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# Clinical Analysis of Transcatheter Arterial Chemoembolization Sequential Microwave Ablation Combined with Targeted Therapy and Immunotherapy in the Treatment of Large Hepatocellular Carcinoma

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## Abstract

**Objective:** To investigate the safety and efficacy of Transcatheter Arterial Chemoembolization (TACE), sequential Microwave Ablation (MWA) combined with targeted therapy and immunotherapy versus TACE combined with targeted therapy and immunotherapy in the treatment of large hepatocellular carcinoma (defined as tumor diameter > 5 cm). **Methods:** The prospective cohort study was conducted, with 81 patients with large hepatocellular carcinoma who were admitted to Jingzhou Central Hospital from 2018 to 2022, they were divided into two groups, 41 patients received TACE sequential MWA combined with targeted therapy and immunotherapy (observation group), and 40 patients received single TACE combined with targeted therapy and immunotherapy (control group). The short-term efficacies after 3 months of treatment, the Disease Control Rate (DCR), the Overall Survival (OS), adverse drug reactions and complications were compared and analyzed between the two groups. **Results:** The Objective Response Rate (ORR) of the observation group was significantly higher than that of the control group (ORR: 85.4% vs 57.5%, $P = 0.005$), The median Progression-Free Survival (PFS) and median OS of the observation group were better than those of the control group (mPFS: 16 months vs 10 months, $P = 0.004$; mOS: 39 months. vs 24 months, $P = 0.008$). The 1-, 2- and 3-year progression-free survival rates of the observation group were 72.9%, 50.4%, and 25.6%, and those of the control group were 30.4%, 11.0%, and 3.7%. The 1-, 2- and 3-year overall survival rates of the observation group were 78.9%, 71.7%, and 65.2%, and those of the control group were 65.1%, versus 42.1% and 36.9%. There was no significant difference in the in-

cidence of adverse drug reactions and complications between the two groups. In this study, the adverse drug reactions were mild in Grades 1 - 2. **Conclusion:** TACE sequential MWA combined with targeted therapy and immunotherapy has efficacy and safety.

## Keywords

Transcatheter Arterial Chemoembolization, Microwave Ablation, Interventional Therapy, Immunotherapy, Hepatocellular Carcinoma

## 1. Introduction

Hepatocellular Carcinoma (HCC) is the sixth most common cancer worldwide and the third leading cause of cancer death, accounting for approximately 8.3% of malignancy mortality [1]. Because of the large number of patients with chronic hepatitis B in China and the insidious onset of HCC, many patients lose the opportunity for surgical resection at the first diagnosis [2]. Barcelona Clinic Liver Cancer (BCLC) recommends that patients with stage B/C inoperable HCC receive TACE and systemic therapies. For large HCC with a tumor diameter > 5 cm, single TACE chemoembolization of the tumor is not ideal due to the large size and heavy load, and MWA can further coagulate the ischemic tumor after TACE. Although TACE combined with MWA treatment can enhance the therapeutic effect of large hepatocellular carcinoma [3] [4], the synergistic action of anti-angiogenic targeted agents and immunotherapy drugs has significant advantages. By changing the Tumormicro-Environment (TME) [5], necrotic tumor cells after chemoembolization form new tumor-associated antigens to modulate the body's immune positivity. The anti-angiogenic targeted agents can prevent the reconstruction and regeneration of tumor vessels, and avoid the compensatory increase of Vascular Endothelial Growth Factor (VEGF) in a hypoxic environment after TACE [6]. This study discusses the efficacy of TACE sequential MWA combined with targeted therapy and immunotherapy for large HCC.

## 2. Data and Methods

### 2.1. Selection of Cases

The prospective cohort study was conducted, with 81 patients with large hepatocellular carcinoma who were admitted to Jingzhou Central Hospital from 2018 to 2022, they were divided into two groups, 41 patients received TACE sequential MWA combined with targeted therapy and immunotherapy (observation group), and 40 patients received single TACE combined with targeted therapy and immunotherapy (control group). The inclusion criteria: 1) First pathological diagnosis HCC and loss of the opportunity of surgical resection; 2) Largest tumor diameter > 5 cm, BCLC Stage B/C; 3) Child-Pugh Grade A or B, KPS ≥ 70; 4) immune function and routine blood indicators are normal.

### 2.2. Treatment Procedures

**TACE Treatment:** With the Seldinger technique, the femoral artery was punctured and a catheter was introduced, and the blood supply vessels of the tumor were identified by imaging under DSA. Then vessels of the tumor were perfused with chemotherapy drugs and iodized oil. After the operation, symptomatic supportive treatment was given. CT scan and MRI enhanced imaging were performed within 1 month after the first TACE treatment, and if there were still residual tumor blood supply vessels, TACE treatment was performed again; if there were fewer tumor blood supply vessels or iodized oil deficiency in the tumor area, sequential MWA treatment was performed.

**MWA Treatment:** Firstly, CT scan is to locate the skin puncture site, a puncture needle is used to puncture the lesion of HCC, repeat CT scan, so that the tip of the puncture needle is located near the edge of the tumor, and the MWA range covers the tumor and exceeds the border by 0.5 - 1 cm, choose the appropriate power and precise time to perform the MWA treatment according to the size of the tumor, and if review the ablation area is hypodense shadow or gasification, the procedure is finished.

### 2.3. Targeted Therapies and Immunotherapy

Before each treatment, patients should recheck blood routine tests, liver and kidney function, and ECG. Two groups of patients were given Lenvatinib, Sorafenib, or Bevacizumab, at the same time, they were given Carelizumab or Sintilimab.

### 2.4. Indicators of Observation

After 3 months of treatment, the recent efficacy was evaluated according to the modified solid tumor efficacy assessment criteria (mRECIST) [7], which was defined as Complete Remission (CR), Partial Remission (PR), Stable Disease (SD), and Disease Progression (PD). Survival status was recorded, and Overall Survival time (OS) was defined as the time from initial treatment to the patient's death or last follow-up, and Progression-Free Survival (PFS) time was defined as the time from initial treatment to the patient's disease progression.

### 2.5. Statistical Analysis

SPSS 25.0 software was used for statistical analysis of the data. T-test or u-test was performed after testing the normality distribution of the measurement data, $\chi^2$ test or Fisher exact method was used for counting data, Kaplan-Meier method was used for survival analysis and survival curves were plotted, and Log-rank method was used for comparison between groups.

## 3. Results

### 3.1. Patients

A total of 81 patients with large HCC were selected in this study, 41 patients re-

ceived TACE sequential MWA combined with targeted therapy and immunotherapy (observation group), and 40 patients received single TACE combined with targeted therapy and immunotherapy (control group). Table 1 shows that the baseline data of both groups were not statistically significant ($P > 0.05$).

### 3.2. Short-Term Efficacies

After 3 months of treatment, cases with CR, PR, SD, and PD in the observation group were 20, 15, 5, and 1, and the above indicators in the control group were 3, 20, 14, and 3. The objective remission rate was better in the observation group than in the control group (ORR: 85.4% vs. 57.5%), and the difference in objective remission rate between the two groups was statistically significant ($\chi^2$ = 7.732, $P = 0.005$); however, the difference in disease control rate between the two groups was not statistically significant (97.6% vs. 92.5%, $\chi^2 = 0.290$, $P = 0.590$).

### 3.3. Survival Situations

81 patients were followed up for 3 - 57 months, with a median follow-up time of 19 months. 28 patients in the observation group had disease progression and 28 patients survived, while 35 patients in the control group had disease progression and 18 patients survived. The median PFS was 16 months (95% CI 9.7 - 22.3) in the observation group and 10 months (95% CI 7.7 - 12.3) in the control group, with a statistically significant difference ($\chi^2 = 8.210$, $P = 0.004$); median OS was 39 months (95% CI 31.8 - 41.0) in the observation group and 24 months (95% CI 18.4 - 30.5), the difference was statistically significant ($\chi^2 = 7.099$, $P = 0.008$). The 1-, 2- and 3-year progression-free survival rates of the observation group were 72.9%, 50.4%, and 25.6%, and the control group was 30.4%, 11.0%, and 3.7%. The 1-, 2-and 3-year overall survival rates of the observation group were 78.9%, 71.7%, and 65.2%, and the control group were 65.1%, versus 42.1% and 36.9% (Figure 1, Figure 2).

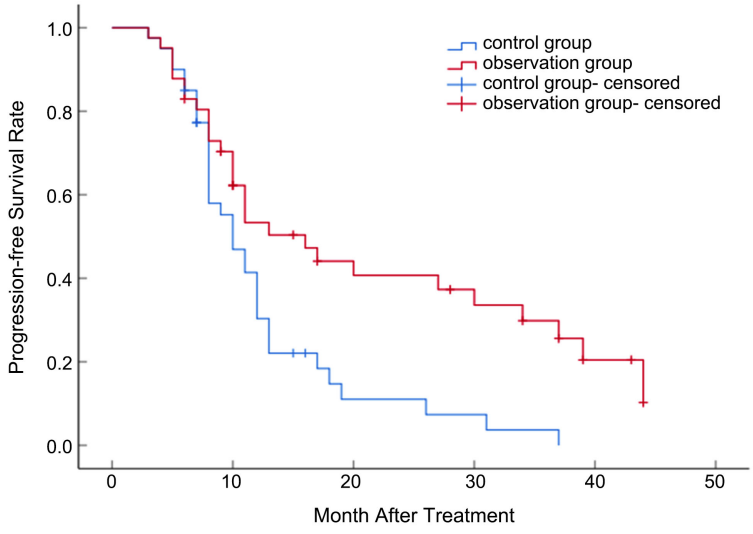


Figure 1. PFS curves of observation group and control group.

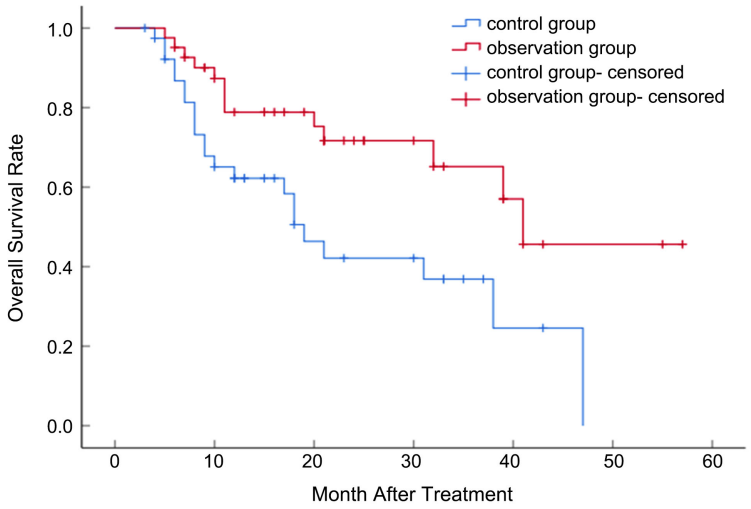


**Figure 2.** OS curves of observation group and control group.

**Table 1.** Baseline characteristics of observation group and control group (n = 81).

| Characteristic | Observation group (n = 41) | Control group (n = 40) | *P*-Value |
|---|---|---|---|
| Age, year | 56 ± 11 | 58 ± 10 | 0.296 |
| Gender | | | |
| Male | 33 | 31 | 0.741 |
| Female | 8 | 9 | |
| Positive for HBsAg | 26 | 26 | 0.882 |
| Negative for HBsAg | 15 | 14 | |
| Number of tumors | 1 (1 - 3) | 1 (1 - 3) | 0.699 |
| Max diameter, cm | 7.2 (6.3 - 9.4) | 7.4 (6.4 - 9.9) | 0.476 |
| Child-Pugh class | | | |
| A | 32 | 34 | 0.421 |
| B | 9 | 6 | |
| BCLC stage | | | |
| B | 28 | 29 | 0.678 |
| C | 13 | 11 | |
| AFP, ng/ml | 490 | 519 | 0.959 |

### 3.4. The Adverse Drug Reactions and Complication

In this study, The immune-related Adverse Events (irAEs) [8] that occurred were all Grades 1 - 2, including 2 cases of immune rash, 1 case of immune pneumonia, and 1 case of hyperthyroidism, and all continued treatment after symptomatic treatment or drug withdrawal. The adverse reactions to targeted drugs were all Grades 1 - 2, including 5 cases of hypertension, 4 cases of oral mucositis, and 7 cases of bone marrow suppression, all of which resolved after symptomatic treatment.

Patients in both groups had treatment complications, such as impaired liver function, pain in the liver area, fever, gastrointestinal bleeding, intrahepatic hematoma, and liver abscess, which were relieved after symptomatic treatment. The difference in the incidence of complications between the two groups of patients was not statistically significant.

## 4. Discussion

At present, TACE is the main treatment method for inoperable hepatocellular carcinoma, and MWA is also often combined with TACE [9]. The hypoxic environment after TACE causes VEFG to increase and continues to develop tumor vascular regeneration. MWA treatment can generate high-temperature heat energy more than 100˚C, leading to tumor further coagulative necrosis, the thermal effect can radiate through as much as 10mm around the lesions. There were some advantages of TACE combined with MWA for large HCC: 1) TACE embolization of tumor vessels reduces microperfusion around the lesion and extends the ablation area by attenuating the cooling effect of surrounding tissues; 2) After TACE treatment, the deposition of iodine oil causes peritumoral edema, while water molecules can enhance the heat conduction of MWA; 3) MWA treatment can cause further necrosis of the microvessels and residual lesions after TACE. Clinical studies [3] [4] [10] have reported that TACE combined with MWA treatment is superior to single TACE treatment in improving the overall survival of patients with HCC. In this trial, the treatment of TACE sequential MWA combined with targeted therapy and immunotherapy further improved the OS and PFS of patients. And there was no difference in the incidence of complications between the two treatment methods.

The anti-angiogenic targeted agents and immunotherapy drugs have gradually become a form of treatment method for HCC. Since the REFLECT trial demonstrated that drug class did not affect the OS [11], drugs of the same therapeutic mechanism were included in the two groups of this study, anti-angiogenic targeted agents can block the RAF/MEK/ERK signal transduction pathway to inhibit the generation of new and old vessels of tumors [12]. The TACTICS trial [13] was the first to confirm the efficacy and safety of Sorafenib combination with TACE in the treatment of HCC, and Zhu [14] showed that TACE combined with MWA followed by oral targeted drugs significantly improved the combined treatment effect. The Programmed Death receptor-1 (PD-1) used in this study can specifically bind to immune checkpoint proteins, prevent tumor cells from "immune evasion" [15], and restore the tumor-killing function of immune cells. The IMBrave150 clinical study [16] demonstrated the efficacy of Atezolizumab and Bevacizumab (an anti-VEGF/PD-L1 combination therapy) in patients with HCC, and this therapy was approved for first-line treatment of advanced hepatocellular carcinoma. The complementary targeted and immunological therapies can enhance the anti-tumor effects: 1) The anti-angiogenic targeted agents can inhibit the effect of VEGF on the immune system, increase the activation of immune

cells, and indirectly increase vascular permeability to release inflammatory factors; 2) The drugs can correct the abnormally proliferating tumor vascular system, improve tumor perfusion and alleviate tumor hypoxia; 3) The immunotherapy drugs can modulate lymphocytes and immune responses to repair the normalization of vascular structures.

## 5. Conclusion

In conclusion, compared with TACE combined with targeted therapy and immunotherapy, TACE sequential MWA combined with targeted therapy and immunotherapy has better efficacy. With the development and usage of more drugs, the advantages of combined therapy can be further validated. Based on the synergistic effect, interventional therapy combined with systemic therapy will be the future trend in the treatment of unresectable HCC in the future.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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