

## RESEARCH COMMUNICATION

# Prospective Study on the Survival of HCC Patients Treated with Transcatheter Arterial Lipiodol Chemoembolization

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### Abstract

**Aim:** Transcatheter arterial embolization irrespective of with or without an anticancer agent and lipiodol has been controversial with regard to survival benefit. Therefore, we conducted a prospective study to analyze the effect of transcatheter arterial lipiodol chemoembolization (TACE) on the survival of HCC. **Methods:** A prospective study was conducted, and a total of 326 patients with primary liver cancer who were newly diagnosed were collected from January 2004 to January 2005 in Zhejiang Provincial People's Hospital of China. A univariate Cox's regression analysis was used to assess the survival of the HCC cases receiving TACE. **Results:** The duration of follow-up for the HCC patients treated with TACE ranged from 3 months to 60 months. For the overall patients, survival rate at 5 years was 42%. Both HBV Ag and HCV Ab positive patients showed significantly low survival rate at 5 years. The multivariate analysis revealed The IV TNM stage was related to an heavy increased risk of death of HCC patients, and Child C grade group showed a significant moderate increased risk. **Conclusion:** Our study showed TACE is associated with a better prognosis of HCC patients, and the HBV infection, TNM stage, Child-Pugh grade and number of TACE may influence the survival probability. Further TACE studies should be assess the quality of life of HCC patients, so as to provide more information for treatment of HCC.

**Keywords:** TACE - survival - HCC - China

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### Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer in men (523 000 cases, 7.9% of the total) and the seventh in women (226 000 cases, 6.5% of the total), and most of the burden is in developing countries, where almost 85% of the cases occur, and particularly in men (Llovet et al., 2003). The major etiologies and risk factors for the development of HCC are a multiple steps involved in hepatocarcinogenesis which have been discussed in recent years. Although these research advanced the measures for the early detection of HCC in patients at risk, the survival of advanced stage HCC patients also showed poor due to the limited therapeutic options and the unapparent clinic presentation. All patients were followed up from the date of diagnosis of HCC and were ended in January, 2010.

With regard to treatment, surgical resection and percutaneous ethanol injection (PEI) are treatment methods for HCC. However, the high intrahepatic recurrence rate in 5 years can be as high as 70%-80% after hepatic surgery, and 83% after PEI, resulting from either intrahepatic metastases from the primary tumor or multicentric occurrence (Chen et al., 1994; Koda et al., 2000; Minagawa et al., 2003). However, the Transcatheter arterial lipiodol chemoembolization showed a benefit on the survival of HCC (Llovet et al., 2002; Lo et al., 2002).

Transcatheter arterial embolization was initially used

to treat HCC by Doyon et al. (1974) and was applied to most inoperable HCC using gelatin sponge particles and anticancer agents in Asia (Doyon et al., 1974). In the mid-1990s, lipiodol was newly introduced to enhance mainly the therapeutic effect. Transcatheter arterial lipiodol chemoembolization (TACE) is now the mainstay of treatment of choice for noncurative HCC (Konno et al., 1983; Solomon et al., 1999). However, the transcatheter arterial embolization irrespective of with and without anticancer agent and lipiodol has been controversial in the survival benefit. Therefore, we conducted a prospective study to analyze the effect of TACE on the survival of HCC.

### Materials and Methods

#### Patients

A total of 337 patients with primary liver cancer who were newly diagnosed in two months were collected from January 2004 to January 2005 in Zhejiang of China. All the patients in our study were underwent TACE as an initial treatment for unresectable HCC and did not get any other therapy, and all of them were clinical pathologically diagnosed as HCC. Moreover, all the patients were neither extrahepatic metastasis to lymph nodes and/or other organs nor any treatment prior to the present TACE. Finally, a total of 337 patients were included in our study, and 11 patients were excluded due to incomplete investigation.

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**Table 1. The Demographic and Clinic Characteristics of HCC Patients**

Characteristics	No. of patients N=326	Death, N(%) N=189	Survival (%)	P value
Age				
<60	135(41.4)	70(37.2)	47.9	0.35
≥60	191(58.6)	119(62.8)	37.9	
Sex				
Men	236(72.4)	141(74.6)	40.3	0.58
Women	90(27.6)	48(25.4)	46.6	
Mean age				
Tumor size (cm)				
<2	60(18.3)	29(15.2)	51.8	0.72
2~3	82(25.2)	44(23.3)	46.4	
3~5	113(34.7)	70(37.1)	38	
>5	71(21.8)	46(24.4)	35.1	
HBV and HCV				
HBs Ag positive	256(78.4)	148(78.3)	42.2	<0.05
HCV Ab positive	37(11.5)	30(81.1)	18.2	
Both positive	4(1.1)	4(2.2)	0	
Both negative	29(9)	8(4.1)	73.6	
TNM stage				
I	30(9.2)	14(7.4)	53.4	0.06
II	112(34.4)	59(31.2)	47.4	
III	162(49.8)	99(52.6)	38.8	
IV	22(6.6)	17(8.8)	22.7	
Child-Pugh grade				
A	134(41.2)	69(36.3)	48.8	0.57
B	150(46.1)	94(49.7)	37.4	
C	41(12.7)	26(14.0)	35.5	
Repeated TACE				
≤1	200(61.3)	103(54.4)	48.6	0.22
2~3	79(24.3)	50(26.7)	36.3	
4~6	42(12.8)	32(16.7)	24.4	
≥7	5(1.6)	4(2.2)	20.3	

The main reasons might be the physical and/or mental health situation.

All patients were followed up from the date of diagnosis of HCC and were ended on January 2010. All patient deaths were the end point irrespective of cause of death. Survival time was calculated from the date of diagnosis to the date of last follow-up from any causes. A total of 326 patients were followed up from January 2004 to January 2011.

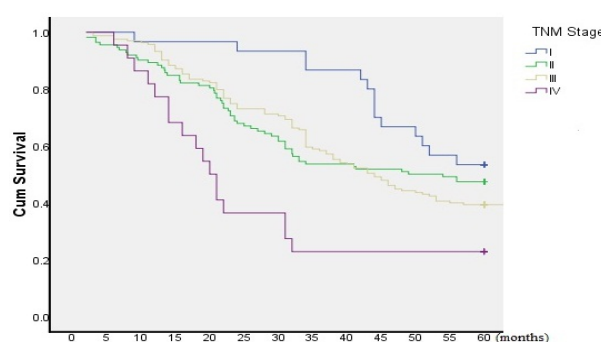
The catheter tip was advanced at the nearest site of the feeding artery as possible. The emulsion of anticancer agent and lipiodol followed by gelatin sponge particles was carefully injected in the x-ray monitoring. The dose of emulsion of anticancer agent and lipiodol and the pieces of embolic materials used for TACE were determined based on the tumor size and extension of the lesions. The patients were followed by CT or MRI every 3-4 months. If the HCC were local recurrence or a second primary HCC was showed, the TACE was performed again.

*Statistical analysis*

All analysis was performed by using SPSS 11.0 software. A univariate Cox’s regression analysis was used to assess the survival of HCC received TACE. The death of patients was defined as the failure event and the time of survival was the time between diagnosis and death. All survived patients were censored at the date of last follow-up. The relative risk [hazard ratio(HR)] and

**Table 2. Multivariate Analysis of Factors Affecting Survival of Patients Treated with TACE**

Variables	Hazard ratio <sup>†</sup>	P value
Age		
<60	1.0(Reference)	-
≥60	1.26(0.83-1.79)	0.32
TNM stage		
I	1.0(Reference)	-
II	1.50(0.63-3.77)	0.31
III	1.85(0.84-4.48)	0.11
IV	3.14(1.18-8.21)	<0.05
Trend		<0.05
Child-Pugh grade		
A	1.0(Reference)	-
B	1.22(0.81-1.83)	0.32
C	1.82(1.03-2.95)	<0.05
Trend		0.13
Repeated TACE		
≤1	1.0(Reference)	-
2~3	1.27(0.76-1.88)	0.3
4~6	1.55(0.87-2.74)	0.12
≥7	2.37(0.61-10.05)	0.15
Trend		<0.05



**Figure 1. Comparison of Survival Rates Stratified by TNM Stage**

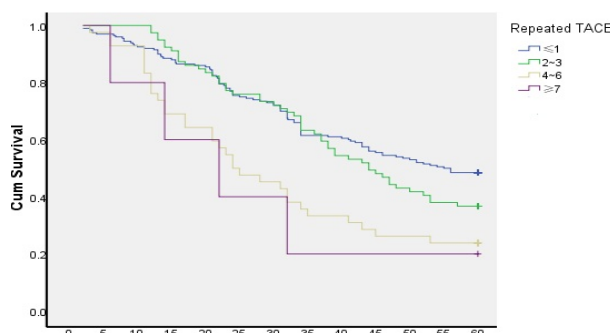
95% CI were calculated from the Cox regression model for all significant predictors from cancer diagnosis to the endpoint of the study (event). Statistical significance was defined as a 2-sided P-value of less than 0.05.

**Results**

The duration of follow-up for the HCC patients treated with TACE ranged from 3 months to 60 months. By final follow-up, 189 patients had died, 126 patients patients were alive, and followed-up had been terminated because of a change in institution for 11 patients. The cumulative survival rates for all patients according to age, sex, tumor size, HBV and HCV, TNM stage, child-pugh grade and repeated TACE are listed in Table 1.

For the overall patients, survival rate at 1 year, 2 year and 5 years was 82%, 74% and 42%, respectively. Both HBV Ag and HCV Ab positive patients showed the lowest survival rate at 5 years, and both negative showed the survival rate at 5 years was as high as 73.6%. The survival rates showed better survival in TNM grade I, II and III than grade IV, but no significant differences were identified between groups. Similarly, Child A and B groups showed a better survival rate at 5 years than C groups, and no significant difference was found between them. Moreover, patients with more repeated TACE showed lower survival.

The multivariate analysis revealed the following 4 factors as independent prognostic variables, including age,



**Figure 2. Comparison of Survival Rates Stratified by Repeated TACE**

TNM stage, Child-Pugh grade and repeated TACE. The hazard ratio of each variable ranged from 1.22 to 3.14. The IV TNM stage of HCC showed a significant increased risk of death, with HR of 3.14 (1.18-8.21) (P for trend: 0.002) (Figure 1). Child B grade group showed a light increased risk of death when compared with child A grade group, and Child C grade group showed a significant moderate increased risk of death (P<0.05). Moreover, the more frequency repeated TACE showed higher risk of death for HCC patients, and a significant trend was found (P for trend: 0.013) (Figure 2).

## Discussion

The prognosis of unresectable HCC is usually poor and these patients are particularly vulnerable to treatment related side-effects. The TACE usually used for the unresectable HCC to lengthen the half-life and increase the average concentration of drug in the tumor, as well as allow more dose-intense delivery in comparison with intravenous administration of chemotherapy (Raoul et al., 1992). These theoretical advantages have made TACE particularly appealing for treatment of HCC patients not amenable to surgical therapy or local ablation (Nakamura et al., 1983; Ikeda et al., 1991; Choi et al., 1992; Bruix et al., 1994; Huppert et al., 1994). Although the TACE has been used since 1983, and there was few studies provide survival benefit of TACE, one study conducted in Barcelona showed the survival probabilities at 1 and 2 years were 82% and 63% for patients who underwent TACE (Llovet et al., 2002). Similarly, another study conducted in Hong Kong showed that in an Asian population, survival of one and two years (57% and 31%) was better for patients treated with chemoembolisation than for individuals receiving supportive care treatment (32% and 11% for one and two years, respectively) (Lo et al., 2002). Our study showed a higher survival rate for patients who underwent TACE, with 82%, 74% and 42% for one, two and five years, respectively. The difference in the studies conducted in Barcelona and Hong Kong may be due to the difference of enrolled patients. More than 80% patients in the Barcelona had cirrhosis caused by the hepatitis C virus, however, the most of the patients treated in Hong Kong had hepatitis B virus. Previous study showed there are ethnic difference in the behavior of HCC influencing prognosis and survival after similar treatment (Chin et al., 1999). In our study, most of the HCC are suffered from hepatitis B virus, and the survival rate

in our study is almost in line with study in Hong Kong.

In our study, TACE seems to provide a better survival rate than previous study conducted in Barcelona and are clearly better than no treatment methods of previous studies (Llovet et al., 2002; Lo et al., 2002). The difference of our finding may be due to the various of characteristics of patients enrolled and the cause of cirrhosis. Moreover, another plausible explanation might be that the average tumor size might be 5 cm in study conducted in Barcelona group and 7 cm for study conducted in Hong Kong.

Our study showed the tumor size, TNM stage, Child-Pugh grade and number of TACE are associated with prognosis of HCC after TACE. Previous study showed that the reduced serum level of AFP after intervention, the number of TACE procedures, small tumor size and homogenous tumor uptake are related to the prognosis of patients treated with TACE (Okuda et al., 1984; Mondazzi et al., 1994; Farinati et al., 1996; Savastano et al., 1999; Lee et al., 2002; Lopez et al., 2002), which showed the difference on the prognosis of HCC could be due to ethnicity, characteristics of patients or chance.

In conclusion, our study showed TACE is associated with a better prognosis of HCC patients, and the HBV infection, TNM stage, Child-Pugh grade and number of TACE may influence the survival probability. Further TACE studies should be assess the quality of life of HCC patients, so as to provide more information for treatment of HCC.

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