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• LIVER CANCER •

Postoperative adjuvant arterial chemoembolization improves survival of hepatocellular carcinoma patients with risk factors for residual tumor: A retrospective control study

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Abstract

AIM: To evaluate the effect of postoperative adjuvant transcatheter arterial chemoembolization (TACE) on the prognosis of hepatocellular carcinoma (HCC) patients with or without risk factors for the residual tumor.

METHODS: From January 1995 to December 1998, 549 consecutive HCC patients undergoing surgical resection were included in this research. There were 185 patients who underwent surgical resection with adjuvant TACE and 364 patients who underwent surgical resection only. Tumors with a diameter more than 5 cm, multiple nodules, and vascular invasion were defined as risk factors for residual tumor and used for patient stratification. Kaplan-Meier method was used to analyze survival curve and Cox proportional hazard model was used to evaluate the prognostic significance of adjuvant TACE.

RESULTS: In the patients without any risk factors for the residual tumor, the 1-, 3-, 5-year survival rates were 93.48%, 75.85%, 62.39% in the control group and 97.39%, 70.37%, 50.85% in the adjuvant TACE group, respectively. There was no significant difference in the survival between two groups (P = 0.3956). However, in the patients with risk factors for residual tumor, postoperative adjuvant TACE significantly prolonged the patients' survival. There was a statistically significant difference in survival between two groups (P = 0.0216). The 1-, 3-, 5-year survival rates were 69.95%, 49.86%, 37.40% in the control group and 89.67%, 61.28%, 44.36% in the adjuvant TACE group, respectively. Cox proportional hazard model showed that tumor diameter and cirrhosis, but not the adjuvant TACE, were the significantly independent prognostic factors in the patients without risk factors for residual tumor. However, in the patients with risk factors for residual tumor adjuvant TACE, and also tumor diameter, AFP level, vascular invasion, were the significantly independent factors associated with the decreasing risk for patients' death from HCC.

CONCLUSION: Postoperative adjuvant TACE can prolong the survival of patients with risk factors for residual tumor, but can not prolong the survival of patients without risk factors for residual tumor.

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INTRODUCTION

Hepatocellular carcinoma is the fifth most common malignant death in the world and is estimated to cause half a million deaths annually[1]. In China, primary liver cancer mortality ranked second after stomach cancer. The age-standardized mortality rate (adjusted by the world population) was 33.7 per 100 000 in male Chinese and 12.3 per 100 000 in female Chinese[2]. Surgical resection is a major treatment for hepatocellular carcinoma (HCC)[3]. However, postoperative recurrence is still high and the main death cause after resection of HCC[4]. The overall recurrence was 30.1%, 62.3% and 79.0% in 1, 3, 5 years after resection of HCC, respectively[5]. Adjuvant therapies were used to prolong the survival and decrease the recurrence of HCC in different centers, such as transcatheter arterial chemoembolization (TACE)[6-13], polyprenoic acid[14], adoptive immunotherapy[15], interferon[16], and iodine-131-labeled lipiodol[17-19]. TACE was one of the most commonly used adjuvant managements for preventing recurrence and prolonging the survival of patients postoperatively. However, the benefits of adjuvant TACE were controversial. From January 1995 to December 1998, a consecutive series of 549 HCC patients with partially hepatectomy were included in this study. Of them, 185 patients received adjuvant TACE and 364 patients received surgical resection only. The aim of this research was to evaluate the benefits of adjuvant TACE in our series and to determine whether the characteristics of HCC such as diameter of tumor size, tumor nodules and vascular invasion could affect the benefits of adjuvant TACE to the patients' survival.

MATERIALS AND METHODS

Patients

This study included 549 patients with HCC who underwent partial hepatectomy. The entry criteria included: 1) All the tumor lesions were removed, which were judged by surgeon's gross inspection; 2) no lymphonode involvement; and 3) no distant metastasis. For all the 549 patients, hepatectomy was performed in Liver Cancer Institute, Zhonghan Hospital, Fudan University from January 1995 to December 1998. There were 465 males and 84 females with a median age of 50 years. According to the UICC TNM classification, 48 patients were in stage I, 382 in stage II, 86 in stage IIIA, and 33 in stage IVA. For their liver function defined by Child-Pugh classification, 539 patients were in class A, 10 in class B, and no patients in class C.

Adjuvant TACE

In the entire series, 185 patients underwent adjuvant TACE and 364 patients who did not undergo adjuvant TACE were assigned as control. Adjuvant TACE was performed 2 mo after hepatectomy. Hepatic arterial angiography was performed and then preventive or therapeutic chemoembolization was done depending on the patients with or without tumor stain in the remnant liver, respectively. The regimen for preventive adjuvant TACE consisted of 5-fluorouracil (5-FU) 0.75 g, cisplatin (DDP) 60 mg, and the emulsion mixed with mitomycin C (MMC) 16 mg and lipiodol 5 mL. Two months later a repeated preventive adjuvant TACE was performed and the regimen was finished. For therapeutic adjuvant TACE, the regimen consisted of 5-FU 1.0 g, DDP 80 mg, and the emulsion of MMC 20 mg and lipiodol 5-10 mL (the volume of lipiodol used for a patient depending on the tumor volume in the patient). TACE was repeated every one and a half month. The interval and times of repeated TACE depended on the response of the patients.

Patient stratification and grouping

The patients were retrospectively stratified into patients without risk factors for the residual tumor and patients with any risk factors for the residual tumor. These risk factors were evaluated according to preoperative ultrosonography, CT scan and postoperative pathological examination. Risk factors were defined as tumor diameter >5 cm, multiple nodules or vascular invasion. These factors were reported to have a close relation with residual tumor or recurrence in the remnant liver of HCC patients[4,20-23]. After stratification, there were 251 patients without risk factors for the residual tumor and 298 patients with risk factors for the residual tumor. After stratification, the patients were further grouped as the adjuvant TACE group and the control group.

Follow-up and statistics

The patients were followed up every 2 to 3 mo with ultrasonography and alpha-fetoprotein (AFP) during the first 2 years after HCC resection and every 3-6 mo afterwards. If the patients were unable to undergo this procedure, they were followed up with telephone or letter every year. The follow-up termination time for all patients was December 31, 2002. The significance of differences in clinical and pathological characteristics between groups was examined with Chi-square test and Student *t* test. Cumulative survival rates were obtained by the Kaplan-Meier method. Cumulative survival comparison between groups was performed with log-rank test. Multivariate analysis for the independent prognostic factors was determined by Cox proportional hazards model. *P* values <0.05 were considered statistically significant.

RESULTS

Clinical and pathological characteristics of adjuvant TACE and control groups

Clinical and pathological characteristics of the patients with or without risk factors for residual tumor in adjuvant TACE and control groups were summarized in Tables 1 and 2, respectively. There were no significant differences in their age, HBsAg positive rate, Child-Pugh class, AFP level, TNM class between two groups, except that the ratio of female *vs* male patients was lower in the adjuvant TACE group than that in control group ($P = 0.005$) without risk factor for residual tumor.

Survival of patients in adjuvant TACE group and control group

Figure 1A presents the Kaplan-Meier survival analysis comparing the patients in control group and adjuvant TACE group without risk factors for the residual tumor. There were no differences in their survival curves between two groups ($P = 0.3956$). The 1-, 3-, 5-year survival rates were 93.48%, 75.85%, 62.39% in the control group and 97.39%, 70.37%, 50.85% in the adjuvant TACE group, respectively. However, for the patients with risk factors for the residual tumor improved survival rates were observed in the adjuvant TACE group, as showed by Figure 2B. There were significant differences between two groups ($P = 0.0216$). The 1-, 3-, 5-year survival rates were 69.95%, 49.86%, 37.40% in the control group and 86.67%, 61.28%, 44.36% in the adjuvant TACE group.

Table 1 Clinical and pathological characteristics in control and adjuvant TACE groups patients without risk factors for residual tumor

Characteristics	Control (n = 174)	Adjuvant TACE group (n = 77)	P value
Gender			
Female	34	5	0.009
Male	140	72	
Age (mean±SD)	50.86±11.61	49.35±10.04	0.323
HBsAg			
Positive	43	11	0.135
Negative	131	66	
Cirrhosis			
Absent	22	6	0.130
Mild	53	33	
Severe	99	38	
Child-pugh Class			
A	165	77	0.134
B	5	0	
AFP (mean±SD, ug/L)	333.91±529.92	406.04±735.16	0.381
TNM classification			
I	28	19	0.108
II	146	58	

Table 2 Clinical and pathological characteristics in control and adjuvant TACE groups patients with risk factors for residual tumor

Characteristics	Control (n = 190)	Adjuvant TACE group (n = 108)	P value
Gender			
Female	33	12	0.147
Male	157	96	
Age (mean±SD)	51.50±11.72	49.63±10.07	0.105
HBsAg			
Positive	47	27	0.588
Negative	143	81	
Cirrhosis			
Absent	41	24	0.563
Mild	69	45	
Severe	80	39	
Child-pugh Class			
A	187	106	0.860
B	3	2	
AFP (mean±SD, ug/l)	501.39±807.14	518.25±707.99	0.856
TNM classification			
II	113	66	0.926
IIIA	55	31	
IVA	22	11	

Multivariates analysis

Cox proportional hazards models were constructed to predict the survival of the patients with adjuvant TACE and other variables including sex, age, HBsAg, cirrhosis, Child-Pugh class, AFP levels, tumor diameter, tumor nodules, and vascular invasion. In the patients without risk factors for residual tumor, the tumor diameter and cirrhosis were statistically significant independent factors associated with an increased risk of death from HCC, but adjuvant TACE had no effect on the survival of patients (Table 3). However, in the patients with risk factors for residual tumor, adjuvant TACE was statistically significant independent factor associated with a decreased risk of the death of patients with HCC. Tumor diameter, AFP level and vascular invasion were significantly independent factors associated with death of patients with HCC (Table 4). These results indicated that adjuvant TACE could improve the survival of patients with risk factors for residual tumor, but did not affect the survival of patients without risk factors for residual tumor.

Table 3 Multivariate Cox proportional hazard analysis to evaluate independent variables in patients without risk factors for residual tumor

Variables	B	Wald	Significance	HR	95% CI lower	upper
Cirrhosis Absent = 1 Mild = 2 Severe = 3	0.689	14.443	0.000	1.991	1.396	2.841
Tumor diameter (cm)	0.235	6.019	0.014	1.264	1.048	1.525

Table 4 Multivariate Cox proportional hazard analysis to evaluate independent variables in patients with risk factors for residual tumor

Variables	B	Wald	Significance	HR	95% CI lower	upper
AFP (μg/L) <20 = 1 21-400 = 2 >400 = 3	0.212	5.333	0.021	1.236	1.033	1.480
Adjuvant TACE Without = 1 With = 2	-0.406	6.041	0.014	0.666	0.482	0.921
Tumor diameter (cm)	0.076	16.327	0.000	1.079	1.040	1.119
Vascular invasion Absent = 1 Present = 2	0.245	7.691	0.006	1.278	1.075	1.520

DISCUSSION

The frequent postoperative recurrence was a main obstacle for long survival after resection of HCC and intrahepatic metastasis was thought to have a close relation with the postoperative recurrence[24]. However, it is difficulty to detect the minimal intrahepatic metastasis before or during operation and the existence of this minimal intrahepatic metastasis contributes to intrahepatic recurrence. Theoretically, treatment of this minimal intrahepatic metastasis should play an important role in preventing of postoperative recurrence of HCC. However, though TACE has been widely used in unresectable HCC patients[25-27], the clinical trial showed there was no confirmed evidence supporting the benefits of adjuvant TACE to patients with resectable HCC[6]. Tanaka and Izumi showed that postoperative adjuvant TACE improved the survival of HCC patients[28,29]. The patients selected in their clinical trials had advanced stages (TNM III or TNM IV) or characteristics of uncompleted encapsulated, intrahepatic metastasis, or vascular invasion which was thought to have a close relation with residual tumor and earlier massive recurrence[22,30]. For these patients postoperative adjuvant TACE played a role in earlier therapy of the residual tumor and could decrease the earlier recurrence and prolong survival. However, TACE has been known to damage remnant liver and deteriorate liver function. This adverse impact is possible to affect long survival of patients with resectable HCC if the resection is truly curative. One of the clinical trials showed that adjuvant chemembolization using the regimen of intravenous epirubicin in combination with transarterial infusion of an emulsion of iodized oil and cisplatin, was even associated with more frequent extrahepatic recurrences and a worse outcome in their group of patients[31]. In that clinical trial, all the patients had no demonstrable evidence of residual disease on ultrasonography and hepatic angiography 1 mo after surgery. These evidences suggested that the benefits of adjuvant TACE depended on the selection of patients. In patients who had high risks of residual tumor or intrahepatic metastasis in remnant liver, adjuvant TACE could improve their survival due to therapeutic actions on the residual tumor. However, in patients with lower risks of residual tumor or intrahepatic metastasis, adjuvant TACE might have less usefulness or even worse actions due to deterioration of remnant liver function.

Our results showed that postoperative adjuvant TACE could improve the survival of patients with risk factors for the residual tumor but not the survival of patients without risk factors for the residual tumor. For further evaluation of the effect of adjuvant TACE on patients with resectable HCC, Cox proportional hazards models were constructed to study if adjuvant TACE was the significantly independent factor associated with the survival. The results showed that in patients without risk factors for residual tumor, the significantly independent prognostic factors

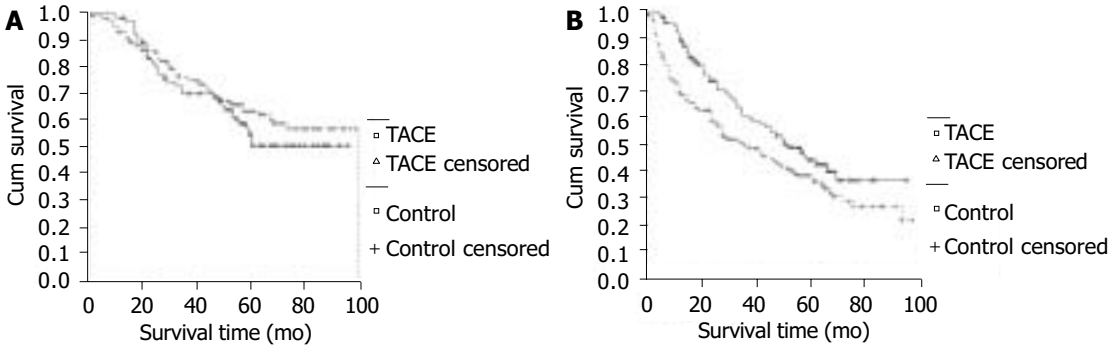

Figure 1 Survival curves of patients in control group and adjuvant TACE group without or with risk factors for residual tumor. A: Survival curve of patients in control group and adjuvant TACE group without risk factor for residual tumor.B: Survival curve of patients in control group and adjuvant TACE group with risk factors for residual tumor.

were tumor diameter and cirrhosis but not the adjuvant TACE. However, in patients with risk factors for residual tumor, adjuvant TACE was the significant prognostic factor. This result suggested that the benefits of adjuvant TACE to patients with resectable HCC depended on the selected patients with or without risk factors for the residual tumor. Therefore adjuvant TACE should be used in patients with higher risks of residual tumor but not in patients with lower risks of residual tumor.

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