Effect of prophylactic transcatheter arterial chemoembolization on hepatocellular carcinoma with microvascular invasion after R0 resection. A case-control study

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INTRODUCTION
Hepatocellular carcinoma (HCC) is one of the most common malignancies in the world¹,² and causes around 500,000 deaths every year.³ Although hepatectomy and liver transplantation are considered to be curative therapies for HCC,¹ HCC often relapses after surgery. Transcatheter arterial chemoembolization (TACE) is thought to prevent recurrence, but its efficacy is a matter of controversy.⁴

OBJECTIVES
To analyze the effect of preventive TACE on recurrence rates and mortality rates among patients with the TNM classification of tumors of patients with stage II HCC (T2N0M0) after R0 resection. Our hypothesis for this study was that TACE would be equally effective for HCC patients with or without MVI.

METHODS
Study design and ethics
In this case-control study, we analyzed recurrence rates and mortality rates among 250 consecutive cases of HCC with TNM classification stage II (T2N0M0) after R0 resection. We compared four groups of patients according to presence of microvascular invasion and use of TACE.

All the patients gave their informed consent to participation in this study. The study was approved by our institution’s ethics committee on January 4, 2005, under the approval protocol number 2005006.
Patients
We followed up all the 250 consecutive patients with HCC who underwent R0 resection between January 2005 and December 2014, over a 36-month period after their surgeries. All of these patients were treated in the Department of Hepatobiliary Surgery, Guizhou Provincial People’s Hospital. The inclusion criteria were as follows:
1. Age more than 16 years and less than 65 years;
2. Histopathological classification of high/medium differentiation;
3. TNM classification as stage II (T2N0M0) for HCC;
4. Treatment by means of extended resection of the tumor, with resection margins of 2 cm;
5. Liver function: Child-Pugh score of not more than 9 points.

The exclusion criteria were as follows:
1. Presence of other serious life-threatening diseases, such as severe coronary heart disease, another malignant tumor, etc.;
2. Evidence of liver abscess, abdominal infection, biliary fistula or intraperitoneal hemorrhage;
3. Pregnancy.

We divided the cohort into four groups: Group 1, who underwent TACE (TACE+) and presented microvascular invasion (MVI+; n = 80); Group 2, who were TACE+ but did not present MVI (MVI−; n = 100); Group 3, who were MVI+ but did not undergo TACE (TACE−, n = 30); and Group 4, who were TACE−/MVI− (n = 40).

TACE
Patients who underwent TACE did so within one to two months after their hepatectomies (Table 1). A hepatic arterial catheter was placed into the proper hepatic artery through the femoral artery using the Seldinger technique, and TACE was performed for the entire remnant liver. Hepatic angiography, computed tomography (CT) angiography, or both, were performed to detect any obvious tumor stains in the remnant liver.

The TACE procedure was a “sandwich” method, in which iodide oil (1 ml to 2 ml) was injected before and after administering chemotherapy. The chemotherapy regimen included fluorouracil, a platin (cisplatin or carboplatin) and adriamycin (doxorubicin or epirubicin). The dosages of fluorouracil, platin and adriamycin were determined according to body surface area and underlying liver function. All patients in this study who underwent prophylactic TACE received only one prophylactic TACE treatment, within two months after their surgery.

In order to make comparisons and avoid bias, we selected the cases with similar age (16 to 65 years), tumor differentiation (high/medium differentiation), tumor stage (T2N0M0) and Child-Pugh score for liver function (not more than nine points) and the cases with fewer complications (cases without liver abscess, abdominal infection, biliary fistula or intraperitoneal hemorrhage, etc.) and clean cutting edges (with resection margins of 2 cm). The aim of making this selection was to minimize other possible factors. We collected data mainly from the medical records (the period of time that was considered for data collection was from January 2005 to December 2017). In a very small number of cases, we collected data through patient follow-up.

Statistical analysis
We analyzed recurrence rates and mortality rates at one, two and three years after the procedures that were performed on these patients. Statistical analyses were performed using SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA). The differences between groups of data were analyzed by means of the chi-square test (two-tailed). P-values < 0.05 were considered statistically significant.

RESULTS
During the study period, 280 patients were admitted to our hospital service presenting HCC, and 30 patients were excluded. The patients included comprised 131 males and 119 females. Their average age was 48.01 years (range: 16-65 years). The recurrence rates and mortality rates for each patient group, over each time period, are shown in Tables 2, 3, 4 and 5.

Tables 2 and 3 show that, among MVI+ patients, those who underwent TACE (TACE+ group) had significantly lower recurrence rates and mortality rates at one, two and three years after their procedures (all P < 0.05) than did those who did not undergo this procedure (TACE− group). The recurrence rates and mortality rates

Table 1. Demographic and clinical data of the four patient groups

|                | Group 1 | Group 2 | Group 3 | Group 4 | P         |
|----------------|---------|---------|---------|---------|-----------|
| N              | 80 (M/F: 43/37) | 100 (M/F: 51/49) | 30 (M/F: 17/13) | 40 (M/F: 21/19) | > 0.05    |
| Age (years)    | 48.62 ± 11.32 | 46.63 ± 11.61 | 45.45 ± 11.51 | 47.55 ± 11.55 | > 0.05    |
| Complications (%) | 0.32 ± 0.13 | 0.35 ± 0.15 | 0.33 ± 0.12 | 0.34 ± 0.14 | > 0.05    |
| Liver function: |         |         |         |         |           |
| Child-Pugh score | 7.5 ± 1.4 | 7.3 ± 1.5 | 7.4 ± 1.3 | 7.4 ± 1.5 | > 0.05    |

The P-values refer to the comparisons of age, complications and liver function Child-Pugh score in each group.

MVI = microvascular invasion; TACE = transcatheter arterial chemoembolization.

Group 1: underwent TACE and had MVI; Group 2: underwent TACE but did not have MVI; Group 3: had MVI but did not undergo TACE; Group 4: did not undergo TACE or have MVI.
among the MVI− patients tended to be lower at one, two and three years for the TACE+ group, but not significantly so (all P > 0.05).

Tables 4 and 5 show that, among both TACE+ and TACE− patients, those who were MVI− had significantly lower recurrence rates and mortality rates at two and three years than did those who were MVI+ (all P < 0.05).

**DISCUSSION**

Although preventive TACE has become a common post-surgical treatment for HCC, its efficacy is still a matter of controversy. Support for TACE is based on the fact that compressing a tumor during surgery may lead to its spread. Postoperative TACE helps to clear up any proliferating, remnant or difficult-to-find tumor cells, and thus reduce early recurrence rates.5,6

A meta-analysis on four randomized controlled trials and three non-randomized controlled trials concluded that postoperative adjuvant TACE improves survival rates at two years and three years after resection.7 The basis for opposing the use of TACE is that TACE can inhibit patients’ immune systems, thereby contributing to tumor recurrence and metastasis.8,9 Our results showed that among MVI− patients, TACE+ patients tended to have lower recurrence rates and mortality rates at one, two and three years, but not significantly so (P > 0.05), which indicates that preventive TACE cannot benefit MVI− patients.

**Table 2. Recurrence rates among patients who did or did not undergo TACE**

| Postoperative time | With TACE | Without TACE | P-value |
|-------------------|-----------|--------------|---------|
| 12 months         | 20/80 (25.0%) | 14/30 (46.7%) | 0.029   |
| 24 months         | 35/80 (43.8%) | 20/30 (66.7%) | 0.032   |
| 36 months         | 44/80 (55.0%) | 23/30 (76.7%) | 0.038   |

**Table 3. Mortality rates among patients who did or did not undergo TACE**

| Postoperative time | With TACE | Without TACE | P |
|-------------------|-----------|--------------|---|
| 12 months         | 17/80 (21.2%) | 13/30 (43.3%) | 0.021 |
| 24 months         | 32/80 (40.0%) | 19/30 (63.3%) | 0.029 |
| 36 months         | 43/80 (53.8%) | 23/30 (76.7%) | 0.029 |

**Table 4. Recurrence rates among patients who presented with or without MVI**

| Postoperative time | With MVI | Without MVI | P |
|-------------------|----------|-------------|---|
| 12 months         | 20/80 (25%) | 20/100 (20.0%) | 0.423 |
| 24 months         | 35/80 (43.8%) | 29/100 (29.0%) | 0.040 |
| 36 months         | 44/80 (55.0%) | 40/100 (40.0%) | 0.000 |

**Table 5. Mortality rates among patients who presented with or without MVI**

| Postoperative time | With MVI | Without MVI | P |
|-------------------|----------|-------------|---|
| 12 months         | 17/80 (21.2%) | 17/100 (17.0%) | 0.469 |
| 24 months         | 32/80 (40.0%) | 26/100 (26.0%) | 0.046 |
| 36 months         | 43/80 (53.8%) | 35/100 (35.0%) | 0.012 |

MVI = microvascular invasion; TACE = transcatheter arterial chemoembolization.
The Milan criteria classify MVI as an independent risk factor for HCC, and its presence in the hepatic or portal veins or the bile duct is an accurate predictor of recurrence risk and overall survival in patients with HCC after R0 liver resection and transplantation. Postoperative adjuvant TACE may be beneficial for HCC patients with MVI.

CONCLUSIONS

The recurrence and mortality rates among MVI+ patients were significantly higher than those of MVI− patients, beyond the first year after TACE (P < 0.05).

Thus, MVI+ patients may benefit from timely administration of postoperative adjuvant TACE if this is done within one to two months after R0 resection of HCC.

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