

Analysis of Prognostic Factors Affecting Patients Receiving TACE after Liver Resection Surgery

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ABSTRACT Objective: To find filtering conditions for conducting TACE treatment after liver resection surgery by analyzing and evaluating various prognosis factors affecting patients receiving TACE and not receiving TACE after having partial hepatectomy of primary hepatocellular carcinoma (HCC). **Methods:** To analyze the prognosis of 221 patients (103 received postoperative interventional therapy and 118 received postoperative non-interventional treatment) receiving primary HCC surgery treatment in our hospital during the period from 2003 to 2008. And analyze the factors affecting prognosis in the group receiving interventional therapy after surgery and the group receiving non-interventional treatment after surgery via Kaplan-Meier and COX regression, which include age, gender, serum HBsAg, tumor size, tumor gross type, with or without cancerembolus formation, and Tumor stage (TNM). **Results:** In one-year survival period in the intervention group, age, sex, serum HBsAg, tumor size, and tumor gross type had no statistical significance ($p>0.05$), while with or without cancerembolus formation, tumor stage were meaningful ($p<0.05$); In the non-intervention group, the age, sex, serum HBsAg had no statistical significance, while the tumor size, tumor gross type, with or without cancerembolus formation, and tumor stage were meaningful; In three-year survival period in the intervention group, indexes above had no statistical significance, but in the intervention group, tumor size, with or without cancerembolus formation, and tumor stage had statistical meaning. **Conclusion:** Giving positive TACE treatment to patients whose tumor are bigger than 5cm and are proved poorly differentiated by postoperative pathology can significantly improve their recent survival rate.

Key Words: Liver neoplasms; TACE; Prognosis

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Introduction

Primary hepatocellular carcinoma (HCC) is one of common diseases in China. The surgery-oriented comprehensive treatment is the primary means to treat this disease^[1], but the recurrence rate is as high as 76%^[2], affecting the prognosis of patients. After years of development, TACE is technologically mature, and it has become another important assistant means for the treatment of HCC. However, there's still controversy on the effect of giving preventive therapy to patients receiving TACE after radical resection surgery^[3]. Therefore, this study aims to analyze various factors affecting prognosis, including: age, gender, serum HBsAg, tumor size, tumor gross type, with or without cancerembolus formation, and tumor stage (TNM), through the complete follow-up data of patients receiving TACE after radical resection surgery^[4], and to provide a theoretical basis for the choice of opportunity and the assessment the prognosis for patients to receive TACE after radical resection surgery.

1 Materials and Methods

1.1 Clinical data

From July 2003 to December 2008, the Affiliated Hospital of

Medical College of Qingdao University has operated 221 cases of liver cancer resection on patients with primary liver cancer, and the postoperative pathology confirmed that they are all hepatocellular carcinomas. There're 103 cases of patients receiving postoperative TACE, 89 male and 14 female, the oldest 74 years old, the youngest 27 years old, antigen surfaces of hepatitis B of 83 cases are positive and 20 negative, 71 cases are pathologically confirmed as high or moderate differentiation, 32 cases are lowly differentiated, 64 cases are in TNM stage I, 20 cases are in stage II, 19 cases in stage III. There're 118 cases of patients not receiving postoperative TACE, 92 male and 26 female, the oldest 82 years old, the youngest 30 years old, antigen surfaces of hepatitis B of 93 cases are positive and 25 negative, 75 cases are pathologically confirmed as high or moderate differentiation^[5], 43 cases are lowly differentiated, 80 cases are in TNM^[6] stage I, 11 cases are in stage II, 27 cases in stage III.

1.2 Treatment

The 118 cases in non-intervention group have no special treatment except for taking liver-protecting drugs and medicines for strengthening the immune. Other than taking medicine as the non-intervention group, the 103 cases in intervention group also receive TACE treatment once per 1 to 2 months, using Seldinger methods.

1.3 Statistical

Establish detailed clinical data files for every patient were analyzed to learn about the survival time of patients through mail, telephone and patient review. Analysis was done by using

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SPSS18.0 statistical software package, Kaplan-Meier methods were used to analyze single factor, and COX proportional hazards regression model was used to do multivariate analysis. Keeping a differentia of $P < 0.05$ is considered statistically significant.

2 Results

2.1 Comparison of the general pathological data of two groups

The differences of two groups of patients with primary liver cancer in gender composition ($\chi^2 = 2.644$, $p = 0.104$), age ($\chi^2 = 0.668$, $p = 0.414$), HBV infection ($\chi^2 = 0.106$, $p = 0.745$), degree of differentiation ($\chi^2 = 0.708$, $P = 0.400$), tumor diameter ($\chi^2 = 1.283$, $p = 0.994$), with or without vascular thrombosis ($\chi^2 = 0.000$, $p = 0.994$) and liver cancer TNM staging ($\chi^2 = 4.786$, $p = 0.091$) had no statistical significance (Table 1).

Table 1 comparison of the general pathological data of two groups (case, %)

		TACE group	N-TACE group	χ^2	P
gender	male	89(86.4%)	92(78%)	2.644	0.104
	female	14(13.6%)	26(22%)		
HBsAg	positive	83(80.6%)	93(78.8%)	0.106	0.745
	negative	20(19.4%)	25(21.2%)		
age	>60year	33(32.0%)	44(37.3%)	0.668	0.414
	≤ 60year	70(68.0%)	74(62.7%)		
differentiated	High Moderately	71(68.9%)	75(63.6%)	0.708	0.400
	poorly	32(31.1%)	43(36.4%)		
tumor diameter	>5cm	55(53.4%)	54(45.8%)	1.283	0.257
	≤ 5cm	48(46.6%)	64(54.2%)		
vascular tumor emboli	have	14(13.6%)	16(13.6%)	0.000	0.994
	no	89(86.4%)	10(86.4%)		
TNM stage	I stage	64(62.1%)	80(67.8%)	4.786	0.091
	II stage	20(19.4%)	11(9.3%)		
	III stage	19(18.5%)	27(22.9%)		

2.2 Survival rate

The 1-year and 3-year survival rate (%) of patients in TACE group was 95.1% and 40.8%; In non-intervention group, the 1-year and 3-year survival rate (%) was 71.2% and 21.2%. The survival rate in intervention group was significantly higher than that in non-intervention group.

2.3 Kaplan-Meier single-factor analysis and Cox regression analysis

The age, gender, serum HBsAg, tumor size, tumor gross type, with or without cancer embolus formation, tumor stage of the Put the patient's age, gender, serum HBsAg, tumor size, tumor gross

type, with or without cancer embolus formation, tumor stage these seven factors were shown in Table chart2, 3 said. And the meaningful facts were put meaningful facts into Cox regression analysis, results were shown in Table 4, 5. In the intervention group, vascular thrombosis and tumor stage were statistically significant at the 1-year survival rate; HBV infection was meaningful at the 3-year survival rate. In non-intervention group, tumor size, tumor gross type, with or without cancer embolus formation, tumor stage were statistically significant; Tumor size, tumor gross type, with or without cancer embolus formation, tumor stage were statistically meaningful at the 3-year survival rate.

Table 2 Kaplan-Meier analysis results of Intervention group

factor		survival rate (%)			Log-Rank Test		
		1year	2year	3year	1year	2year	3year
sex	male	94.4	69.7	43.8	$\chi^2 = 0.781$	$\chi^2 = 5.494$	$\chi^2 = 4.639$
	female	100	35.7	21.4	$P = 0.377$	$P = 0.019$	$P = 0.031$
age	≤ 60year	95.5	67.2	40.3	$\chi^2 = 0.065$	$\chi^2 = 0.674$	$\chi^2 = 0.050$
	>60year	94.4	61.1	41.7	$P = 0.799$	$P = 0.412$	$P = 0.823$

HBV influence	yes	94	69.9	44.6	$\chi^2=1.210$	$\chi^2=4.361$	$\chi^2=3.251$
	no	100	45	25	$P=0.271$	$P=0.037$	$P=0.071$
differentiated	High Moderately	97.2	67.6	40.8	$\chi^2=2.069$	$\chi^2=0.728$	$\chi^2=0.032$
	poorly	90.6	59.4	40.6	$P=0.150$	$P=0.394$	$P=0.857$
tumor diameter	$\leq 5\text{cm}$	97.9	60.4	35.4	$\chi^2=1.519$	$\chi^2=0.736$	$\chi^2=1.357$
	$>5\text{cm}$	92.7	69.1	45.5	$P=0.218$	$P=0.391$	$P=0.244$
Vascular tumor emboli	have	64.3	68.5	41.6	$\chi^2=37.043$	$\chi^2=6.724$	$\chi^2=1.736$
	no	100	42.9	35.7	$P=0.000$	$P=0.010$	$P=0.188$
TNM stage	I stage	98.4	68.3	41.3	$\chi^2=7.080$	$\chi^2=2.907$	$\chi^2=0.267$
	II stage	95.2	66.7	38.1	$P=0.029$	$P=0.234$	$P=0.875$
	III stage	84.2	52.6	42.1			

Table 3 Kaplan-Meier analysis results of no intervention group

fact		survival rate (%)			Log-Rank Test		
		1year	2tear	3year	1year	2tear	3year
sex	male	72.8	39.1	19.6	$=0.674$	$=0.227$	$=0.549$
	female	65.4	46.2	26.9	$P=0.421$	$P=0.634$	$P=0.459$
age	$\leq 60\text{year}$	72.7	37.9	19.7	$=0.235$	$=0.106$	$=0.075$
	$>60\text{year}$	69.2	44.2	23.1	$P=0.628$	$P=0.745$	$P=0.748$
HBV influ ence	yes	72	36.6	18.3	$=0.096$	$=2.740$	$=2.690$
	no	71	56	32	$P=0.757$	$P=0.098$	$P=0.101$
differentiated	HighModerately	84	46.7	21.3	$=15.636$	$=6.888$	$=2.672$
	poorly	48.8	30.2	20.9	$P=0.000$	$P=0.009$	$P=0.102$
tumor diameter	$\leq 5\text{cm}$	85.9	56.3	29.7	$=15.36$	$=18.473$	$=16.492$
	$>5\text{cm}$	53.7	22.2	11.1	$P=0.000$	$P=0.000$	$P=0.000$
Vascular tumor emboli	have	43.8	12.5	0	$=9.753$	$=10.696$	$=13.940$
	no	75.5	45.1	24.5	$P=0.002$	$P=0.001$	$P=0.000$
TNM stage	I stage	78.8	50	27.5	$=9.857$	$=14.295$	$=14.953$
	II stage	70	30	10	$P=0.020$	$P=0.003$	$P=0.002$
	III stage	48.1	18.5	7.4			

Table 4 COX analysis results of no intervention group

	B	SE	Wald	df	Sig.	Exp(B)
sex	.222	.401	.306	1	.580	1.249
age	.166	.362	.212	1	.645	1.181
HBsAg influence	.266	.473	.316	1	.574	1.305
Differentiated	1.392	.385	13.067	1	.000	4.021
tumor diameter	1.384	.482	8.228	1	.004	3.989
Vascular tumor emboli	.721	.506	2.031	1	.154	2.057
TNM stage			.703	3	.873	
I stage	-.354	.505	.492	1	.483	.702
II stage	-.591	.782	.571	1	.450	.554
III stage	-11.230	574.840	.000	1	.984	.000

Table 5 COX analysis results of intervention group

	B	SE	Wald	df	Sig.	Exp(B)
sex	-2.296	99.042	.001	1	.982	.101
age	21.336	52.356	.166	1	.684	1.845E9
HBsAg influence	10.529	385.661	.001	1	.978	37385.444
differentiate	20.989	52.345	.161	1	.688	1.305E9
tumor diameter	34.119	90.695	.142	1	.707	6.573E14
Vascular tumor emboli	54.249	134.700	.162	1	.687	3.633E23
TNM stage	-5.412	29.964	.033	1	.857	.004

3 Discussion

One important means in assistant treatment before and after the surgery of primary liver cancer is TACE. However, for primary liver cancer that can be cured by surgical resection, it's still controversial whether to give TACE treatment and when to give [3]. The question is whether TACE treatment can improve the resection rate, reduce the recurrence, improve the prognosis of patients, and what kind of TACE treatment can be chosen to fully play its role and reduce its side effects to a minimum. On one hand, doing TACE treatment after the curative resection surgery of the hepatocellular carcinoma is believed to kill effectively residual cancer cells, reduce the recurrence, and significantly improve survival rate [7,8]; On the other hand [9], TACE is said to further damage liver function of the patients, decrease immune function, and on the contrary, it has a negative impact on survival rate [10]. Currently the analysis of TACE is mostly dominated by single factor analysis, so the analysis results are varying [6]. Single factor analysis may make the meaningful variable not significantly meaningful in multivariate analysis. This study analyzes factors affecting prognosis through Kaplan-Meier and COX regression analysis to provide basis for HCC patients to choose TACE treatment after surgery. It's practically meaningful.

In the intervention group, factors relevant to patients with 1-year prognosis, including the formation of vascular thrombosis and tumor stage, and factor related to 3-year survival rate is HBV infection. In non-intervention group, factors relevant to patients with 1-year prognosis are tumor size, tumor gross type, with or without cancer embolus formation, and tumor stage; and factors related to 3-year survival rate are tumor size, with or without cancer embolus formation, and tumor stage.

Some scholars believe [11] that the prognosis of elderly patients is poorer than young men, but the characters of cancer in young patients are often poor, with the risk of early metastasis and recurrence, affecting the prognosis [12]. The study by Takenake K [13] on elderly patients showed that the postoperative mortality rate of patients > 70 years old equals to that of patients < 70 years old, except that the incidence of liver failure of the former was higher, which was related to the level of liver function in elderly patients. There are more female patients having complete encapsulated tumor, their tumors are less aggressive, so their prognosis are better than male patients [14,15]. HBV infection cancer patients tend to have

cirrhosis, which often do not exist as an independent factor [16]. In this study, whether in the intervention group or in non-intervention group, the patient's age, gender and whether infected with HBV are not statistically significant, so they're not considered to be indexes affecting patients' survival rates after surgery.

If the diameter of the tumor is too large, cancer tissue will be left because we should retain sufficient normal liver tissue in the removal process. What's more, with the increasing of cancer, the internal pressure of the tumor also increases. When the pressure of operating the surgery in the surgical removal and the pressure created by itself combined exceed portal pressure, the tumor cells can easily break the membrane into the portal vein to cause spreading [17]. In this study, tumor diameter in the intervention group was not statistically significant, but in non-intervention group, the tumor diameter can affect 1-year and 3-year survival rates. Patients with large mass liver cancer should actively take TACE treatment after surgery in order to eliminate residual cancer tissue and improve survival time.

Patients, whose tumor differentiation is later according to pre-operative evaluation and postoperative pathologic is low, are easy to have early postoperative recurrence which can affect prognosis, because of the low degree, highly malignant, invasive strong tumor [18,19]. Pathology after surgery confirms that recently the survival rate of patients with vascular thrombosis was significantly lower than that of patients with vascular thrombosis, and the treatment effect of the former is poor [20]. In this study, these factors are all important factors in both non-intervention group and the intervention group, but in the 3-year survival period the vein tumor cancer embolus and tumor stage are not the factors that affect the survival rate, so considering from the long-term survival of patients, the intervention treatment is more meaningful for these two factors.

To sum up, patients with a tumor diameter bigger than 5cm, the formation of venous thrombosis and later stage of tumor differentiation should be actively receiving TACE treatment after surgery, in order to prolong survival time of patients, which is especially meaningful for the early survival of patients.

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影响肝切除术后行 TACE 患者预后因素的分析

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摘要 目的:对原发性肝细胞肝癌(HCC)肝部分切除术后行经肝动脉化疗栓塞(TACE)的病人和未行 TACE 病人影响其预后的多种因素进行分析和评价,为肝切除术后是否行 TACE 治疗寻找筛选条件。方法:对我院 2003~2008 年期间在我院肝胆外科行原发性肝细胞肝癌手术治疗 221 例(术后介入治疗 103 例,术后非介入治疗 118 例)患者进行全面随访了解患者的预后情况,分别对术后接受介入治疗和非介入治疗两组通过 Kaplan-Meier 及 COX 回归分析影响预后的因素,包括:年龄、性别、血清 HBsAg、肿瘤直径、肿瘤大体分型、有无癌栓形成、肿瘤分期(TNM)共 7 项指标。结果:在 1 年生存期内介入治疗组中的性别、年龄、血清 HBsAg、肿瘤直径、肿瘤大体分型无统计学意义($p>0.05$),有无癌栓形成及肿瘤分期有意义($p<0.05$);非介入组内年龄、性别、血清 HBsAg 无统计学意义,肿瘤直径、肿瘤大体分型、有无癌栓形成、肿瘤分期有意义;在 3 年生存期内介入治疗组中的以上指标无统计学意义,而非介入组在肿瘤直径、有癌栓形成及肿瘤分期方面与统计学意义。结论:对于肿瘤直径 $>5\text{cm}$ 及术后病理证实为低分化的患者给予积极 TACE 治疗可明显提高近期生存率。

关键词 原发性肝细胞肝癌 经肝动脉化疗栓塞(TACE) 预后;

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