]. J Interv Radiol 2013;22(5):415–7. https://doi.org/10.3969/j.issn.1008-794X.2013.05.016.

[30] Vouche M, Lewandowski RJ, Atassi R, et al. Radiation lobectomy: time-dependent analysis of future liver remnant volume in unresectable liver cancer as a bridge to resection[J]. J Hepatol 2013;59(5):1029–36. https://doi.org/10.1016/j.jhep.2013.06.015.

[31] Pinato DJ, Murray SM, Forner A, et al. Trans-arterial chemoembolization as a loco-regional inducer of immunogenic cell death in hepatocellular carcinoma: implications for immunotherapy[J]. J Immunother Cancer 2021;9(9):e003311. https://doi.org/10.1136/jitc-2021-003311.