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Original Article

Clinical value of prophylactic transcatheter arterial chemoembolization treatment in patients with hepatocellular carcinoma

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Abstract: Objective: To investigate the feasibility of surgical resection combined with prophylactic transcatheter arterial chemoembolization (TACE) in reducing the recurrence and improving the survival rate of patients with hepatocellular carcinoma (HCC). Methods: In this retrospective study, 76 patients with HCC treated in our hospital from February 2016 to December 2018 were enrolled. Among them, 31 patients who received radical surgery alone were enrolled as the control group, and 45 patients who received prophylactic TACE within 6 months after radical surgery were enrolled as the study group. All cases were followed up for 36 months. The recurrence rate, survival rate, and median survival time of patients at 1, 2, and 3 years after surgery were compared between the two groups. Patients in the study group were divided into subgroup A (interventional therapy within 1 month), subgroup B (interventional therapy within 1-2 months), subgroup C (interventional therapy within 2-3 months), and subgroup D (interventional therapy within 3-6 months). The recurrence rate within 1 year was compared among the four subgroups. Finally, the clinical indicators affecting the recurrence of HCC were analyzed. Results: The recurrence rate at 1, 2 and 3 years after surgery in the study group was lower than that in the control group (all $P<0.05$). The survival rate at 1, 2 and 3 years after surgery in the study group was higher than that in the control group (all $P<0.05$). The median survival time of patients in the study group was slightly higher than that in the control group, with no significant difference ($P>0.05$). The 1-year recurrence rate of patients in subgroups A and B was significantly lower than that in subgroups C and D ($P<0.05$). The incomplete envelope, tumor diameter ≥5 cm, and combined cirrhosis were the main causes of recurrence of HCC ($P<0.05$). Conclusion: Prophylactic TACE significantly reduced the postoperative recurrence rate and improved the survival rate of patients with HCC. The optimal treatment efficacy was associated with interventional therapy within 1-2 months after surgery, while incomplete envelope, tumor diameter ≥5 cm, and combined cirrhosis were the high-risk factors for HCC recurrence.

Keywords: Surgical resection, hepatocellular carcinoma, interventional therapy, recurrence rate, survival rate

Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer [1], which can be divided into primary liver cancer and metastatic liver cancer according to its development origin, among which primary liver cancer is more common. Data show that the incidence of HCC ranks the fifth in malignant tumors and the third in mortality [2]. Epidemiological surveys show that there are more than 600,000 new cases of liver cancer worldwide each year, accounting for 5.6% of all cancer cases. A survey has indicated that there are about 350,000 cases of liver cancer in China, accounting for 11.6% of cancer cases [3, 4]. With the change of lifestyle and dietary habits, the incidence of liver cancer has been increasing annually, seriously threatening the life and health of patients. The main causes of liver cancer include viral infection, alcohol consumptions, water pollution, and immune diseases. Its clinical manifestations mainly include liver pain, fever, and emaciation. Patients with advanced liver cancer are often accompanied by hepatic encephalopathy and liver and kidney failure [5].

At present, the treatment modalities of liver cancer include biological repair, surgical treatment, and systemic treatment, among which radical resection is the most commonly used surgical treatment and it has good efficacy for all kinds of liver cancer [6, 7]. However, in clinical practice, most patients with HCC have high recurrence rate and poor prognosis after radical resection [8]. It has been found that postoperative prophylactic interventions for HCC can aid in killing tumor cells as well as residual tumor cells, thus reducing the recurrence rate [9]. Transcatheter arterial chemoembolization (TACE) refers to the therapeutic measures in which a catheter is inserted selectively or super-selectively into the target artery of the tumor blood supply, and then a mixture of chemotherapy agent and lipiodol emulsifier is injected at an appropriate speed to occlude the target artery, thus blocking the blood supply to tumor cells and ultimately leading to ischemic necrosis or inhibiting tumor growth. Previous studies have pointed out that targeted injection can concentrate the chemotherapy drugs in the local tumor 10-100 times higher than systemic administration, thus exerting high concentration and lasting chemotherapy effect, and the local injection of drugs can minimize the damage to the normal cells with a higher safety [10]. At present, TACE has been widely used in the treatment of HCC, which plays a positive role in improving the clinical symptoms of patients and prolonging their survival. However, there are few studies related to the prophylactic TACE for patients with HCC. In this study, we found that prophylactic TACE after hepatectomy significantly reduced postoperative recurrence rate and improved survival rate in patients with HCC.

Materials and methods

Baseline data

In this retrospective analysis, 76 patients with HCC treated in our hospital from February 2016 to December 2018 were enrolled. Among them, 31 patients who received radical surgery alone were included as the control group, and 45 patients who received prophylactic TACE within 6 months after radical surgery were enrolled as the study group.

Inclusion criteria: (1) patients with HCC that were diagnosed by pathological, histological or cytological diagnosis; (2) patients with HCC that were confirmed by imaging tools; and (3) patients with complete medical records.

Exclusion criteria: (1) patients with psychiatric disorders; (2) patients with systemic infections; (3) patients with expected survival ≤6 months; (4) patients with other malignant tumors; and (5) patients with severe organ dysfunction.

The study was approved by the Ethics Committee of Xingtai People's Hospital, and patients' privacy was well protected during the use of patient data.

Intervention methods

Patients in the study group received radical surgery followed by prophylactic TACE, while those in the control group received radical surgery alone. Patients in both groups underwent preoperative routine examinations, cardiopulmonary functional assessments, and preoperative routine preparations. In the control group, patients underwent open hepatic tumor resection under general anesthesia before surgery. The abdominal cavity was explored to search for tumors, and then regular lobectomy, segmental resection or irregular hepatectomy was performed by hepatobiliary surgeons in our hospital. Patients in the study group received radical resection of liver cancer in the same way as those in the control group. After surgery, the Seldinger method was used to implement preventive interventional therapy. The specific measures were as follows: After routine disinfection of the surgical area and local disinfection of the puncture site, a 5F arterial catheter was placed under the guidance of DSA, and the location, number and size of the tumor blood supply arteries were determined by angiography, and then the chemotherapy agents including pirarubicin (Hanhui Pharmaceuticals Company Limited, article no. ZW210301) 20-40 mg, carboplatin (Qilu Pharmaceutical Co., Ltd., approval No. H10920028) 200-300 mg, hydroxycamptothecin (Harbin Medisan Pharmaceutical Co., Ltd., approval No. H20044498) 5-10 mg, mitomycin (Jiangsu Hengrui Medicine Co., Ltd., approval No. H20023070) 4-10 mg, and iodine glycerin (Beijing Haiderun Pharmaceutical Co., Ltd., approval No. H11021298) and 20-40 mg were injected into the targeted arteries through the catheter. The perfusion process was slow, and the presence of arterio-

Table 1. Comparison of baseline data ($\chi \pm s$)/[n (%)]

General data		Study group (n=45)	Control group (n=31)	t/X^2	*P*
Gender	Male	25	16	0.115	0.735
	Female	20	15		
Mean age (years)		43.26 ± 3.26	43.01 ± 3.66	0.347	0.729
Mean weight (kg)		65.49 ± 4.33	65.19 ± 4.56	0.32	0.75
Mean disease duration (years)		1.09 ± 0.23	1.13 ± 0.19	0.856	0.394
Child-Pugh classification	A	30	20	0.038	0.846
	B	15	11		

venous fistula in the tumor was regarded. In case of arteriovenous fistula, drug injection was suspended, gelatin sponge was injected through the catheter, and drug infusion was continued after the fistula was closed; after the completion of infusion, the catheter was removed and the puncture site was bandaged and immobilized. Patients in the study group were followed up for 1 month after TACE to determine whether there was tumor recurrence and evaluate whether the targeted blood vessels were completely embolized with lipiodol. In case of residual lesions, TACE treatment was performed again according to the patient's liver function and tolerance (finally, of the patients in the study group, 12 received TACE once, 15 received TACE twice, and 11 received TACE more than three times). Patients in both groups were followed up after surgery, and regular examinations including liver function, blood samples, chest X-ray and CT were checked to observe the presence of recurrent or metastatic lesions.

Outcome measurements

The effect of interventional therapy on the recurrence rate and survival rate: The recurrence rate and survival rate were calculated and compared between groups.

The timing of interventional therapy on recurrence rate: Patients in the study group were divided into four subgroups according to the timing of receiving preventive interventions: subgroup A (n=11, within 1 month), subgroup B (n=10, within 1-2 months), subgroup C (n=12, within 2-3 months), and subgroup D (n=11, within 3-6 months), and the recurrence rates of patients in the four subgroups were compared at 1 year after surgery.

Analysis of factors influencing recurrence of HCC: The age, gender, liver function, presence of cirrhosis, tumor size, intact envelope and other clinical indicators of the 75 patients with HCC were counted, and the correlation between the above indicators and recurrence of HCC was analyzed.

Statistical methods

In this study, IBM SPSS Statistics 22.0 was utilized for data processing and analysis. The count data (%) were examined using chi-square test, while the measurement data ($\bar{x} \pm s$) were examined using t-test. The postoperative survival rate of the two groups was analyzed using Kaplan-Meier curve, the risk factors for HCC recurrence were analyzed using Cox regression model for univariate and multifactor analysis, and F test was used for comparison of differences among multiple groups. GraphPad Prism 8.0 was used for image rendering. $P<0.05$ indicated a significant difference [11].

Results

Comparison of baseline data between the two groups

Baseline data such as gender, age, disease duration, and Child-Pugh classification of liver function [12] were compared between the two groups, and the differences between the two groups were not statistically significant ($P> 0.05$), suggesting that the two groups were comparable (**Table 1**).

Comparison of recurrence rate between the two groups

The recurrence rate of patients in the study group was lower than that of patients in the

Table 2. Comparison of recurrence rate at 1, 2 and 3 years after surgery between the two groups [n (%)]

Group	Number of cases	1 year postoperatively	2 year postoperatively	3 year postoperatively
Study group	45	2 (4.44)	6 (13.33)	10 (22.22)
Control group	31	6 (19.35)	10 (32.26)	14 (45.16)
X^2	-	4.333	3.955	4.47
P	-	0.037	0.047	0.034

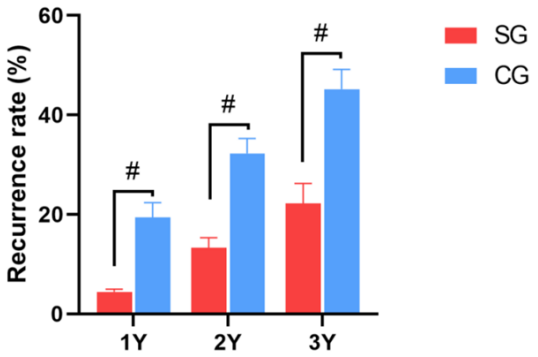

Figure 1. Comparison of recurrence rate between the two groups of patients at 1, 2 and 3 years after surgery. Compared with the control group, #P<0.05. t-test was applied.

control group at 1, 2 and 3 years after surgery (P<0.05) (**Table 2** and **Figure 1**).

Comparison of survival rate between the two groups

The survival rate at 1, 2 and 3 years after surgery in the study group was significantly higher than that in the control group (P<0.05) (**Table 3** and **Figure 2**).

Comparison of median survival time between the two groups

The median survival time of patients in the study group was (32.09 ± 0.51) months, while that of patients in the control group was (31.55 ± 0.66) months, and the difference between the two groups was not statistically significant (P>0.05).

Effect of interventional timing on recurrence rate of HCC

The overall difference in the recurrence rate among the four subgroups was statistically significant (P<0.05). There was no significant difference between subgroups A and B (P>0.05), but the recurrence rate of subgroups A and B was significantly lower than that of subgroups C and D (P<0.05) (**Table 4** and **Figure 3**).

Factors influencing postoperative recurrence

Patients' age, gender, tumor site, and liver function grade had no correlation with postoperative recurrence of HCC (P>0.05), while incomplete envelope, tumor diameter ≥5 cm, and combined cirrhosis were correlated with recurrence of HCC (P<0.05) (**Table 5**).

Discussion

Liver cancer is a common malignant tumor threatening human health [13]. Statistical data show 790,000 new cases of liver cancer were reported worldwide in 2013. The incidence of liver cancer is correlated with regions, especially in China, with a high incidence of 27.04/100,000 and it has an increasing annual trend [14, 15]. The risk of liver cancer increases over time [16]. With aging of the population in China, it is foreseeable that liver cancer will become an important factor affecting the economic and social development of China [17]. At present, the treatment options include: (1) radical surgical excision; (2) non-surgical treatment: (i) endovascular interventional therapy, i.e. hepatic artery chemoembolization; (ii) extravascular interventional therapy, including radiofrequency ablation, microwave ablation, cryotherapy, and hyperthermia treatment; (3) other therapies, including biological therapy, hormone therapy, and traditional Chinese medicine therapy [18]. Among the above modalities, radical surgery is still the primary option. However, only about 20% of all HCC patients can undergo radical surgery, and the postoperative recurrence rate of HCC is high, which may be related to various factors such as the scope of resection, levels of tumor markers, and immune function [19]. The recurrence of HCC is more difficult to treat and can cause secondary damage to patients physically and mentally. Therefore, how to take preventive measures to

Table 3. Comparison of survival rate at 1, 2 and 3 years after surgery between two groups [n (%)]

Group	Number of cases	1 year postoperatively	2 year postoperatively	3 year postoperatively
Study group	45	44 (97.78)	40 (88.89)	35 (77.78)
Control group	31	26 (83.87)	21 (67.74)	13 (41.94)
X^2	-	4.882	6.429	10.134
P	-	0.027	0.023	0.001

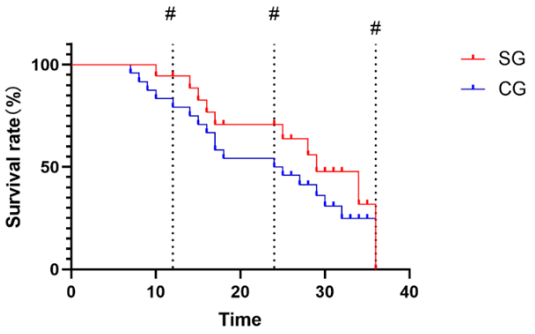

Figure 2. Comparison of survival rate between the two groups at 1, 2 and 3 years after surgery. Compared with the control group, #P<0.05. Chi-square test was applied.

reduce the recurrence rate of HCC has become a crucial problem for medical workers.

Preventive interventional therapy refers to inducing tumor necrosis by blocking the blood supply after radical surgery, or infusing chemotherapeutic drugs through the tumor blood supply artery to kill tumor cells, which is more targeted than traditional chemotherapy and less damaging to other organs of the body. A previous study [20] found that the recurrence rate in 79 patients after 1 year was 13.9%, among which the recurrence rate of patients with prophylactic transhepatic artery chemoembolization was 12.2% and the tumor-free survival was (21.6 ± 1.5) months, and the recurrence rate of transhepatic artery chemoinfusion was 15.8% and the tumor-free survival was (17.4 ± 3.0) months; the difference between the two groups was not significant, and scholars believed that both of the above-mentioned modalities can reduce the recurrence rate of HCC after surgery and improve the survival rate of patients. Another study [21] found that the median survival time, survival rate and mean survival of patients in the observation group who underwent combined interventional therapy were higher than those in the control group, and scholars indicated that interventional therapy could reduce the incidence of postoperative complications and prolong the survival of patients with liver cancer.

In this study, the recurrence rate of patients in the study group who received interventional therapy at 1, 2, and 3 years after surgery was lower than that of patients in the control group, and the median survival time of patients in the study group was also higher than that in the control group. The liver is an organ with abundant blood flow, and with the proliferation of cancer cells, the secretion of cell adhesion factors increases and enters the blood and surrounding organs, providing conditions for the regrowth of malignant tumors [22]. It has also been found that cancer cells show invasive growth in the liver and are prone to form microsatellite lesions, so that the boundaries between the lesions and surrounding organs are unclear, and it is difficult to remove the lesions completely during radical surgery on the one hand, and on the other hand, the extrusion of the lesions is prone to dislodge the cancer emboli and cause the lesions to metastasize, thus leading to higher recurrence rate after radical surgery and lower postoperative survival rate of patients [23]. In contrast, interventional therapy can prevent the regeneration of tumor cells in two ways. First, it infuses chemotherapeutic drugs into the vasculature of the lesion to completely kill malignant cells, and it was found that the concentration of chemotherapeutic drugs in the liver tissue is about 400 times that of the systemic concentration in interventional therapy, and the concentration of drugs in the lesion is 10 times higher than that in the liver [24], which can kill malignant cells while reducing systemic toxic reactions. Second, the blood supply to the lesion is blocked by applying iodine oil to further stimulate the fibrosis necrosis and shrinkage of the tumor. It was demonstrated that more than 75% of the blood supply to the liver cancer lesion comes from the hepatic artery, and

Table 4. Effect of different interventional timing on the recurrence rate of liver cancer

Recurrence status 1 year after surgery	Time of initial postoperative intervention			
	Subgroup A	Subgroup B	Subgroup C	Subgroup D
Recurrence	1	1	4	5
Non-recurrence	10	9	8	6
Total	11	10	12	11
Recurrence rate	9.09%	10.00%*	33.33%#	45.45%#

Note: Compared with subgroups A and group B, #P=0.033, 0.022, compared with subgroup A, *P=0.943.

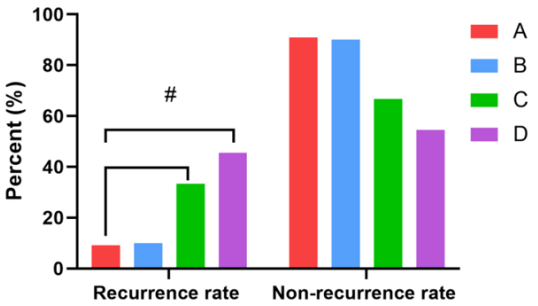

Figure 3. Effect of different timing of intervention on the recurrence rate. Compared with subgroup A, #P<0.05. Chi-square test was applied.

blocking the hepatic artery can substantially reduce the blood supply to the lesion and accelerate the necrosis of malignant cells [25]. The results of this study also showed that the recurrence rate of HCC in patients who received interventional therapy 1-2 months after surgery was significantly lower than that of patients who received interventional therapy 3-4 months after surgery. It is believed that liver tissue has a strong regenerative ability and will undergo significant compensatory hyperplasia under the stimulation of surgical resection, and the structure and function of the residual liver can generally be restored to a greater extent in about 1 month. Therefore, the degree of liver function damage is relatively smaller when TACE treatment is implemented at this time. However, the early implementation of interventional therapy after surgery will also cause greater damage to the liver function of the patient. Scholars suggest that interventional therapy is best performed 4-6 weeks after surgery. The reason is that the patient's immune function has basically recovered at this time, and the remaining cancer cells are in the stage of rapid proliferation, and the killing effect of the drug can be maximized [26], which is consistent with the results of this study.

Finally, the results also showed that incomplete envelope, tumor diameter ≥5 cm, combined cirrhosis were closely correlated with the recurrence of HCC. The reasons are as follows: (1) lesions with incomplete or absent envelope have a higher chance of cell proliferation, which makes resection of the lesion more difficult and prone to recurrence; (2) lesions with larger tumor diameter have a higher risk of microscopic lesions; (3) generally, liver cancer often occurs on the basis of cirrhosis, and for patients with cirrhosis, although the lesions are removed, the proliferation of liver cancer cells has not been eliminated, and the hepatocytes integrated by hepatitis virus still have a higher chance of mutation, thus the recurrence is high.

In conclusion, interventional therapy after hepatectomy can significantly reduce the postoperative recurrence rate and improve the survival rate of patients with HCC, and the best timing for interventional therapy is 1-2 months after surgery, and incomplete envelope, tumor diameter ≥5 cm, and combined cirrhosis are the high-risk factors for recurrence of HCC. The innovation of this study lies in the focus on the prognostic factors of liver cancer patients and the effect of postoperative prophylactic TACE on the prognosis of patients with liver cancer by means of controlled analysis, which can provide better clinical data to support the improvement of quality of life of patients with liver cancer. The shortcoming of this study lies in the incomplete analysis of factors influencing postoperative recurrence of HCC patients. This study was a retrospective analysis and the data of the included patients had certain limitations. The next step is to conduct a prospective analysis to address this shortcoming and to demonstrate in detail the risk factors influencing postoperative recurrence of HCC patients.

Table 5. Analysis of factors influencing recurrence after liver cancer surgery

Factors		Number of cases (n=76)	Number of recurrence cases			*F*	*P*
			1 year	2 years	3 years		
Gender	Male	42	5	9	14	0.086	0.958
	Female	34	3	7	10		
Age	≥40 years old	46	5	10	13	0.842	0.342
	<40 years	30	3	6	11		
Tumor site	Left liver	25	3	11	16	2.578	0.276
	Right liver	51	5	5	8		
Liver function classification	A	50	6	11	17	0.266	0.875
	B	26	2	5	9		
Tumor diameter	Less than 5 cm	26	1	12	20	14.448	0.001
	≥5 cm	50	7	4	4		
Envelope condition	Complete	30	1	3	5	4.598	0.025
	Incomplete	46	7	13	19		
Combined cirrhosis	Yes	51	6	14	20	5.036	0.021
	No	25	2	2	4		

Disclosure of conflict of interest

None.

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