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Observation of efficacy of TACE combined with HIFU on patients with middle-advanced liver cancer

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Abstract. – OBJECTIVE: To study the efficacy of transarterial chemoembolization (TACE) combined with high-intensity focused ultrasound (HIFU) in patients with middle-advanced liver cancer.

PATIENTS AND METHODS: A total of 100 patients with middle-advanced liver cancer treated in our hospital from January 2015 to January 2018 were selected and randomly divided into TACE group (control group, n=50) and TACE combined with HIFU group (experimental group, n=50) according to different therapeutic regimens. The efficacy was observed after the operation, the blood was collected to detect the postoperative liver function indexes aspartate aminotransferase (AST) and alanine aminotransferase (ALT), the postoperative complications were observed. Also, the immune indexes cluster of differentiation 3+ (CD3+), CD4+, and CD8+ were determined. Moreover, the quality of life (QOL) score was compared between the two groups, the 1-, 2-, 3-, and 5-year survival rates were observed after the operation. Also, the changes in the levels of tumor markers α-L-fucosidase (AFU), alpha-fetoprotein (AFP), carbohydrate antigen 19-9 (CA19-9), and carcinoembryonic antigen (CEA) were observed.

RESULTS: In experimental group, the levels of AST, ALT, and blood urea nitrogen (BUN) after the operation were significantly decreased ($p<0.05$), while the postoperative efficacy was significantly superior to that in control group ($p<0.05$). The incidence of postoperative complications was significantly reduced ($p<0.05$), the levels of CD3+, CD4+, CD8+, and natural killer (NK) cells were markedly increased ($p<0.05$). Also, the QOL score was evidently better than that in control group ($p<0.05$) and the 1-, 2-, 3-, and 5- year survival rates after the operation were evidently higher than those in control group ($p<0.05$). After treatment, the levels of AFU, AFP, CA19-9, and CEA were remarkably lower than those before treatment in both groups, while they were remarkably lower in experimental group than those in control group ($p<0.05$).

CONCLUSIONS: TACE combined with HIFU in the treatment of patients with middle-advanced liver cancer can restore the hepatic metabolism, enhance the immunity, improve the QOL, prolong the survival time of patients, and significantly reduce the tumor markers. Also, it has fewer adverse reactions and definite overall efficacy, which is worthy of popularization and application.

Key Words:
TACE combined with HIFU, Middle-advanced liver cancer, Efficacy, Complications, Tumor markers.

Introduction

Cancer is one of the major causes of death in the world and there are more than 200 types of cancer. Among them liver cancer is reported to be the most typical one[1]. Primary liver cancer is considered as one of the most frequent cancers worldwide, as well as the most common causes

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of cancer-related deaths. In the United States, the mortality rate of primary liver cancer ranks 5th in males and 8th in females[2]. Indeed, liver cancer is usually diagnosed in middle-aged and elderly people, it is mostly accompanied by cirrhosis, and its morbidity rate is expected to increase[3]. Primary liver cancer usually causes death within 6-20 months after a definite diagnosis[4]. Hepatitis B virus infection is the leading cause of liver cancer around the world, especially in Asia and Africa. Other related risk factors include alcoholism, smoking, overweight, metabolic syndrome, and diet[5]. In countries without the national liver cancer monitoring project, up to 30-35% of patients have macrovascular infiltration and/or extrahepatic spread at the initial diagnosis, while the most common distant metastatic sites are lung, bone, and adrenal gland[6,7]. The survival time of untreated patients with metastatic liver cancer rarely exceeds 62 days, and it is currently mainly treated with chemotherapy, radiotherapy, and surgery[8]. Besides, the development of vaccine and antiviral therapies has improved the long-term control of chronic hepatitis B or C; however, it promoted the development of cirrhosis and liver cancer. Hepatitis C virus contamination usually occurs in adulthood and causes more serious consequences in elderly patients, such as severe histological damage and cirrhosis[9]. Cognitive disorder, a common postoperative neurological complication, often occurs in patients with liver cancer[10], and its clinical manifestations include memory disorder and gradual decline in attention and information processing ability, which is mainly characterized by anxiety, personality changes, and memory impairment. It is indeed associated with prolonged hospital stay, reduced quality of life (QOL), as well as increased morbidity and mortality rates[11]. Liver dysfunction may also occur due to inflammatory response, further promoting the development of liver cancer[12]. However, there are serious side effects and high risks in the traditional treatment, and the overall efficacy is still limited despite encouraging progress[13]. Therefore, continuing to explore alternative therapeutic regimens is essential to improve the prognosis of liver cancer. Exploring the molecular mechanism of liver cancer may offer great help to the development of new and effective therapeutic methods for liver cancer.

The optimal therapeutic method for liver cancer is liver transplantation; however, it is difficult to find the donor. Other therapeutic methods include resection, transarterial chemoembolization (TACE), and direct cauterization, such as radiofrequency ablation (RFA), laser ablation, cryotherapy, microwave therapy, and high-intensity focused ultrasound (HIFU)[14,15]. In non-surgical treatment, TACE is the most widely used and it is combined with other topical treatment to improve the therapeutic effect. Studies[16] have demonstrated that the efficacy of combined treatment of TACE and percutaneous ethanol injection of TACE and RFA is superior to that of TACE alone. It is also reported that TACE combined with HIFU has good efficacy in the treatment of advanced liver cancer[17]. HIFU is a non-invasive treatment that induces coagulation necrosis of target tissues using ultrasonic wave without damaging the adjacent normal tissues[18]. The ultrasound, despite high-temperature heating, induces coagulation necrosis and acoustic cavitation, which is used to treat the target solid tumor under strong ultrasonic irradiation and lead to bubble breakage in the liquid, causing tissue necrosis[19].

In the present work, the patients with middle-advanced liver cancer treated in our hospital were selected and randomly divided into TACE group and TACE combined with HIFU group according to different therapeutic regimens. The postoperative efficacy and complications were observed, the immune function indexes were detected, and the QOL was compared between the two groups. Also, the postoperative survival rate was observed, hoping to verify the efficacy of TACE combined with HIFU on liver cancer.

Patients and Methods

General Data

A total of 100 patients with middle-advanced liver cancer treated in our hospital from January 2015 to January 2018 were selected and randomly divided into TACE group (control group, n=50) and TACE combined with HIFU group (experimental group, n=50) according to different therapeutic regimens. The patients signed the informed consent before the study. Inclusion criteria: patients diagnosed with liver cancer *via* pathological examination and CT, those without other severe complications before the operation, those not allergic to therapeutic drugs used and those who underwent no treatment before. Exclusion criteria: patients with acute myocardial infarction, neurological diseases, severe coronary heart disease, valvular disease or other cardio-cerebrovascular diseases, those with severe

secondary infection, or pregnant or lactating patients. The clinical research program including all the examinations in the experiment was approved by the Ethics Committee of our hospital. The specific clinical data of patients are shown in Table I. The Child-Pugh classification includes three levels according to the presence or absence and severity of hepatic encephalopathy, ascites, serum bilirubin, serum albumin concentration, and prothrombin time. Also, it is divided into grade A, B, and C based on the score. The higher score corresponds to the poorer liver reserve function. The tumor-node-metastasis (TNM) staging was performed based on the range of primary tumor (T), presence or absence and range of regional lymph node metastasis (N), and presence or absence of distant metastasis (M). The higher the stage, the more severe the disease will be. There were no significant differences in the general data between the two groups.

Treatment Methods

In control group, after femoral artery puncture using the Seldinger technique, the digital angiography of the hepatic artery was performed through the abdominal aorta. According to the examination results, the supplying vessels of the tumor were completely embolized using the mixture of an appropriate amount of ultra-fluid lipiodol (10-30 mL), Epirubicin (30-60 mg), and platinum-based chemotherapy drugs. After the operation, the liver was routinely protected and the condition of patients was observed at any time. In experimental group, HIFU was performed at 7 d after TACE alone using the JC200 HIFU system (frequency: 0.96 MHz, focal region sound intensity: 8000 W/cm^2). Under general anesthesia, the treatment region was cleaned for skin preparation, and the treatment position was adjusted, followed by injection of artificial pleural effusion according to the patient's condition. After the safe acoustic channel was constructed, HIFU was performed, during which the gray changes of the target tissues, skin, and adjacent organs were closely monitored, with the coverage range of 1 cm beyond the border of the tumor. After the operation, the liver was routinely protected and the condition of patients was observed at any time.

Observation of Clinical Efficacy in Both Groups

Evaluation criteria for efficacy: according to the mRECIST, the efficacy is divided into complete remission (CR; all target lesions disappear, there are no new lesions, and tumor markers are normal for at least 4 weeks), partial remission (PR; the sum of the maximum diameter of target lesions declines by ≥30% for at least 4 weeks), stable disease (SD; the sum of maximum diameter of target lesions declines <PR or increases <PD) and progressive disease (PD; the sum of maximum diameter of target lesions increases by at least ≥20%, or there are new lesions). Overall effective rate = CR + PR. The efficacy in both groups was evaluated by medical workers and the number of cases in each level was counted and recorded in detail to accurately reflect the clinical efficacy of patients in both groups.

Observation of Postoperative Complications in Both Groups

The postoperative complications, such as jaundice, ascites, gastrointestinal reactions, and liver discomfort, in both groups were observed and recorded in detail by medical workers. Finally, the postoperative complications in both groups were summarized.

Detection of Serum Hepatic Metabolism Indexes

The biochemical indexes of hepatic metabolism will be changed when liver cancer occurs and the detection of specific changes can indicate the occurrence and development of the disease. 5 mL of fasting peripheral venous blood was drawn from patients in the morning, placed in the EP (Eppendorf) tube containing the anticoagulant ethylenediaminetetraacetic acid (EDTA), and centrifuged at 3500 g at room temperature for 10 min. Then, the supernatant was collected to detect the hepatic metabolism indexes aspartate aminotransferase (AST), alanine aminotransferase (ALT), and blood urea nitrogen (BUN) to monitor the condition of liver cancer.

Detection of Immune Indexes

After treatment, 5 mL of venous blood was drawn from the arm, placed in the EP tube containing the anticoagulant, and centrifuged at 2000 g at room temperature for 15 min. Next, the supernatant was collected to detect the serum immune indexes cluster of differentiation 3+ (CD3+), CD4+, CD8+, and natural killer (NK) cells using the full-automatic flow cytometer (FACSCalibur; BD Biosciences, Franklin Lakes, NJ, USA)) according to the instructions. The level of each index was recorded in detail and the changes in the above immune indexes were analyzed.

QOL Score

The Karnofsky performance scale (KPS) score was given 100 points: all normal, without uncomfortable symptoms and signs; 85 points: able to move normally, with mild symptoms and signs; 70 points: able to take care of themselves in daily life, but unable to maintain normal life and work; 55 points: able to take care of themselves mostly in daily life, but others' help is needed sometimes; 40 points: unable to take care of themselves in daily life, and special care and help are needed; 25 points: totally unable to take care of themselves in daily life, seriously ill, and hospitalization and active supportive treatment are needed; 10 points: critically ill and dying, and 0 point: death. The score was given and recorded in detail by at least 3 medical workers in both groups. The total score is 100 points and the higher score corresponds to the higher QOL of the patients.

Postoperative Survival Rate

Patients were followed up through outpatient and telephone once a year for 3 consecutive years. The postoperative survival rate was recorded and the 5-year survival rate was predicted using the Kaplan-Meier method.

Levels of Tumor Markers Đ-L-Fucosidase (AFU), Alpha-Fetoprotein (AFP), Carbohydrate Antigen 19-9 (CA19-9), and Carcinoembryonic Antigen (CEA)

The levels of tumor markers AFU, AFP, CA19-9, and CEA were determined *via* the chemiluminescence immunoassay using Cobas2000 full-automatic immunoassay analyzer according to the operation procedure based on the instructions of the kits. The level of each index was recorded in detail and the changes in the above tumor markers were analyzed.

Table I. Clinical data of patients

Parameter	Control group	Experimental group
Sample size	50	50
Number of females	24	25
Mean age (years old)	55±10	56±11
Mean weight (Kg)	44±12	45±11
BMI (kg/m^2)	21.9±1.0	22.4±1.1
Portal vein invasion	18	20
Middle liver cancer	20	21
Advanced liver cancer	30	29
Child-Pugh classification		
A	10	9
B	19	20
C	21	21
Hepatitis A virus infection	9	8
Hepatitis B virus infection	32	33
Hepatitis C virus infection	9	9
TNM stage I-II	19	20
TNM stage III-IV	31	30

Statistical Analysis

All raw data obtained in the experiments were statistically analyzed using Statistical Product and Service Solutions (SPSS) 20.0 software (IBM, Armonk, NY, USA) and multiple comparisons were performed. The χ^2-test was performed for the percentage and the experimental results were expressed as mean ± standard deviation (χ±SD). $p<0.05$ suggested that the difference was statistically significant. The bar graph was plotted using GraphPad Prism 6.0 (La Jolla, CA, USA).

Results

Clinical Efficacy in Patients

As shown in Table II, the total effective rate of clinical treatment was 90% in experimental group and 60% in control group, and there was a statistically significant difference ($p<0.05$).

Detection Results of Serum Hepatic Metabolism Indexes

As shown in Table III, the levels of AST, ALT, and BUN in experimental group significantly declined ($p<0.05$), indicating that the liver function of patients returns to normal after TACE combined with HIFU, and the efficacy is better.

Postoperative Complications

There were 29 cases of postoperative complications in control group, mainly including jaundice, ascites, gastrointestinal reactions, and liver discomfort. There were only 5 cases of postoper-

Table II. Efficacy observed.

Group	CR	PR	SD	PD	Total effective rate (%)
Control group	15	15	10	0	60
Experimental group	20*	25*	5*	0	90*

Note: Comparison of efficacy. The total effective rate of clinical treatment is 90% in experimental group and 60% in control group. *$p<0.05$ *vs.* control group

Table III. Detection results of serum hepatic metabolism indexes

Group	AST (U/L)	ALT (U/L)	BUN (mmol/L)
Control group	64.4±2.4	72.8±2.0	11.1±1.2
Experimental group	28.5±2.3*	39.7±1.2*	6.5±1.0*

Note: The levels of AST, ALT and BUN in experimental group obviously decline. *p<0.05 *vs.* control group.

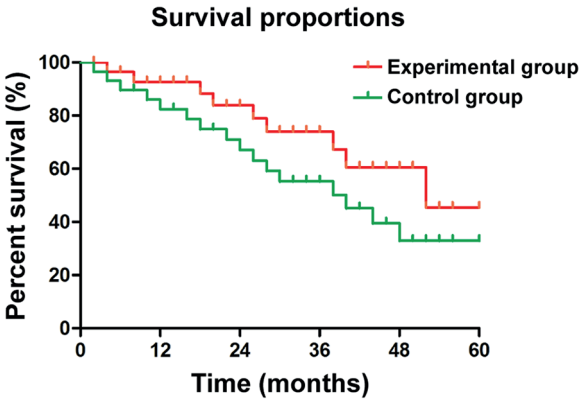

Figure 1. Postoperative survival rate. It is found with the follow-up that the postoperative survival rate within 5 years in experimental group is evidently higher than that in control group (p<0.05), and the median survival rate in experimental group is also superior to that in control group (p<0.05).

ative complications in experimental group, showing statistically significant differences (p<0.05) (Table IV), demonstrating that the effect of TACE combined with HIFU is significant with fewer adverse reactions and postoperative complications.

Detection Results of Immune Indexes

The levels of CD3+, CD4+, CD8+, and NK cells in experimental group were significantly higher than those in control group (p<0.05) (Table V).

Postoperative Survival Rate

It was found with the follow-up that the postoperative survival rate within 5 years in experimental group was evidently higher than that in control group (p<0.05) (Figure 1), indicating that the efficacy of TACE combined with HIFU can be effectively maintained within 5 years after the treatment.

Levels of Tumor Markers AFU, AFP, CA19-9, and CEA

There were no statistically significant differences in the levels of tumor markers AFU, AFP, CA19-9, and CEA between the two groups before treatment (p>0.05). After treatment, their levels were evidently lower than those before treatment, while they were also evidently lower in experimental group than those in control group (p<0.05) (Table VI).

QOL Score

The mean QOL score was 80 points in experimental group and 50 points in control group and the difference was significant between the two groups (p<0.05) (Figure 2).

Discussion

Liver cancer is the 5th most common malignant solid tumor, as well as the 3rd major cause of cancer-related death. Liver cancer usually occurs in the damaged liver, such as in patients with chronic hepatitis and cirrhosis, whose liver function has deteriorated[20]. The liver histological background and liver function may also be different in young

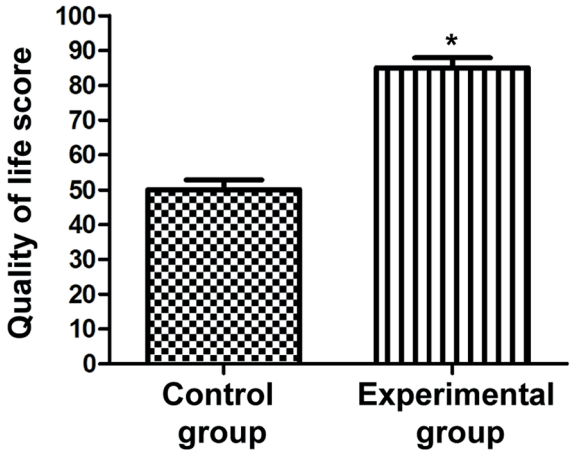

Figure 2. QOL score. The mean QOL score is 80 points in experimental group and 50 points in control group, and the difference is significant between the two groups (p<0.05) *p<0.05 *vs.* control group.

Table IV. Postoperative complications.

Group	Jaundice	Ascites	Gastrointestinal reactions	Liver discomfort
Control group	5	8	8	8
Experimental group	1*	1*	2*	1*

Note: There are 29 cases of postoperative complications in control group, mainly including jaundice, ascites, gastrointestinal reactions and liver discomfort. There are only 5 cases of postoperative complications in experimental group, showing statistically significant differences ($p<0.05$). *$p<0.05$ *vs.* control group

Table V. Detection results of immune indexes CD3+, CD4+, CD8+ and NK cells.

Group	CD3+	CD4+	CD8+	NK (%)
Control group	38.4±2.1	31.7±2.1	25.5±1.2	12.8±3.1
Experimental group	50.8±2.5*	45.5±1.1*	36.3±2.1*	20.4±2.1*

Note: The levels of CD3+, CD4+, CD8+ and NK cells in experimental group are significantly higher than those in control group ($p<0.05$). *$p<0.05$ *vs.* control group.

and elderly patients, which may affect the operation result. Currently, there are several therapeutic methods that may cure early liver cancer, including surgical resection, local ablation, and liver transplantation[21]. TACE is considered as an effective palliative treatment. However, regardless of the condition of disease, other treatments can also be adopted for patients with advanced liver cancer, including radiotherapy, chemotherapy, alkylating agent cisplatin or topoisomerase inhibitor doxorubicin. Long-term chemotherapy has great side effects and high treatment expenses, increasing the burden on patients and their families, and harming the development of social welfare[22,23]. In the present study, TACE alone and TACE combined with HIFU were performed, and the postoperative efficacy was observed. It was found that the total effective rate of clinical treatment was 90% in experimental group and 60% in control group, and there was a statistically significant difference. Besides, liver dysfunction may occur due to the inflammatory response, further promoting the development of liver cancer. In this work, the levels of AST, ALT, and BUN in experimental group markedly. declined, indicating that the liver function of patients returns to normal after TACE combined with HIFU, and the efficacy is better. Furthermore, there were 29 cases of postoperative complications in control group, mainly including jaundice, ascites, gastrointestinal reactions, and liver discomfort. There were only 5 cases of postoperative complications in experimental group, showing statistically significant differences, demonstrating that the effect of TACE combined with HIFU is significant with fewer adverse reactions and postoperative complications, which has higher application value and is worthy of popularization, similar to the previous studies[24].

Table VI. Levels of tumor markers AFU, AFP, CA19-9 and CEA.

Group	AFU (μ/L)	AFP (ng/mL)	CA19-9 (U/L)	CEA (ng/mL)
Control group				
Before treatment	70.18±1.28	153.18±2.10	80.54±2.74	32.74±1.65
After treatment	44.52±2.41*	56.89±2.78*	41.03±1.35*	22.93±2.74*
Experimental group				
Before treatment	71.49±1.77	150.96±2.14	82.85±1.31	31.99±4.80
After treatment	22.45±2.34*#	24.89±2.37*#	22.21±2.57*#	10.09±1.11*#

Note: After treatment, the levels of AFU, AFP, CA19-9 and CEA are evidently lower than those before treatment, while they are also evidently lower in experimental group than those in control group ($p<0.05$). *$p<0.05$ *vs.* before treatment, #$p<0.05$ *vs.* control group in the same period

After the operation, the response of immune T-cells to autologous tumor cells or autologous tumor lysate can be detected to evaluate the efficacy[25]. Among them, CD8+ acts on one or more immune neo-epitopes, and can also simultaneously induce CD4+, CD3+, and NK cells, which is important for an effective anti-tumor immune response[26]. According to other researches[27], the survival time will be prolonged twice that of control group when the levels of immune markers CD4+ and CD8+ are increased significantly. In this study, the levels of CD3+, CD4+, CD8+, and NK cells in experimental group were significantly higher than those in control group. In a prospective randomized report[28], TACE alone and TACE combined with HIFU were compared and it was reported that TACE combined with HIFU can reduce the tumor size and improve the 5-year survival rate. In this study, the postoperative 5-year survival rate in experimental group was evidently higher than that in control group, indicating that the efficacy of TACE combined with HIFU can be effectively maintained within 5 years after treatment. Moreover, the mean QOL score was 80 points in experimental group and 50 points in control group and the difference was significant between the two groups. As the most commonly currently used tumor marker for liver cancer screening, AFP has a high specificity. CEA is a broad-spectrum tumor marker and CA19-9 is called a gastrointestinal tract-related antigen that is related to the occurrence of pancreatic cancer, gallbladder cancer, and gastrointestinal tumor. AFU is a kind of lysosomal acid hydrolase, whose expression level markedly rises in the serum of patients with tumors[29-31]. Finally, after treatment, the levels of AFU, AFP, CA19-9, and CEA were evidently lower than those before treatment, while they were also evidently lower in experimental group than those in control group, similar to the previous studies[32]. To sum up, the above findings suggest that TACE combined with HIFU has good efficacy in the treatment of middle-advanced liver cancer, effectively reducing the pain and economic burden of patients.

Conclusions

We demonstrated that HIFU combined with TACE in the treatment of middle-advanced liver cancer can significantly increase the QOL, improve the prognosis and complications, raise the survival rate and immunity, and reduce the tumor markers in patients. Also, it has definite efficacy, which is worthy of popularization.

Conflict of Interests

The Authors declare that they have no conflict of interests.

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