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Original Article

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Clinical Efficacy of Transcatheter Arterial Chemoembolization Combined With Percutaneous Microwave Coagulation Therapy for Advanced Hepatocellular Carcinoma

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Abstract

Background: The aim of the study was to explore the clinical efficacy of transcatheter arterial chemoembolization (TACE) combined with percutaneous microwave coagulation therapy (PMCT) for advanced hepatocellular carcinoma (HCC).

Methods: Eighty-three advanced HCC patients were divided into the experimental group (TACE + PMCT, 57 cases) and the control group (TACE alone, 26 cases). They received TACE treatment first, and computed tomography (CT) or hepatic artery angiography was performed 3 - 4 weeks after each treatment. Based on the comprehensive evaluation of iodine oil deficiency, fistula recanalization, residual lesions, and lesion progression, TACE or PMCT treatment was selectively performed, and three consecutive treatments were considered as one treatment cycle.

Results: The experimental group had a response rate (RR) of 49.1%, and the control group had a RR of 38.4%. The reduction rate of alpha-fetoprotein (AFP) in the experimental group was significantly higher than the control group ($P < 0.05$). The cumulative survival rates in the experimental at 1-, 1.5-, and 2-year post-treatment were higher than the control group. The cumulative recurrence and metastasis rates in the experimental at 1.5-, and 2-year post-treatment were significantly lower than those in the control group ($P < 0.05$). In addition, there were no significant differences in treatment-related complications in the two groups.

Conclusions: The combined treatment of TACE and PMCT for advanced HCC is a safe, feasible, and effective treatment method, prolonging the survival time, and reducing the recurrence and metastasis rate, without increased toxic and side effects.

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Introduction

Hepatocellular carcinoma (HCC) is a common cancer with increased incidence and mortality worldwide [1]. The primary treatment currently available in clinical practice for HCC is surgical resection. However, only 15-30% of patients meet the surgical criteria due to the difficulty in early diagnosis [2]. Chinese clinical guidelines recommend interventional therapy, which provides nearly 30 months of survival benefit for patients with middle-to-advanced HCC [3-5]. Meanwhile, guidelines from the National Comprehensive Cancer Network (NCCN) and European Association for the Study of Liver Disease (EASL) suggest non-surgical therapies such as interventional therapy and systemic therapy for conversion therapy before surgical resection [6]. The development of translational therapy has been carried out on various solid tumors, such as gastric cancer, rectal cancer, and HCC, and is continuously expanding [7]. The ultimate goal of this approach is to transform unresectable tumors into resectable tumors [8-10]. Currently, there are a variety of treatment modalities that have been proposed for HCC [11].

Transcatheter arterial chemoembolization (TACE) is now the preferred treatment for inoperable mid-to-advanced stage HCC, owing to its minimal invasiveness, straightforward procedure, high safety, strong repeatability, and dependable short-term effectiveness [12]. This method offers the combined benefits of tumor perfusion chemotherapy and tumor vascular embolization therapy. It not only enhances the concentration of chemotherapy in the tumor region but also minimizes systemic toxicity and side effects [13]. By embolizing tumor blood vessels, this approach not only cuts down on the tumor's blood supply, but also the embolic agent lipiodol (LP) acts as a carrier for chemotherapy drugs. This reduces the dilution and washout of the drugs by blood flow [14]. The gradual release of drugs from the treatment ensures a prolonged impact on HCC lesions. Nevertheless, post-TACE treatment, only about 20% to 50% of the tumor tissue becomes completely necrotic. Even with repeated treatments, residual cancer often persists, leading to a 5-year survival rate of 9% to 16.2% [15]. Moreover, a significant number of HCC

patients present with arterial and venous fistulas, advanced liver cirrhosis, and portal hypertension, along with multiple arterial blood supplies. Embolizing these arteries can lead to severe complications, resulting in the discontinuation of embolization therapy, which in turn impacts its clinical effectiveness [16].

Recent studies have increasingly emphasized the importance of comprehensive approaches in treating HCC [17]. Percutaneous microwave coagulation therapy (PMCT) has emerged as a crucial element in the comprehensive treatment of HCC, due to its minimal invasiveness, straightforward procedure, high precision, and strong repeatability [18]. Presently, numerous studies have focused on the use of PMCT alone, or in combination with TACE, for treating HCC lesions smaller than 5 - 10 cm in diameter. However, there are few studies on the application of TACE combined with PMCT for treating middle and advanced-stage HCC with larger lesions [19]. In this study, we aimed to explore the clinical efficacy and application value of TACE combined with PMCT for advanced HCC.

Materials and Methods

Subjects

This is a retrospective observational study approved by the Ethics Committee of the Tangdu Hospital of the Fourth Military Medical University. All patients have signed an informed consent form. From February 2019 to September 2022, a total of 125 patients with locally advanced HCC (American Joint Committee on Cancer (AJCC) T3/T4) underwent TACE combined with PMCT (experimental group) or TACE alone (control group) in the Interventional Department of the Tangdu Hospital of the Fourth Military Medical University. The study data were selected based on a comprehensive review of medical records from patients who underwent treatment at our hospital. The assignment of patients to either the experimental group or the control group was based on clinical judgments and patient preferences. Among them, 83 patients with complete eligible data were observed and analyzed. In this study, 57 patients who underwent combined treatment of TACE and PMCT were designated as the experimental group, while 26 patients who received only TACE treatment were selected as the control group. Diagnostic criteria included: 1) All cases were diagnosed as HCC through imaging examinations such as computed tomography (CT), magnetic resonance imaging (MRI), and B-ultrasound, combined with alpha-fetoprotein (AFP) values and clinical manifestations; 2) Some cases were confirmed by liver biopsy pathology; 3) The staging was determined accordingly to the AJCC Version 9 Cancer Staging System. Inclusion criteria were: 1) Middle- to late-stage HCC patients with complete clinical records; 2) Patients voluntarily accept the above treatment and sign a consent form; 3) Patients with Child-Pugh grading of liver function as A or B; 4) There were no contraindications to TACE or PMCT in all biochemical indicators; 5) Karnofsky score $\geq$ 60. Exclusion criteria were: 1) Patients diagnosed with diffuse HCC; 2) Patients with severe heart, lung, and kidney dysfunction and systemic cachexia; 3) The number of HCC lesions is greater than 4 or the diameter of HCC lesions is greater than 15 cm.

This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Preoperative preparation

All enrolled patients were undergoing their first TACE surgery. The protocol included an iodine allergy test conducted a day before the surgery, preparation of bilateral inguinal skin, and a requirement for fasting 6 h before the surgery. PMCT was conducted 2 - 3 days after TACE. For the PMCT surgery, patients were instructed to fast for 3 - 4 h beforehand, and they received an intramuscular injection of 75 mg of dipyridamole and 10 mg of diazepam 5 min before the procedure. Dosages were adjusted for elderly patients or those in poorer physical condition as necessary. Additionally, patients in both groups signed various consent forms before undergoing the surgery.

TACE

The Seldinger technique was utilized for percutaneous femoral artery catheterization, involving the placement of a 5F arterial catheter sheath and catheter. Routine angiography of the celiac artery and superior mesenteric artery was conducted to assess the location, number, size, vascular variation, and tumor blood supply of the HCC, including the artery shape, presence of portal vein tumor thrombus, and arterioportal fistula. Appropriate catheters were selected for super-selective access to the hepatic artery and tumor-supplying vessels. In cases with challenging or small tumor-supplying arteries, 3F microcatheters were used. The tumor-supplying artery was then infused with 750 - 1,000 mg of 5-fluorouracil (5-FU) and 40 - 60 mg of epirubicin (EPI) or cisplatin (DDP). The tumor-supplying artery was embolized using a mix of 10 - 14 mg of mitomycin C (MMC) and 10 - 30 mL of LP, with additional embolization using gelatin sponge particles as needed. In HCC patients with hepatic arterioportal fistula, small fistulae with low shunt flow were initially embolized using gelatin sponge particles. After re-examination and angiography confirming the disappearance of the fistula, embolization treatment was administered. In cases of large fistulae with high shunt flow, if the fistula could be avoided, super-selective embolization of the tumor liver or sub-liver segment was performed, with careful monitoring for reflux during the procedure. If reflux occurred, embolization was immediately stopped, and large gelatin sponge particles, strips, or spring coils were used to embolize the fistulae and tumor-supplying arteries directly. Post-surgery, the catheter was removed, bleeding was controlled by compression, and a local pressure bandage was applied for 12 - 24 h.

PMCT

The selection of the patient's body position was dependent on the lesion's location. For right liver lesions, the intercostal space was typically chosen as the puncture point, with the pa-

tient lying on their left side. Conversely, for left liver lesions, a subcostal puncture point was selected, and the patient was positioned supine. After pinpointing the lesion with ultrasound, routine disinfection and tissue placement were carried out. Local anesthesia was then administered via the needle channel using 5 - 10 mL of 2% lidocaine. Under ultrasound guidance, the puncture needle was inserted through the liver into the active area of the tumor, replaced with a microwave antenna, and connected to a microwave treatment device. The initial output power was controlled between 40 - 80 W for 15 - 20 min, depending on the lesion size, the required range of thermocoagulation, and the patient's tolerance. Multi-point, multi-knife simultaneous, or staged treatment approaches were employed in cases where the residual tumor was larger (diameter > 5 cm). Post-surgery, the needle was withdrawn, the puncture site was disinfected, and a pressure bandage was applied. The postoperative care included hemostasis, liver protection, anti-inflammatory treatment, and general symptomatic support.

Observation and follow-up indicators

Laboratory examination

Before routine surgery and on the 3-, 7-, and 14-day post-surgery, fasting peripheral blood was collected for blood routine, liver and kidney function enzymology, and AFP quantification. Typically, the lab tests were performed monthly for the first 6 months following treatment, and every 3 months thereafter.

Imaging examination

Routine preoperative and postoperative liver contrast-enhanced CT examinations were performed every 3 - 4 weeks. After the treatment period, contrast-enhanced CT examinations were performed every 3 months and then every 6 months after 1 year. CT physicians who are proficient in MSCT measurement software compared and measured the changes in tumor size before and after treatment.

Efficacy evaluation

The treatment efficacy is evaluated based on the World Health Organization (WHO) solid tumor measurement guidelines. After treatment, a contrast-enhanced CT scan of the liver confirmed the presence of new lesions in the liver tissue connected to the lesion, indicating local tumor progression (LTP); other new lesions within or outside the liver are distant recurrence (DR). The mid-term and long-term efficacy are evaluated based on the survival rate, calculated from the date of TACE treatment for the patient.

Statistical analysis

Data were analyzed with GraphPad 9.0 Software. Data were reported as the mean ± standard deviation (SD). The differences between the two groups were analyzed using Student's *t*-test. $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics of participants

In our study, we compared the clinical characteristics of patients with advanced HCC who were divided into a control group (n = 26) and an experiment group (n = 57) to evaluate the efficacy of TACE combined with PMCT. The demographic and clinical parameters assessed included gender distribution, tumor diameter, AFP level, Child-Pugh score, clinical stages, presence of portal vein tumor thrombus, and merge HCC with arterioportal shunts (hepatic arterio-portal shunts (HAPS)). Gender distribution showed no significant difference between the two groups (Table 1).

Efficacy outcomes of therapeutic intervention

We next evaluated the clinical efficacy of the different treatments for advanced HCC. In the experiment group, there were 11 cases of complete response and 17 cases of partial response, compared to three cases of complete response and seven cases of partial response in the control group. The number of patients with stable disease was also higher in the experiment group compared to the control group. The objective response rate, which includes patients who achieved a complete or partial response, was higher in the experiment group (49.1%) compared to the control group (38.4%). Similarly, the disease control rate, encompassing patients with complete response, partial response, and stable disease, was greater in the experiment group (82.4%) than in the control group (69.2%) (Table 2).

Changes in AFP levels after treatment

After the intervention, the distribution of AFP levels across different thresholds showed significant variation between the two groups ($P = 0.045$). In the experiment group, there was a notable increase in the number of patients achieving an AFP level of ≤ 20 ng/mL, rising to 19 from 4 in the control group. The patients with AFP levels ranging from 20 to 400 ng/mL were 21 in the experiment group compared to 7 in the control group (Table 3).

Survival analysis over 2 years

At 0.5 years after treatment, 69.2% of the control group and 80.7% of the experiment group were still alive, and at the 1-year interval, with 61.3% survival in the control group compared to 75.4% in the experiment group. The survival advantage for the experiment group was further evident at 1.5 years (50.0% vs. 66.7%) and maintained at 2 years (30.8% vs. 52.6%) (Table 4).

Table 1. Clinical Characteristics

	Control group (n = 26)	Experiment group (n = 57)	P value
Gender (male/female)			1.0
Male	22	49	
Female	4	8	
Tumor diameter			0.834
< 5 cm	6	16	
≥ 5 cm	20	41	
AFP level			0.371
≤ 20 ng/mL	2	4	
20 - 400 ng/mL	4	17	
≥ 400 ng/mL	20	36	
Child-Pugh score			0.401
A	6	20	
B	20	37	
Clinical stages			0.990
Phase IIa	2	4	
Phase IIb	21	46	
Phase IIIa	3	7	
WHO classification			0.857
Grade I	12	27	
Grade II	8	21	
Grade III	3	5	
Grade VI	3	4	
Portal vein tumor thrombus	8	22	0.658
Merge HAPS	4	9	1.0

AFP: alpha-fetoprotein; WHO: the World Health Organization; HAPS: hepatic arterio-portal shunts.

Table 2. Analysis of Clinical Efficacy

	Control group (n = 26)	Experiment group (n = 57)
Response		
Complete response	3	11
Partial response	7	17
Stable disease	8	19
Progressive disease	8	10
Objective response rate	38.4%	49.1%
Disease control rate	69.2%	82.4%

Table 3. Quantitative Analysis of AFP After Treatment

	Control group (n = 26)	Experiment group (n = 57)	P value
AFP level			0.045
≤ 20 ng/mL	4	19	
20 - 400 ng/mL	7	21	
≥ 400 ng/mL	15	17	

AFP: alpha-fetoprotein.

Table 4. Analysis of Survival Time

	Control group (n = 26), n (%)	Experiment group (n = 57), n (%)	P value
0.5 years	18 (69.2%)	46 (80.7%)	0.271
1 year	16 (61.3%)	43 (75.4%)	0.205
1.5 years	13 (50.0%)	38 (66.7%)	0.224
2 years	8 (30.8%)	30 (52.6%)	0.096

Table 5. Analysis of Cumulative Recurrence and Metastasis Rates

	Control group (n = 26), n (%)	Experiment group (n = 57), n (%)	P value
0.5 years	4 (15.4%)	5 (8.8%)	0.451
1 year	9 (34.6%)	12 (21.1%)	0.276
1.5 years	13 (50.0%)	17 (29.8%)	0.08
2 years	18 (69.2%)	21 (36.8%)	0.008

Recurrence and metastasis rates following treatment

At the 0.5-year mark, the recurrence and metastasis rate was slightly lower in the experiment group (8.8%) compared to the control group (15.4%). By the 1-year interval, the control group had a recurrence and metastasis rate of 34.6%, while the experiment group's rate was significantly lower at 21.1%. This trend continued at the 1.5-year post-treatment (50.0% vs. 29.8%). The disparity between the groups further widened by the 2-year interval (69.2% vs. 36.8%, P = 0.008) (Table 5).

Treatment-related complications

The occurrence of treatment-related complications including fever, pain, nausea and vomiting, transaminase levels, and jaundice were not different. These findings indicate that the addition of PMCT to TACE does not significantly increase the risk of complications (Table 6).

Discussion

The liver is the sixth most common site of human primary cancer, which usually occurs in the context of cirrhosis and inflammation [20]. HCC has become one of the three most lethal tumors in China [21]. Patients with HCC in the early stage often have no obvious clinical symptoms, and the disease has progressed to the middle and late stage when it is found, thus missing the best opportunity for surgery, resulting in a low resection rate of surgical lesions [22]. In addition, most patients with HCC are complicated with severe cirrhosis, so patients often find it difficult to accept intervention and various ablation operations, and treatment methods are relatively scarce [23]. In this study, the experimental group showed superior efficacy over the control group.

Primary HCC is one of the most common malignant tumors in Asia and China. HCC in China accounts for about 40-50% of the global HCC, and the incidence is second only to lung cancer and gastric cancer, ranking third. The mortality rate of the malignant tumor was second [24]. HCC has the characteristics of high malignancy, rapid progression, and poor prognosis. The average survival time of untreated patients with HCC is 2 - 6 months. Although surgical resection is the best way to cure HCC, only 10-15% of patients with HCC have the chance of operation when they are found, and the recurrence rate is as high as 40-60% in 5 years after the operation [25]. Moreover, in patients who can be operated on, because of the multicentric origin of the tumor and the tumor adjacent to the large blood vessels and bile ducts in the liver, combined with severe liver cirrhosis and liver dysfunction, the surgical method and effect of radical resection will be affected [25]. We found that after one cycle of treatment, the AFP levels were significantly decreased, and the average rate of AFP quantification decrease after treatment in the experimental group was higher than that in the control group.

Table 6. The Occurrence of Complications

	Control group (n = 26), n (%)	Experiment group (n = 57), n (%)	P value
Fever	14 (53.8%)	29 (50.9%)	0.760
Pain	9 (34.6%)	23 (40.3%)	0.054
Nausea and vomiting	17 (65.4%)	40 (70.2%)	0.068
Elevated transaminase	11 (42.3%)	24 (42.1%)	0.931
Jaundice	5 (19.2%)	13 (22.8%)	0.427

Primary HCC has a high degree of malignancy, and occult onset, and is mostly in the middle and late stages at the first diagnosis [26]. The average survival time of untreated HCC patients was 2 - 6 months, and only a small proportion of HCC patients could be resected surgically [27]. The recurrence rate of large HCC in 5 years after operation was as high as 40-60%. Moreover, resection of large HCC will lead to low immune function, which will promote the rapid growth of residual cancer [28]. TACE is the most commonly used diagnostic and therapeutic technique for unresectable advanced HCC. The short-term curative effect of simple treatment is good, but the long-term curative effect is not ideal [29]. The complete ablation and survival rates of large HCC treated with PMCT alone decreased [30]. The complete ablation rate of PMCT for HCC with diameter < 3 cm and > 5 cm was 98% and 59%, and the 5-year cumulative survival rate was 60% and 25%, respectively [31]. The reason is that for large tumors with rich blood supply, tumor blood vessels, as a huge cooling pool, are easy to take away heat and affect the temperature rise, so ablation is not complete [31]. In addition, for lesions near the hepatic hilum, large blood vessels, and bile ducts, PMCT treatment is prone to damage blood vessels, bile duct bleeding or bile fistula, gallbladder perforation, and bile peritonitis, so some special parts are also limited [32]. Our study showed that the cumulative survival rates of the experimental group within a 2-year follow-up showed an increased survival rate than the control group, indicating the effectiveness of the combination therapy in treating advanced HCC than TACE alone.

In recent years, scholars at home and abroad have emphasized the importance of comprehensive treatment of HCC [33]. PMCT has become an important part of the comprehensive treatment of HCC due to its advantages of mild trauma, simple operation, high accuracy, and good repeatability [34]. At present, the main research at home and abroad is the application of PMCT alone or TACE + PMCT in the treatment of early HCC less than 5.0 cm, while the research on TACE combined with PMCT in the treatment of advanced HCC with large lesions is less [35]. In this study, after treatment, fever, pain, nausea, vomiting, elevated transaminase, jaundice, and other symptoms occurred in both groups to varying degrees, which were alleviated after liver protection, jaundice, and symptomatic treatment, without other serious complications.

In recent years, technological developments in the medical field have been rapid and continuously evolving. Particularly transformative is the introduction of the Internet of Things (IoT) within medical practice, revolutionizing how healthcare providers monitor and manage illnesses. A notable example is the "Internet of Medical Things" (IoMT), a connected infrastructure of medical devices, software applications, and health systems and services. IoMT enhances patient monitoring, treatment personalization, and clinical management [36, 37].

In advanced HCC treatment, IoT plays a significant role. Integrating IoT technologies allows real-time data collection from medical devices like imaging systems and liver function monitors. The data provide continuous updates on patient status, enabling timely adjustments in treatment plans. IoT devices can monitor the efficacy of therapies like TACE and PMCT in real-time, alerting healthcare teams to necessary interventions. IoMT also facilitates remote monitoring and management, reducing hospital visits, especially beneficial for advanced HCC patients with significant physical debilitation [38].

The Internet of Surgical Things (IoST) represents another advancement where connected surgical instruments and devices enhance precision and outcomes. IoST enables real-time data analysis, remote monitoring, and improved communication between surgical devices [39]. Integrating IoT solutions in treatment modalities like TACE and PMCT could further enhance clinical outcomes and patient quality of life by making healthcare delivery more precise, personalized, and responsive.

Conclusions

In conclusion, TACE combined with PMCT is a safe, feasible, and effective treatment for advanced HCC. Reasonable control of the indications of the combined treatment of HCC can improve clinical efficacy and prolong the survival time of patients.

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Financial Disclosure

None to declare.

Conflict of Interest

The authors declare no conflict of interest.

Informed Consent

Informed consent was obtained from all participants.

Author Contributions

Guarantor of integrity of the entire study: CL. Study concepts: CL and HHR. Study design: CL. Definition of intellectual content: CL. Literature research: ZQW and HHR. Clinical studies: HHR. Experimental studies: HHR, JC. Data acquisition: ZQW and HHR. Data analysis: HHR, ZQW, and JC. Manuscript preparation: ZQW and HHR, and JC. Manuscript editing: ZQW and CL. Manuscript review: CL.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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