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Original Article

Concurrent chemoradiotherapy improves prognosis and quality of life of patients with metastatic and recurrent hepatocellular carcinoma

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Abstract: Objective: This study retrospectively analyzed the effect of concurrent chemoradiotherapy on prognosis and quality of life of patients with metastatic and recurrent hepatocellular carcinoma (HCC). Methods: This is a retrospective analysis. Data from 60 patients with metastatic and recurrent HCC admitted from Oct. 2020 to Feb. 2021 were chosen and grouped according to the treatment plans. Each group contained 30 cases. The control group was treated with chemotherapy, and the observation group received concurrent chemoradiotherapy. The two groups were treated continuously for two rounds, with 21 days in each round. The therapeutic efficacy, toxic side effects, pre- and post-treatment quality of life, changes in vascular endothelial growth factor (VEGF) and cyclooxygenase-2 (COX-2), and survival during follow-up were compared between the two groups. Results: The total therapeutic efficacy of the observation group was higher than that of the control group ($P<0.05$). The post-treatment Karnofsky score in the observation group was higher than that in the control group ($P<0.05$). The post-treatment protein expressions of VEGF and COX-2 and peripheral blood mononuclear cells were lower than those before treatment in the two groups ($P<0.05$), and were lower in the observation group than those in the control group ($P<0.05$). The observation group had superior survival times than the control group ($P<0.05$). Conclusion: Concurrent chemoradiotherapy has good short-term and long-term efficacy for patients with metastatic and recurrent HCC. It greatly improves patients' quality of life and down-regulates VEGF and COX-2 expression.

Keywords: Concurrent chemoradiotherapy, hepatocellular carcinoma, metastasis, recurrence, prognosis, quality of life

Introduction

Primary liver cancer refers to primary malignancy of hepatocytes or intrahepatic bile duct epithelial cells. Hepatocellular carcinoma (HCC) is the most influential pathological type of primary liver cancer [1]. Liver cancer ranks 5th in incidence and 3rd in mortality worldwide. Over half of the world's annual cases of liver cancer are in China [2]. Due to the high malignancy and poor clinical prognosis of the patients, surgical resection is the most effective treatment for this disease at present. However, the high postoperative recurrence and metastasis immensely affects the therapeutic effect of surgical resection [3]. For patients with recurrence and metastasis of liver cancer, their clinical prognosis is poor with very high mortality. Therefore, seeking effective treatments to improve patient's life quality and prolong their survival time has become the focus of clinicians.

Radiotherapy and chemotherapy are the current commonly used methods for the clinical treatment of malignant tumors [4]. In fact, the poor prognosis of HCC is not only caused by local recurrence. Many patients have developed small metastases by the time the lesions are removed, which leads to the end of their lives. Chemotherapy can improve the sensitivity and therapeutic effect of radiotherapy. Therefore, patients need to receive adjuvant chemoradiotherapy regardless of current disease progression. According to studies, postoperative chemoradiotherapy can enhance patient's tolerance, curb HCC, improve the

effect of radical surgery and reduce the recurrence rate of metastasis, thus protecting and sustaining liver function and ameliorating life quality [5, 6]. Researchers have found that concurrent chemoradiotherapy, which is non-invasive, has high accuracy, reliability and fewer side effects for patients with metastatic and recurrent HCC, especially for those in an advanced stage [7]. Compared with chemotherapy or radiotherapy alone, the concurrent chemoradiotherapy can improve efficacy and has synergistic effects. Research data have shown that concurrent chemoradiotherapy can improve local control rate and reduce recurrence rate [8, 9]. Chemoradiotherapy is characterized by the use of chemotherapeutic agents to sensitize radiotherapy and minimize the generation of cross-resistant tumor cells. In addition, chemotherapeutic drugs directly kill small lesions and distant metastases, and radiotherapy directly irradiates local lesions [10]. The combination of these two therapies can produce a maximum affect on tumor cells in a short period of time. Therefore, concurrent chemoradiotherapy can achieve better therapeutic effect by controlling local lesions, improving clinical symptoms, maximizing the prevention and treatment of distant metastasis, reducing the probability of metastasis and recurrence, and ameliorating prognosis and quality of life [11-14].

However, there are few clinical reports on the application of concurrent chemoradiotherapy in patients with metastatic and recurrent liver cancer. In order to further improve the short-term efficacy and quality of life, and prolong survival time of patients with HCC recurrence and metastasis, this study retrospectively analyzed the effect of concurrent chemoradiotherapy on the prognosis and quality of life in patients with HCC recurrence and metastasis.

Information and methods

General information

Data from 60 patients with metastatic and recurrent HCC who were admitted to our hospital from October 2020 to February 2021 were retrospectively analyzed. The patients were divided into two groups according to different treatments, with 30 cases in each group. The control group was treated with chemotherapy alone, and the observation group received concurrent chemoradiotherapy. The study was conducted with the approval of the Ethics Committee of the Affiliated Hospital of Hebei Engineering University.

Inclusion criteria

(1) Patients who met one of the following two criteria for postoperative recurrence of liver cancer: ① Hepatocellular carcinoma was detected by two imaging methods; ② HCC and alpha fetoprotein were over 400 ng/ml in one imaging of the record. (2) Patients who met one of the following two diagnostic criteria for metastatic HCC: ① Metastatic HCC was diagnosed by pathology; ② The patient had a history of primary tumor resection, and contrast-enhanced imaging showed typical metastatic HCC during clinical follow-up. (3) Patients had not received chemoradiotherapy before or had stopped receiving chemoradiotherapy for 1 month prior.

Exclusive criteria

(1) Patients had other severe diseases in the urinary tract, digestive tract or respiratory tract. (2) Patients had multiple organ failure and/or severe infection. (3) Patients had incomplete disease information. (4) Patients had malignant tumors other than liver cancer. (5) Patients had serious mental illness. (6) Patients had contraindications to radiotherapy or chemotherapy.

Methods

The control group was given chemotherapy with oral Xeloda (Shanghai Roche Pharmaceutical Co., Ltd.; National Medicine Zhunzi H20073024). The patients were given 2500 mg/m^2 orally twice a day for 14 days and then it was stopped for 7 days as a course of treatment. Patients received two rounds of treatment.

The observation group received concurrent chemoradiotherapy with 3D conformal radiotherapy and oral Xeloda. External irradiation was performed with 6-15 mV X-ray irradiation from a Valian accelerator and 3D conformal radiotherapy. For a single mass with diameter ≤5 cm or multiple non-adjacent masses, the target volume was given a single dose of 5-6 Gy three times a week for a total of 6-8 times. For ≥5 cm or diffuse masses, the conventional

dose segmentation was used for continuous irradiation, once a day with 1.6-2 Gy each time, 5 times a week. The maximum, minimum, average and median doses were 60 Gy, 36 Gy, 53.3 Gy and 54.5 Gy, respectively. The patient took 2500 mg/m^2 Xeloda twice a day from the first day of radiotherapy, and stopped taking the drug for 7 days after 14 days, as one course of treatment. The patients received 2 courses of treatment.

Outcome measures

Primary outcomes: (1) Efficacy: The efficacy of patients was classified as complete remission (CR), partial remission (PR), stable disease (SD) and progressive disease (PD). CR indicates that the patient showed complete disappearance of lesion and no deterioration in CT examination after 4 weeks. PR is defined as a decrease of more than 25% in the maximum diameter of the lesion multiplied by the diameter perpendicular to the lesion, with no deterioration during the 4-week monitoring period. SD indicates no significant improvement or no new lesions. PD indicates a further increase in the extent of metastasis or the appearance of new lesions. Objective response rate = PR + CR. (2) Quality of life: Changes in quality of life before and after treatment were observed. Karnofsky functional status (KPS) score was adopted for evaluation, with a score ranging from 0 to 100 points. Patients with better quality of life had higher KPS scores. (3) Survival time: The post-treatment survival of the patients was followed up, with death as the end point event, and the follow-up deadline was May 31, 2022.

Secondary outcomes: (1) Side effects: The toxicity and side effects were observed in both groups. (2) Serum level of vascular endothelial growth factor (VEGF) and cyclooxygenase-2 (COX-2): The peripheral venous blood was collected in the patients before and after treatment, and centrifuged for 10 min, with a radius of 15 cm and a rotating speed of 2000 r/min. After the serum was collected, the levels of VEGF and COX-2 were determined by enzyme-linked immunosorbent assay (ELISA) using VEGF ELISA kit (Abcam, ab209882) and COX-2 ELISA kit (Abcam, ab285325). (3) Protein expressions of VEGF and COX-2 in mononuclear cells: Peripheral venous blood was collected in patients. Mononuclear cells were separated by Ficoll density gradient centrifugation (American GE company), and total protein was extracted and detected using the BCA protein concentration assay kit (Shanghai Biyuntian Biotechnology Co., Ltd.). The samples were mounted by electrophoresis and transferred to the membrane. After the PVDF membrane was sealed with milk at 37°C for 1 h, primary antibodies was added and incubated at 4°C overnight. Primary antibodies included VEGF antibody (Abcam, USA, ab32152, dilution ratio 1:3000) and COX-2 antibody (Abcam company, USA, ab179800, dilution ratio 1:2000). Subsequently, horseradish peroxidase-labeled secondary antibody (Shanghai Biyuntian Biotechnology Co., Ltd.) was added to the samples and incubated at 37°C for 1 h. After the membrane was rinsed with TBST, ECL luminescent solution was added for development.

Statistical approach

Data analyses were conducted by SPSS 26.0. The measurement data were represented by ($\bar{x} \pm s$), and analyzed by t-test. The count data were represented by *n* (rate), and analyzed by χ^2 test. Kaplan-Meier survival curves were drawn for survival analysis, and Log-Rand test was used to compare the survival curves. $P< 0.05$ indicates that the difference is statistically significant.

Results

Clinical data

The two groups showed no significant difference in general data ($P>0.05$) (**Table 1**).

Comparison of efficacy between the two groups

In the observation group, there were 5 cases of CR (16.67%), 13 cases of PR (43.33%), 9 cases of SD (30.00%) and 3 cases of PD (10.00%), with an objective response rate of 60.00%. In the control group, there were 2 cases of CR (6.67%), 8 cases of PR (26.67%), 14 cases of SD (46.67%) and 6 cases of PD (20.00%), with an objective response rate of 33.33%. The objective response of the observation group was higher than that of the control group ($P<0.05$) (**Table 2**).

Table 1. Comparison of clinical data between the two groups

Clinical data	Observation group (n=30)	Control group (n=30)	t/X^2/Z	P
Sex				
Male	18	19	0.071	0.791
Female	12	11		
Age (years old, ±s)	48.72±7.94	48.41±9.28	0.139	0.890
BMI (kg/m^2, ±s)	22.87±1.94	23.08±1.87	0.427	0.671
TNM Staging				
Stage IIIb	9	10	0.077	0.781
Stage IV	21	20		
Type				
Postoperative recurrence	16	17	0.067	0.795
Metastatic hepatic carcinoma	14	13		
Diameter of tumor				
≥5 cm	18	16	0.272	0.602
<5 cm	12	14		

BMI: Body Mass Index; TNM: Tumor Node Metastasis.

Table 2. Comparison of efficacy between the two groups cases (%)

curative effect	Observation group (n=30)	Control group (n=30)	X^2	P
CR	5 (16.67)	2 (6.67)	-	-
PR	13 (43.33)	8 (26.67)	-	-
SD	9 (30.00)	14 (46.67)	-	-
PD	3 (10.00)	6 (20.00)	-	-
Objective response	18 (60.00)	10 (33.33)	4.286	0.038

CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease.

Table 3. Comparison of KPS scores between the two groups ($\bar{x}$ ± s, points)

Time	Observation group (n=30)	Control group (n=30)	T	P
Pre treatment	63.52±3.18	64.30±3.27	0.937	0.353
Post treatment	84.78±4.65*	76.43±4.07*	7.401	<0.001

Note: Compared with before treatment, *$P<0.05$. KPS: Karnofsky Functional Status.

Comparison of two groups' KPS score

Both groups' KPS scores increased after treatment compared with those pretreatment ($P<0.05$). The post-treatment KPS score in observation group was higher than that in the control group ($P<0.05$) (**Table 3**).

Comparison of toxic and side effects

In the observation group, 5 cases had bone marrow transplantation (16.67%), 8 patients had abnormal liver or kidney function (26.67%), 13 had gastrointestinal reactions (43.33%) and 6 had fatigue (20.00%). In the control group, there were 3 cases of bone marrow transplantation (10.00%), 5 cases of abnormal liver and kidney (16.67%), 10 cases of gastrointestinal reaction (33.33%) and 4 cases of fatigue (13.33%). The two groups' had insignificant difference in toxic side effects (P>0.05) (**Table 4**).

Comparison of serum VEGF and COX-2

The post-treatment VEGF and COX-2 were lower than those pre-treatment in both groups ($P<0.05$). Also, after treatment, the levels in the observation group were lower than those in the control group ($P<0.05$) (**Figure 1**).

Comparison of VEGF and COX-2 protein expressions

The post-treatment levels of VEGF and COX-2 protein expressions dropped in both groups compared with pre-treatment ($P<0.05$). The levels after treatment were lower in the observation group than those in the control group ($P<0.05$) (**Figure 2**).

Survival analysis

The survival analysis of the two groups showed that the observation group had better survival than the control group (X^2=4.306, P=0.038) (**Table 5** and **Figure 3**).

Discussion

High metastasis and recurrence are the primary causes that impact the prognosis of HCC. It has been reported that the 5-year recurrence

Table 4. Comparison of toxic side effects between the two groups cases (%)

toxic and side effects	Observation group (n=30)	Control group (n=30)	χ^2	*P*
Myelosuppression	5 (16.67)	3 (10.00)	0.144	0.704
Hepatorenal Disorders	8 (26.67)	5 (16.67)	0.884	0.347
Gastrointestinal Reaction	13 (43.33)	10 (33.33)	0.635	0.426
Fatigue	6 (20.00)	4 (13.33)	0.480	0.488
Total	21 (70.00)	17 (26.67)	1.148	0.284

Note: In the observation group, 2 patients had 3 kinds of adverse reactions at the same time, and 7 patients had 2 kinds of adverse reactions at the same time; 1 patient in the control group had 3 kinds of adverse reactions at the same time, and 3 patients had 2 kinds of adverse reactions at the same time.

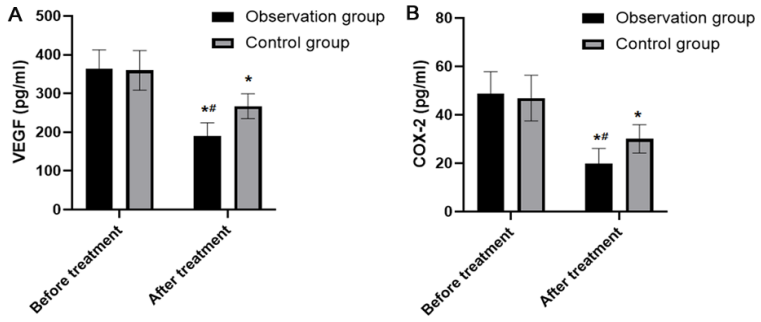

Figure 1. Comparison of serum VEGF and COX-2 levels between the two groups. A: Serum VEGF expression before and after treatment; B: Serum COX-2 expression before and after treatment. Note: Compared with before treatment, *P<0.05; compared with the control group, #P<0.05. VEGF: Vascular Endothelial Growth Factor; COX-2: Cyclooxygenase-2.

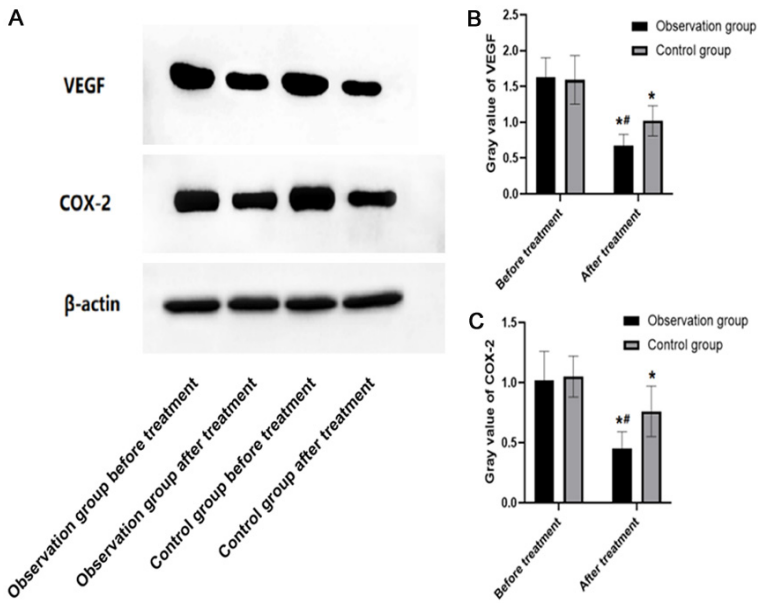

Figure 2. Protein expression of VEGF and COX-2. A: Expression of VEGF and COX-2 in PBMCs; B: Gray value histogram of VEGF protein; C: Gray value histogram of COX-2 protein. Note: Compared with before treatment, *P<0.05; compared with the control group, #P<0.05. VEGF: Vascular Endothelial Growth Factor; COX-2: Cyclooxygenase-2.

of HCC after radical resection is 54.1% to 61.5%, and the recurrence rate of metastasis after local treatment is even higher [14].

According to this study, the total response rate of the observation group was higher than that of the control group, which indicated that concurrent chemoradiotherapy could help to improve patients' short-term efficacy. The post-treatment KPS score of the observation group was also higher than that of the control group, demonstrating that concurrent chemoradiotherapy could improve patients' quality of life. The survival of the observation group was better than that of the control group, which suggesting that concurrent chemoradiotherapy could improve the survival rate of patients. Our findings are similar to a previous study [15], which found that compared with single chemotherapy, concurrent chemoradiotherapy could effectively improve patients' clinical efficacy. Although the adverse reactions may be improved, the difference was not significant.

Concurrent chemoradiotherapy can kill tumor cells to the greatest extent and inhibit tumor progression, thereby prolonging the survival of patients. Tumor angiogenesis is a major cause of tumor progression. When the tumor is inactive, it is usually a small lesion and will not metastasize [16]. However, as the disease progresses, the angiogenic phenotype will be activated, following a phase of strong angiogenic activity, also known as the vascularization phase [17]. VEGF, a common clinical angiogenic factor, is involved in the occurrence and progress of tumors.

Table 5. Comparison of 1-year survival rates between the two groups

Group	Number of Cases	Survival rate (%)
Observation group	30	25 (83.33)
Control group	30	18 (60.00)
χ^2	-	4.022
P	-	0.045

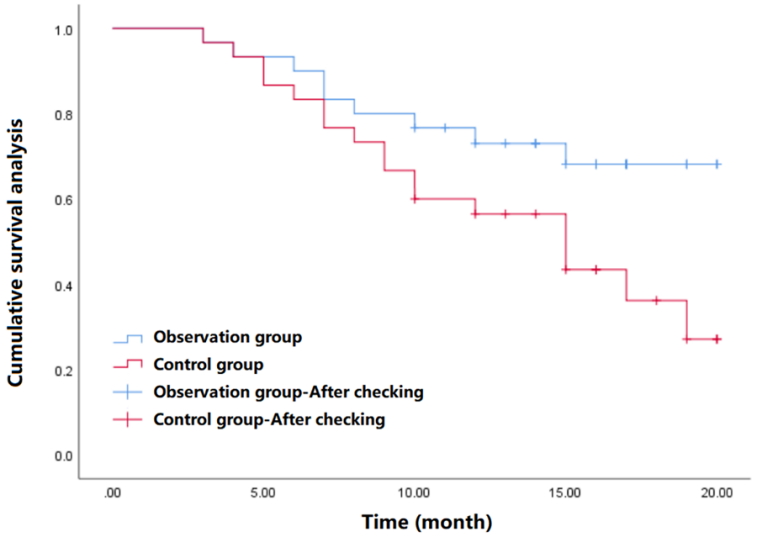

Figure 3. Comparison of survival between the two groups. The survival of the observation group was better than that of the control group (*P<0.05*).

Its expression increases remarkably when tumors occur, and it promotes tumor metastasis [18]. COX-2 is a rapid response gene with inducible expression, and it is involved in processes such as inflammatory response and tumor progression. COX-2 can inhibit tumor cell apoptosis, reduce immunity, and ultimately lead to accelerated angiogenesis and tumor metastasis [19]. This study demonstrated that the post-treatment serum levels and gray values of VEGF and COX-2 in the observation group were lower than those in the control group, suggesting that concurrent chemoradiotherapy could down-regulate VEGF and COX-2 expression. Therefore, we believe that concurrent chemoradiotherapy can effectively inhibit tumor neovascularization, promote the apoptosis of tumor cells, and inhibit the further metastasis of tumors. This might also be one of the internal mechanisms of how concurrent chemoradiotherapy improved clinical efficacy.

However, the sample size included in this study is small, and the research results, especially the comparison of adverse reactions, may be biased. Partial scholars believe that compared with chemotherapy alone, concurrent chemoradiotherapy has a higher incidence of adverse reactions in patients [20]. According to this study, however, we found that there was no significant difference in the incidence of adverse reactions between the two groups, which may be related to the small sample size. Thus, the sample size needs to be expanded to acquire more reliable clinical data in future studies.

In conclusion, concurrent chemoradiotherapy can lead to a good prognosis for metastatic and recurrent HCC. It can improve the quality of life in patients and down-regulate VEGF and COX-2 expression.

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Disclosure of conflict of interest

None.

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