

Original Article

Clinical intervention effect of TACE combined with 3DCRT in patients with primary liver cancer

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Abstract: Objective: To investigate the clinical intervention effect of transcatheter arterial chemoembolization (TACE) combined with three-dimensional conformal radiotherapy (3DCRT) in patients with primary liver cancer (PLC). Methods: A total of 110 PLC patients admitted to our hospital were selected and divided into the study group (SG, n=60, treated with TACE combined with 3DCRT) and the control group (CG, n=50, treated with TACE alone) in accordance with the different clinical intervention measures. The clinical intervention effect and the changes of tumor factors and quality of life scores were compared between the two groups before and after intervention, and the three-year survival and the incidence of adverse reactions were evaluated. Results: The objective response rate (ORR) and disease control rate (DCR) in the SG (78.33% and 95.00%) were higher than those in the CG (38.00% and 80.00%), whereas the carcinoembryonic antigen (CEA) and alpha fetoprotein (AFP) levels in the SG were lower than those in the CG ($P < 0.05$). After intervention, the quality of life score in the SG was higher than that in the CG ($P < 0.05$). The SG was superior to the CG in follow-up survival ($P < 0.05$). Conclusion: TACE combined with 3DCRT has a high safety and leads to remarkable clinical intervention effects, marked improvement of the serological indices, better quality of life, as well as satisfactory long-term survival.

Keywords: TACE, 3DCRT, primary liver cancer, clinical intervention, effect, influence

Introduction

Liver cancer (LC) is a common malignant tumor in clinical practice [1]. According to the statistics of the World Health Organization in 2014, the numbers of new LC cases and deaths ranked first worldwide, accounting for about 50.5% of the numbers of new cancer cases and deaths [2, 3]. Primary liver cancer (PLC) is the most common pathological type of hepatocellular carcinoma (HCC), accounting for 91.5% of all liver cancers, and is subdivided into three categories: nodular, massive, and infiltrative. With the changes in lifestyle habits and dietary structure of Chinese people in recent years, the prevalence rate of LC has been on the rise [4, 5].

Transcatheter arterial chemoembolization (TACE) is a minimally invasive technique to treat liver tumors by restricting a tumor's blood supply, leading to ischemia and hypoxia and thus

inducing neoplasm necrosis. Currently, TACE is the preferred option for the treatment of LC patients who have missed the optimal time for surgical resection [6, 7]. Multiple studies have confirmed that TACE exerts excellent intervention effects on various tumors. Since 1978, TACE has been extensively implemented with definite efficacy [8]. Currently, the intervention approaches (anticancer drugs, drugs combined with microparticles, microspheres) for embolism have been developed in clinical practice, and have been extensively used in the treatment of LC. However, with the widespread use of TACE, clinical oncologists have found that TACE demonstrates poor efficacy in patients with HCC > 5 cm [9]. A study has indicated that a larger lump indicates a poorer intervention effect of TACE, which may be related to the double blood supply in intrahepatic lumps [10]. 3DCRT is a common radiation therapy that has been extensively implemented over these years.

3DCRT can eliminate tumor cells without affecting the physiological function of normal tissues through the targeted radiological intervention [11]. Recently, more and more clinical reports on 3DCRT have indicated that 3DCRT can significantly prolong the overall survival (OS) of patients [12].

The purpose of this study was to investigate the feasibility of TACE combined with 3DCRT in the treatment of PLC patients, so as to provide a clinical reference for improvement of the quality of life and OS of PLC patients.

Materials and methods

General data

A total of 110 PLC patients admitted to our hospital from January 2014 to January 2018 were selected as the study subjects, and divided into the study group (SG, n=60, treated with TACE combined with 3DCRT) and the control group (CG, n=50, treated with TACE alone) in accordance with the different clinical intervention measures.

Inclusion criteria: (1) patients diagnosed as PLC by pathology and imaging, and required surgical treatment [13]; (2) those with clear consciousness and ability to cooperate with the investigation; (3) those aged over ≥ 18 years; (4) those with complete medical records; (5) this study was approved by the Ethics Committee of Affiliated Jiangnan Hospital of Zhejiang University of Traditional Chinese Medicine, Hangzhou Xiaoshan District Hospital of Traditional Chinese Medicine, Hangzhou Xiaoshan District Hospital of Traditional Chinese Medicine General Hospital; (6) patients voluntarily signed informed consent form; (7) those with Child-Pugh class A or B for hepatic function.

Exclusion criteria: (1) patients complicated by mental illness or consciousness disorders; (2) those with poor compliance with the investigation; (3) those with recurrent LC or distant metastasis; (4) those with diffuse intrahepatic lesions; (5) those with the estimated OS less than 6 months; (6) drug or alcohol addicts.

Rejection criteria: (1) voluntary withdrawal during the investigation; (2) loss to follow up during the investigation.

Intervention approaches

The CG was treated with TACE alone following the specific measures: chemotherapy drugs (e.g., 40-80 mg of Epirubicin, 20-40 mg of Pirarubicin and 20-30 mg of Hydroxycarbamide) were selected, and the combined use of two drugs was implemented according to the actual conditions of patients, and iodinate oil was selected as the embolization agent. The Seldinger technique was used to puncture the patient's right femoral artery. Under the guidance of the guide wire, RH catheter was placed, the celiac arteriogram was performed, and the site, size, and number of lesions and blood supply were understood. Then, the super-selective microcatheterization was inserted to the tumor feeding artery, and chemotherapy drugs were perfused. When the blood flow in patients' celiac artery significantly slowed down or stopped, embolism was stopped. The embolism results were determined by the second radiography. After surgery, conventional hepatoprotective treatment was performed, and timely follow-ups were carried out.

The SG was treated with TACE combined with 3DCRT, and the measures of TACE were the same as those adopted in the CG. The intervention measures for 3DCRT were as follows: the preoperative continuous enhanced computed tomographic scanning was performed to delineate the patient's body surface contour, vital tissues and organs and reconstruction of target region were conducted, and the expansion of 2 cm around the gross tumor volume was performed to set the planned target volume. Upon determination of the target region, the coplanar or non-coplanar irradiation was confirmed, and the radiation therapy was carried out. The treatment was performed once a day, 5 times a week, and the median radiation dose was 50 Gy. If there is no obvious adverse reaction during the intervention, the radiation dose can be increased as much as possible.

Observational indices and assessment criteria

Comparison of differences in clinical efficacies of interventions between the two groups: At 1 month after intervention, the clinical intervention effects in the two groups were evaluated. The evaluation method was adopted in accordance with the World Health Organization's

response evaluation criteria in solid tumors (RECIST), namely, the intervention effects were divided into complete response (CR, disappearance of all target lesions for more than 4 weeks), partial response (PR, at least a 30% decrease in the sum of the longest diameter of target lesions), stable disease (SD, neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD) and progressive disease (PD, at least a 20% increase in the sum of the longest diameter of target lesions or appearance of one or more new lesions). Objective response rate (ORR) = (CR + PR)/total number of cases ×100%, disease control rate (DCR) = (CR + PR + SD)/total number of cases ×100% [14].

Analysis of changes of serological indices in the two groups during the intervention: Before intervention and at 3, 6, 12 and 24 months after intervention, blood samples were collected in the two groups. After centrifugation, the serum was collected, alpha fetoprotein (AFP) and carcinoembryonic antigen (CEA) levels were measured by enzyme-linked immunosorbent assay (ELISA), and each index was detected for three consecutive times. The average value was taken as the final result. The differences in serological indices were compared between the two groups, and the serological indices were compared between the two groups before and after intervention.

Analysis of changes of quality of life in the two groups before and after intervention: Before intervention and 1 year after intervention, the quality of life of patients in the two groups were evaluated using Karnofsky performance scale (KPS) and Quality of Life (QOL) scale, respectively. The functional status of patients with tumors was evaluated using KPS. A lower score indicated a worse health status of subjects. QOL scale comprises 12 dimensions (e.g., appetite, spirit, sleep and fatigue), and a scoring system of 0 to 60 points was adopted. A higher score indicates a higher QOL of subjects.

Evaluation of survival rates in the two groups: The survival curves in the two groups were plotted, respectively, and the 1-3-year survival rates were calculated in the two groups after intervention.

Comparison of differences in incidence rates of adverse reactions between the two groups: The incidence rates of multiple adverse reactions (e.g., leukopenia, impaired hepatic function, and gastrointestinal reactions) were recorded in the two groups, the differences between the two groups were compared, and the differences in the intervention measures were evaluated.

Statistical method

The collected data were input into an EXCEL table for processing, and SPSS 22.0 was adopted for statistical analysis. The validity of collected data was detected using normal distribution. The enumeration data conforming to normal distribution were expressed as [n (%)]. The differences between groups were analyzed using chi-square test. The measurement data were expressed as mean ± standard deviation. The differences between groups were analyzed using t test, and the comparison of differences in continuous variables in the two groups was detected using t test. The OS in the two groups was investigated using Kaplan-Meier approach. $P < 0.05$ indicated a statistically significant difference, and the study graphs were plotted using Graphpad Prism 8 [15].

Results

Comparison of differences in general data between the two groups

A total of 110 subjects were selected in this study, and divided into the SG (n=60) and the CG (n=50). The clinical data (e.g., gender, age, size of tumors, tumor type, intrahepatic arteriovenous shunts and total bilirubin level) were recorded in the two groups, and the differences were compared between the two groups. The results exhibited that there was no remarkable difference in the clinical data between the two groups ($P > 0.05$), and the clinical data were comparable (**Table 1**).

Comparison of differences in clinical efficacy of interventions between the two groups

The clinical efficacy of interventions was evaluated in the two groups. The results demonstrated that there were 12 patients with CR, 35 patients with PR, 10 patients with SD, and 3 patients with PD, and ORR and DCR were 78.33% and 95.00% respectively in the SG,

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Table 1. Comparison of general clinical indices between the two groups ($\chi \pm s$)/[n (%)]

General clinical data		Study group (n=60)	Control group (n=50)	t/ χ^2	P
Gender	Male	37	28	0.547	0.362
	Female	23	22		
Average age (year)		45.98±4.33	46.01±4.29	0.036	0.987
Average weight (kg)		64.29±3.91	64.34±3.89	0.066	0.917
Average total bilirubin ($\mu\text{mol/L}$)		19.89±0.28	19.93±0.18	0.871	0.386
Tumor size		5.49±1.22	5.51±1.29	0.083	0.934
Tumor type	Nodular	10	10	0.652	0.204
	Massive	50	40		
Intrahepatic arteriovenous shunts	No	15	11	0.712	0.136
	Yes	45	39		

Table 2. Comparison of clinical efficacies of interventions between the two groups [n (%)]

Group	n	CR	PR	SD	PD	ORR	DCR
Study group	60	12 (20.00)	35 (58.33)	10 (16.67)	3 (5.00)	47 (78.33)	57 (95.00)
Control group	50	5 (10.00)	14 (28.00)	21 (42.00)	10 (20.00)	19 (38.00)	40 (80.00)
χ^2	-	-	-	-	-	18.486	5.888
P	-	-	-	-	-	< 0.001	0.015

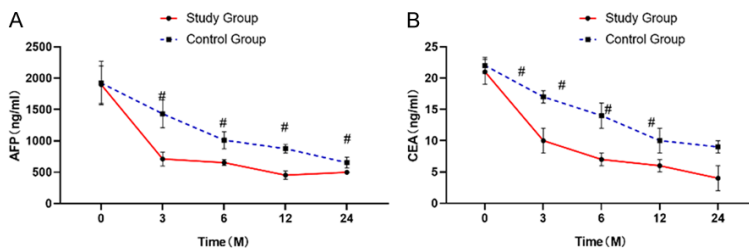


Figure 1. Analysis of changes of serological indices in the two groups during the intervention. The analysis of changes in AFP (A) and CEA (B) levels in the two groups were analyzed. The results revealed that the AFP and CEA levels in the two groups showed a downward trend during treatment, and the AFP and CEA levels in the study group were lower than those in the control group at 3, 6, 12 and 24 months after intervention ($P < 0.05$). #indicates a statistically significant difference in the same indices at the same time points between the two groups.

AFP and CEA levels in the two groups after intervention were markedly reduced compared with those before intervention, and the AFP and CEA levels in the two groups at 3, 6, 12 and 24 months after intervention were lower than those before intervention ($P < 0.05$). The comparison within groups demonstrated that the AFP and CEA levels in the SG were lower than those in the CG at 3, 6, 12 and 24 months after intervention ($P < 0.05$) (**Figure 1**).

while CR, PR, SD, PD, ORR and DCR were 10.00%, 28.00%, 42.00%, 20.00%, 38.00% and 80.00% respectively in the CG. There were statistically significant differences in ORR and DCR between the two groups ($P < 0.05$) (**Table 2**).

Analysis of changes of serological indices in the two groups during the intervention

Before intervention and at 3, 6, 12 and 24 months after intervention, AFP and CEA levels were evaluated in the two groups, and the differences between groups and within groups were compared. The results suggested that the

Analysis of changes of quality of life in the two groups before and after intervention

The quality of life was evaluated using KPS and QOL scale in the two groups before and after intervention, and the differences between the two groups were compared. The results revealed that there was no significant difference in the scores of the KPS and QOL scale between the two groups before intervention ($P > 0.05$). After intervention, the scores of KPS and QOL scale in the two groups were notably elevated compared with those before intervention ($P < 0.05$). After intervention, the scores of KPS and

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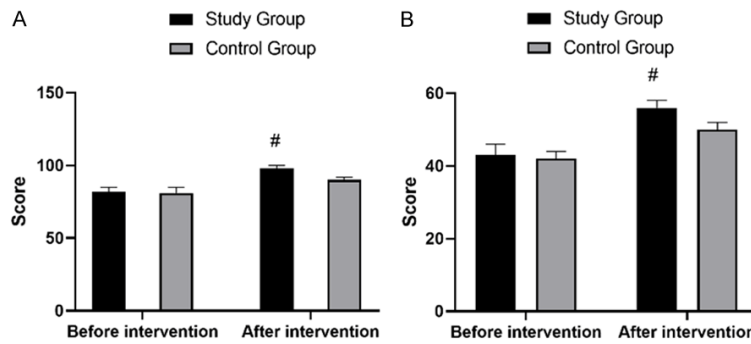


Figure 2. Analysis of changes of quality of life in the two groups before and after intervention. There was no statistically significant difference in the scores of KPS and QOL scale between the two groups before intervention ($P > 0.05$). After intervention, the scores of KPS and QOL scale in the study group were noticeably higher than those in the control group ($P < 0.05$). #indicates a statistically significant difference in the same indices between the two groups.

QOL scale in the SG were noticeably higher than those in the CG ($P < 0.05$) (Figure 2).

Evaluation of survival rates in the two groups

The patients in the two groups were followed up for 3 years, the 1-3-year survival rates were recorded in the two groups after intervention, and the comparison of differences in the 1-3-year survival rates was performed between the two groups. The results showed that the 1-3-year survival rates in the SG (71.67%, 41.67% and 30.00%) were remarkably higher than those in the CG (50.00%, 20.00% and 14.00%) ($P < 0.05$) (Table 3). Meanwhile, the survival curves in the two groups were plotted respectively, and the results showed that the survival rate of patients in both groups decreased with the follow-up time. The comparison of the survival of patients in the two groups showed that the survival rate of patients in the SG was significantly higher than that in the CG at the three time points of 12, 24, and 36 months after intervention, and the difference between groups was statistically significant ($P < 0.05$) (Figure 3).

Comparison of incidence rates of adverse reactions between the two groups

There were 6 cases with leukopenia, 3 cases with impaired hepatic function, and 5 cases with gastrointestinal reactions, with the total incidence rate of adverse reactions of 23.33% in the SG during the intervention. In the CG, there were 10 cases with leukopenia, 4 cases

with impaired hepatic function, and 5 cases with gastrointestinal reactions, with the total incidence rate of adverse reactions of 38.00%. There was no statistically significant difference in the incidence rate of adverse reactions between the two groups ($P > 0.05$) (Table 4).

Discussion

In recent years, with the changes of lifestyle habits and dietary structure of Chinese people, the prevalence rates of various cancers have been on the rise [16]. LC,

the malignant tumor of liver, ranks 5th and 3rd respectively in the incidence rate and the number of deaths among malignant tumors [17]. The number of new LC cases can reach more than 600,000 worldwide every year, accounting for 5.6% of the number of cancer cases in the same period. The number of new LC cases in China accounts for about 55% in the world and about 80% in Asia. An investigation suggests that there are about 350,000 LC cases in China, accounting for 11% [18] of the number of cancer cases in the same period. Currently, the exact molecular mechanism of liver cancer remains unclear, but most studies indicate that virus infection, contaminated drinking water, alcohol, and hepatic cirrhosis are closely related to the incidence and progression of LC [19].

In this study, the clinical intervention effect of TACE combined with 3DCRT on PLC patients was analyzed through grouping. The results demonstrated that the ORR and DCR in the SG (78.33% and 95.00%) were significantly higher than those in the CG (38.00% and 80.00%), suggesting that TACE combined with 3DCRT exhibited a higher efficacy. A controlled study on 100 PLC patients has shown that the total effective rate of TACE combined with radiotherapy (93.8%) is remarkably higher than that of TACE alone (75.0%) [20], which is similar to the results of this study. It is believed that radiotherapy can eliminate tumor cells through increasing the radiation dose in the target area, and is thus superior to TACE alone.

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Table 3. Comparison of 3-year survival rates between the two groups (X ± o)/[n (%)]

Group	n	1-year survival rate	2-year survival rate	3-year survival rate	Median OS (months)
Study group	60	43 (71.67)	25 (41.67)	18 (30.00)	20.12±2.32
Control group	50	25 (50.00)	10 (20.00)	7 (14.00)	13.29±2.39
t/X ²	-	5.424	5.902	3.976	15.165
P	-	0.02	0.015	0.046	< 0.001

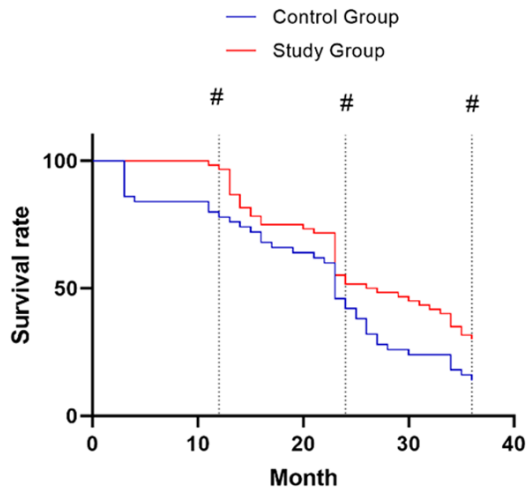


Figure 3. Evaluation of survival rates in the two groups. The survival rate in the study group was significantly higher than that in the control group at 12, 24 and 36 months after intervention ($P < 0.05$). #indicates a statistically significant difference in the survival rate at the same time points between the two groups.

The authors believe that TACE in the interventional therapy is currently considered as the preferred option for patients with unresectable PLC, especially for patients with multifocal or diffuse liver cancer. Multiple clinical practices have revealed that TACE exhibits a satisfactory short-term efficacy, and there are marked ischemia and necrosis at the lesion sites after surgery [21, 22]. However, a study has previously indicated that TACE is not applicable to all PLC patients. For example, some PLC patients with a lesion diameter of > 5 cm undergoing TACE show an increased portal venous blood flow and the establishment of collateral circulation. It is difficult to completely stop the tumor's blood supply through performing TACE alone, and the residual tumor cells often occur, elevating the postoperative recurrence rate [23]. 3DCRT can make the distribution of high-dose region consistent with the shape of target area in the three-dimensional direction, so as to obtain a high radiation dose at the tumor sites,

and improve the intervention effects when 3DCRT combined with TACE is implemented [24].

In this study, the changes in AFP and CEA levels and KPS and QOL scale scores were further compared between the two groups after intervention. The results revealed that the AFP and CEA levels in the SG were lower than those in the CG after intervention, while the scores of KPS and QOL scale in the SG were higher than those in the CG, suggesting that 3DCRT combined with TACE was conducive to improving the quality of life of patients. A retrospective analysis of PLC patients has shown that TACE combined with 3DCRT can improve anxiety and depression of patients due to a significant relief of clinical symptoms and a marked increase in patients' confidence in treatment [25]. The authors believe that TACE is performed to treat LC by restricting a tumor's blood supply using chemotherapy drugs. However, it inevitably causes damages to the normal tissues of patients, contributing to postoperative adverse reactions. Using 3DCRT combined with TACE, the dosage of chemotherapy drugs can be significantly reduced, or the therapeutic process can be shortened, so as to minimize the damage to patients' body function. Therefore, the patients have a higher quality of life. This has been demonstrated in the comparison of the incidence rates of adverse reactions between the two groups in this study. Finally, the comparison of the survival rates in the two groups after 3-year follow-ups shows that TACE combined with 3DCRT can improve the long-term survival rate of the patients. It has been reported that the 1-, 2-, and 3-year survival rates of patients treated with 3DCRT combined with TACE (71.5%, 42.3%, and 24.0%) are noticeably higher than those of patients treated with TACE alone (59.6%, 26.5%, and 11.1%) [26], which is similar to the results of this study. This may be due to the reason that TACE alone can elevate the incidence of the establishment of collateral circulation in the

Table 4. Comparison of incidence rates of adverse reactions between the two groups during the intervention [n (%)]

Group	n	Leucopenia	Impaired hepatic function	Gastrointestinal reactions	Total incidence rate
Study group	60	6 (10.00)	3 (5.00)	5 (8.33)	14 (23.33)
Control group	50	10 (20.00)	4 (8.00)	5 (10.00)	19 (38.00)
χ^2	-	-	-	-	2.794
<i>P</i>	-	-	-	-	0.095

patients, resulting in residual cancer cells or small intrahepatic metastases in the regions around the tumors. 3DCRT combined with TACE can shrink the tumor more quickly, relieve the symptoms, and markedly improve the survival rate of patients.

In summary, TACE combined with 3DCRT has a high safety and leads to remarkable clinical intervention effects, marked improvement of the serological indices, better quality of life, and satisfactory long-term survival. Therefore, TACE combined with 3DCRT is feasible for PLC patients. The deficiency of this study is that the influences of underlying health conditions on the intervention results can not be ruled out, which should be considered in future studies.

Disclosure of conflict of interest

None.

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