JBUON 2014; 19(3): 692-697
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Three-dimensional conformal radiotherapy in combination with transcatheter arterial chemoembolization in the treatment of hepatocellular carcinoma

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Summary

Purpose: *This study aimed to investigate the efficacy and safety of transcatheter arterial chemoembolization (TACE) in combination with three-dimensional conformal radiotherapy (3D-CRT) in the treatment for locally advanced unresectable hepatocellular carcinoma (HCC).*

Methods: *From March 2000 to March 2009 a total of 158 patients with unresectable HCC treated and followed at our hospital were divided into TACE group (N=80) and TACE combined with 3D-CRT group (N=78). The TACE group was treated 3-6 times. In the combination group, 2-3 TACE courses were administered and 3D-CRT was performed 2 weeks after the last TACE. Three months after the end of treatment, imaging and serum AFP were carried out to assess the treatment efficacy.*

Results: *The response rates of TACE and the combination groups were 53.7% (43/80) and 71.8% (58/78) ($p<0.05$). The 1, 2, and 3-year survival rates of patients in the TACE and combination groups were 58.75, 36.25, 16.25%, and 78.48, 55.12 and 25.64% ($p<0.05$), respectively. Treatment compliance was good, with at least 2 TACE administrations for each case and at least 52 Gy for radiotherapy. In the TACE and the combination group, there were 2 and 3 cases with grade III/IV toxicity, respectively, without treatment-related death.*

Conclusion: *3D-CRT in combination with TACE significantly improve the therapeutic outcome in patients with locally advanced unresectable HCC, without creating severe toxicity.*

Key words: *primary hepatocellular carcinoma, three-dimensional conformal radiotherapy, transcatheter arterial chemoembolization*

Introduction

HCC ranks fifth in morbidity and third in mortality among malignant neoplasms worldwide, with more than 500000 patients suffering from HCC every year. The ideal therapy is radical resection of liver segment or lobe, but approximately 80% of the patients should not or could not undergo surgery due to various reasons [1]. Recently, non-surgical treatments of HCC have been developed, benefiting many patients. TACE produces higher remission rates in the treatment of HCC, and is considered as the first choice of non-surgical treatment. For multifocal or diffuse HCC, TACE is the main treatment method, with good short-term results [2] and can cause necrosis of cancer tissues of different degrees. However, after hepatic artery embolism, due to increased portal vein blood supply in the liver and establishment of collateral circulation, pure TACE cannot achieve complete tumor necrosis, which is the cause of disease recurrence. In addition, many administrations of TACE may lead to drug resistance and liver function damage.

Liver has poor tolerance to radiation, and the therapeutic effect of low-dose conventional external beam radiotherapy is extremely limited in HCC. Therefore, the liver is regarded as an

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Received: 13/03/2014; Accepted: 13/04/2014

organ not suitable for radiotherapy. 3D-CRT has enhanced the irradiation dose to tumors, and reduced the irradiation dose on normal liver tissue, increasing thus the effectiveness of radiotherapy in the treatment HCC. At present, 3D-CRT is the mainstream technology of external beam irradiation in the treatment of HCC [3,4]. Theoretically, TACE can kill most tumor cells, shrink the tumor volume, narrow the radiation field and improve the radiation tolerance of normal liver tissue. In addition, precise and high-dose 3D-CRT can block the portal vein blood supply and compensatory blood supply, and significantly reduce recurrence rates after TACE. However, in clinical practice it is inconclusive whether the efficacy of 3D-CRT in combination with TACE is superior to 3D-CRT or TACE alone, and whether the side effects of 3D-CRT increase after combining with TACE. Therefore, we carried out this randomized controlled trial to compare the efficacy of TACE in combination with 3D-CRT vs TACE alone in cases of locally advanced unresectable HCC.

Methods

General data

From March 2000 to March 2009 a total of 158 patients with unresectable HCC treated and followed were divided into the TACE group (N=80) and TACE combined with 3D-CRT group (N=78). This study was conducted in accordance with the declaration of Helsinki and after approval from the Ethics Committee of Wenzhou Medical College. Written informed consent was obtained from all participants.

Inclusion criteria

Liver function Child-Pugh class A; Eastern Cooperative Oncology Group performance status (ECOG PS) 0-1; no cirrhosis, jaundice and ascites; no severe illnesses except HCC; no history of liver radiotherapy; no contraindications for chemotherapy and radiotherapy; adequate bone marrow, renal and cardiac function; expected survival longer than 3 months; age 18-70 years.

There were 118 (74.7%) males in the two groups and only in 26 (16.5%) of 158 cases were diagnosed by biopsy or FNB. No patient met the criteria for radical surgery according to at least one senior surgical oncologist or general surgeon. The range of tumor diameter was 3-16 cm (median 7.5).

TACE therapy

TACE comprised hepatic arterial infusion chemotherapy and hepatic artery embolization. Percutaneous catheterization of the femoral artery was performed using the Seldinger method [5], in which the tube is inserted into the arteria hepatica propria or the left and right hepatic arteries according to tumor location. The chemotherapeutic drugs were injected through the catheter, followed by peripheral embolization with lipiodol emulsion and central embolization with gelfoam.

Chemotherapeutics and doses

5-fluorouracil (Shenyang Double Ding Pharmaceutical Co., Ltd., Shenyang, China), 750-1000 mg; cis-platinum (Jiangsu Hansoh Pharmaceutical Co., Ltd., Lianyungang, China) 40-60 mg; farmorubicin (Pfizer Pharmaceutical Co., Ltd., Wuxi, China), 40-80 mg; mitomycin (Pfizer Pharmaceutical co., Ltd., Wuxi, China), 6-10 mg. Patients in the combination group underwent 2-3 courses of TACE; 3D-CRT was delivered 2 weeks after the last course of TACE if liver function tests were normal. Liver function tests and serum biochemistry (serum ALT, normal 7-40 U/L; AST, normal 13-25 U/L; total bilirubin 33.4-19.0 μmol/L; creatinine, normal 40-106 μmol/L) were closely monitored during TACE so as to give supportive and/or and symptomatic treatment if necessary. Full (100%) of the planned dose of each chemotherapeutic drug was given when ALT, AST, total bilirubin and creatinine levels were <2 times the upper limit of normal (ULN) and 50% when the levels were between 2-5 times the ULN.

3D-Conformal radiotherapy

Radiotherapy was designed with CMS- Xi0 radiation treatment planning system (CMS- Xio TPS, Computerized Medical Systems Inc., USA). Varian23EX linear accelerator (Varian Medical Systems, California, USA) was employed to perform 6 MV high-energy X-ray radiotherapy as follows: the patient was fixed with vacuum pad and scanned under enhanced spiral CT scanning machine with 3-5 mm scanning slices; data was transmitted through the network to TPS system. Radiotherapist, hepatobiliary surgeon and radiologist delineated all the important organs, viscera outlines, gross tumor volume (GTV) and clinical tumor volume (CTV, typically included the GTV plus 0.5-1.5 cm margin that varied due to specific location and breathing movement), and then the planning target volume (PTV, including the CTV plus 0.5cm margin); they also defined the radiotherapy dosage of important organs. Target areas included intrahepatic tumor and portal vein tumor emboli. After the target area and related organs were outlined, a physicist optimized the radiotherapy planning. Generally, radiotherapy was delivered in 4-6 fields and the crucial organs' doses (small intestine, stomach, spinal cord, heart, kidney, normal liver tissue, etc.) met the criteria of radiation dose limits to normal organs. The radiotherapist and hepatobiliary surgeon evaluated the plan together after it was designed and radiotherapy was confirmed and delivered if the plan met the clinical requirements. The sum of the radiation doses received by each individual ranged from 50 to 62

Gy (median 58) with 2-2.5 Gy/day, 5 days a week. Liver function was regularly monitored during treatment so as to protect liver and apply symptomatic treatment if needed.

Efficacy evaluation

According to response evaluation criteria in solid tumors (RECIST), treatment efficacy was divided into complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD); CR and PR were considered as objective response. Serum alpha fetoprotein (AFP) levels served as complementary information of efficacy evaluation. Response rate (RR) was the sum of CR+PR, and 1-, 2-, and 3-year survival rates were analyzed. Enhanced CT or MRI scans review was performed every 3-6 months and AFP was checked every 1-2 months for 3 years after stopping treatment. Out of routine schedule, imaging methods were carried out when AFP levels increased.

Toxicity

Toxic effects were evaluated according to the US NCI-CTC (common toxicity criteria).

Statistics

Data was analyzed with SPSS13.0 software (SPSS Inc, Chicago, IL). Survival was estimated from the first day of treatment to the last follow up visit or death from any cause until December 2012. Survival was calculated with the Kaplan-Meier method and differences were assessed with the log rank test. Comparisons between groups were made using the x^2 test. A p-value < 0.05 was considered as statistically significant.

Results

Patient baseline data

Patient baseline demographics and clinical characteristics of both groups are shown in Table 1. No statistically significant differences between the groups were observed (p>0.05).

Number of TACE courses

Three to 6 TACE courses were administered in the TACE group; the patients of the combination group underwent 2-3 courses of TACE and 3D-CRT was delivered 2 weeks after the last course of TACE.

Short-term efficacy

The treatment was completed as planned in all cases with no interruptions or patients' decision for treatment discontinuation. The change of tumor size was assessed according to clinical examination and abdominal CT or MRI three months after treatment. Short-term assessment of treatment efficacy was performed 3 months after the end of therapy (Table 2). In the TACE alone group there were 2 CRs, 41 PRs, 26 SDs and 11 PDs, for an objective RR of 53.7%. In the combination group there were 9 CRs, 49 PRs, 17 SDs and 5 PDs, for an objective RR of 71.8%; the difference between the two groups was statistically significant (p<0.05). In addition, one patient in the TACE group and 3 patients in the combination group underwent successful tumorectomy after treatment due to significant reduction of tumor size.

Table 1. Patient and disease characteristics of the two groups

Characteristics	*TACE group (N=80) N (%)*	*Combination group (N=78) N (%)*
Median age, years (range)	55 (18-76)	54 (22-72)
Gender		
Male	60 (62.5)	58 (74.4)
Female	19 (37.5)	21 (25.6)
Tumor size (cm)		
>10	35 (43.8)	36 (46.2)
≤10	45 (56.2)	42 (53.8)
Tumor lesions		
Single	56 (70.0)	52 (66.7)
Multiple	24 (30.0)	26 (33.3)
Stage		
III	42 (52.5)	40 (51.3)
IV	37 (46.3)	39 (47.4)

p>0.05 in all categories

Adverse reactions

Common adverse reactions of patients in the two groups included fever (15 cases in each group), right upper quadrant pain and serum transaminases elevation <grade 3 NCI-CTC (7 and 9 cases, respectively), which subsided after administration of polyene phosphatidylcholine capsules and diammonium glycyrrhizinate and symptomatic treatment; no significant differences in adverse reactions were observed between the two groups. Leukopenia was noticed in 4 cases of the TACE group and in 11 cases of the combination group (x^2 3.8, p>0.05), among which there were 2 and 3 cases with grade III/IV, respectively (p<0.05). Two patients had upper gastrointestinal hemorrhage in both TACE and the combination

Table 2. Comparison of short-term therapeutic efficacy between the two groups

Groups	*CR N (%)*	*PR N (%)*	*SD N (%)*	*PD N (%)*	*RR (%)*
TACE group (N=80)	2 (2.5)	41 (51.3)	26 (32.5)	11 (13.8)	43 (33.7)
Combination group (N=78)	9 (11.5)	49 (62.8)	17 (21.8)	5 (6.4)	58 (74.4)
x^2	4.98	2.16	2.29	2.34	7.27
p-value	<0.05	>0.05	>0.05	>0.05	<0.01

CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, RR: CR+PR

groups (p>0.05).

Survival

The median follow-up was 27.5 months (range 2-121) for the combination group and 29.4 moths (range 2-107) for the TACE group. The median survival time was 17.8 months (range 2-107) for the TACE group and 19.4 months (range 2-121) for the combination group (p>0.05). One-, 2-, and 3-year survival rates of patients were markedly different between TACE and the combination groups (p<0.05, Table 3 and Figure 1).

Discussion

HCC ranks third in morbidity and is the second leading cause of cancer-related deaths in China. At present, surgery is the main radical therapeutic method. However, most patients are diagnosed at middle or advanced stages, with reduced liver function related to cirrhosis or the disease itself, making liver operations more difficult or even hazardous, with poor overall curative benefit. Recently, non-surgical treatments for HCC have been developed, including TACE, which benefit many patients. Radiotherapy plays a crucial role in the non-surgical therapy of this condition [6-8].

Currently, TACE is being considered as the preferred treatment for unresectable HCC at middle or advanced stages. Researches show that the efficacy of TACE is superior to symptomatic treatment. However, since there exists double blood supply in the margin of HCC, this may lead to TACE failure. At the same time, the tumor blood supply, coupled with residual liver tumor cells' contributes to intrahepatic or distant dissemination of disease after TACE through collateral circulation or recanalization of the embolized blood vessel(s). On the other hand, a disadvantage of TACE is poor control of the portal vein area surrounding the tumor, thus it is difficult to completely eradicate the tumor [9,10].

Liver has been previously classified as radiation-resistant organ, while modern basic and clinical research considers HCC as early response tissue that is sensitive to radiotherapy [11-13]. Moreover, 3D-CRT has changed the traditional concept of radiotherapy for liver cancer in recent years because the radiation dose for intrahepatic tumors can be dramatically improved in conformal radiotherapy whilst, at the same time, the doses are kept in the accepted radiation dose limits for the remaining normal liver tissue, spinal cord, heart, kindey and gastrointestinal tissue [5,14,15]. Theoretically, interventional treatments and radiotherapy are complementary. Radiotherapy can kill live residual cancer cells after TACE, especially cells with better oxygenation in the tumor edge area due to good blood supply by the

Table 3. Comparison of survival rates between the two groups

	One-year survival rate (%)	*Two-year survival rate (%)*	*Three-year survival rate (%)*
TACE group (N=80)	58.75	36.25	16.25
Combination group (N=78)	78.48	55.12	25.64
x^2	6.91	17.73	9.10
p-value	<0.05	<0.05	<0.05

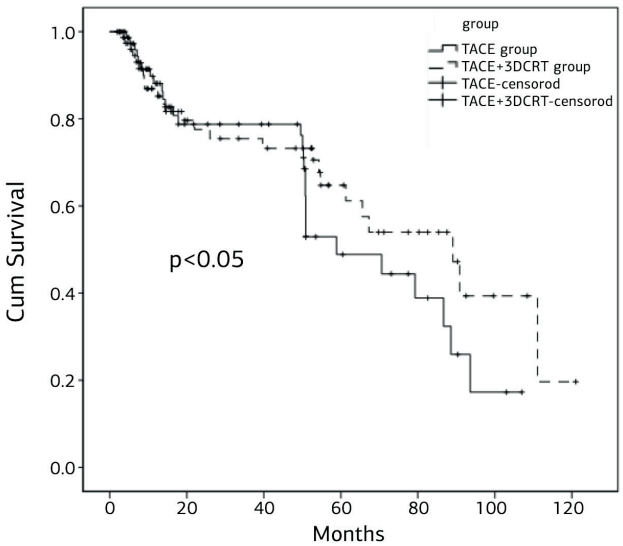

Figure 1. Cumulative survival rates of the two groups.

portal vein, while the effectiveness of 3D-CRT is even stronger. At the same time, chemotherapeutics used in TACE simulteneously increase the efficacy of radiotherapy. TACE has good efficacy on the central bulk of tumor tissue (cells with insufficient oxygen are not sensitive to radiotherapy), and decreases the tumor volume, which in turn reduces the radiation field, thus minimizing the damage to normal liver tissue [16-18].

In order to clarify whether the efficacy of 3D-CRT combined with TACE is better than 3D-CRT or TACE alone in the treatment of HCC, and whether the side effects of 3DC-RT after TACE will increase, we compared the efficacy on locally advanced unresectable HCC between TACE in combination with 3D-CRT and TACE alone. The results showed that, both the TACE-alone group and the combination group achieved good results. Short-term response rates were 53.7% in the TACE group and 71.8% in the combination group ($p<0.05$), which indicated that conventional TACE combined with radiotherapy facilitated the inhibition of tumor growth and obtained better local control. One, 2-, and 3-year survival rates of patients in the TACE-alone and the combination groups were 58.75, 36.25 and 16.25%, and 78.48, 55.12 and 25.64 ($p<0.05$), respectively, suggesting that the improvement of local control in HCC was also connected with significantly improved long-term survival.

It is speculated that the improvement of short-term efficacy and long-term survival in the combination group may be correlated with the following factors: 1) TACE in combination with radiotherapy eliminates live residual cancer cells and increases local control ratio as well as long-term effects. 2) Arterial chemotherapy synchronizes the tumor cells' cycle, which facilitates radiotherapy to destroy cancer cells. Furthermore, retention of chemotherapeutics from embolization in liver tumor cells has sensitizing effect on subsequent 3D-CRT and accelerates tumor necrosis. 3) TACE damages large numbers of cancer cells, promotes the residual cells from non proliferative phase into cell proliferation and oxygenates hypoxic cells, which helps reduce the radiation load and improve sensitivity to radiotherapy. 4) Alternated radiotherapy and chemotherapy work on different cell subsets of the same tumor. Arterial chemotherapy synchronizes tumor cell cycle and reduces tumor cell resistance to treatment, which makes the cancer cells vulnerable and destroyable to radiotherapy. 5) The peripheral tumor forms collateral circulation that results in tumor cell proliferation after TACE, but the subsequent of radiotherapy can effectively kill the oxygenated tumor cells. 6) For certain tumors with little blood supply and poor filling of lipiodol emulsion, 3D-CRT can increase the radiation dose and tumor local control rate. 7) 3D-CRT is performed after TACE to extend the retention of iodine oil and drugs in tumors, which avoids repeated TACE and severe liver dysfunction.

In recent years, an increasing number of studies on TACE combined with 3D-CRT in the treatment of HCC appears in the literature [19-22], in which the model of 3D-CRT combined with TACE are the same but the methods of radiation dose fractionations are different. Generally, higher fractionation dose (3-10 Gy) in a total of 20-40 Gy with few number of radiation fields (2-4) are conducted. However, no long-term efficacy reports exist so as to draw a firm conclusion so far. In our study, radiotherapy dose was 2-2.5 Gy/day, 5 fractions a week, which was more consistent with the behavioral radiobiology and better tolerated by the patients with mild side effects. In addition, attention should be paid on the damage of liver functionality in the combined therapy. Liang [6] reported that the liver function was evidently decreased when the volume of the liver that received 30 Gy was more than 40%. Therefore, radiation should include all the tumor foci in less radiation fields and exclude normal liver tissue as much as possible to protect normal tissue from irradiation, which is hard to achieve with conventional radiotherapy. Through modern advanced radiotherapy TPS, 3D-CRT can optimize the number of radiation fields and dose fractionation to increase radiation dose in the tumor and protect the surrounding normal liver tissue. According to the results of this study, it is worth performing further prospective randomized phase III clinical trials with larger number of patients.

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