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To evaluate if the prognosis of curative resection in HCC patients is affected by alcholism

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***Abstract*: To investigate the relationship of alcoholism history and prognosis of the patients with primary hepatocellular carcinoma (HCC) after curative resection. The clinical data of 606 cases of primary HCC underwent curative resection from January 2001 to December 2011 in Affiliated Hospital of Medical College Qingdao University were analyzed retrospectively. By Kaplan-Meier method, median overall survival (OS) in alcoholism group (n=136) and non-alcoholism group (n=470) was 54.0 and 74.0 months ,respectively (Log-rank test: P = 0.045); the median disease-free survival (DFS) was 31.0 and 43.0 months (P = 0.261). COX regression model analysis results show that no- isolate type， size of tumor≥5cm， GGT＞64 U ml and alcoholism history are affect the HCC patients OS independent risk factors，no-isolate type， size of tumor≥5cm,tumor cut edge<0.5cm and GGT＞64 U ml are influence DFS independent risk factors. The prognosis of HCC patients with alcoholism patients after resection is poor. History of alcoholism not influence patients DFS independent risk factors, but history of alcoholism patients inflammatory state clearly, even if alcohol prohibition after the surgery the recurrence rate is higher than no history of alcoholism，affect the prognosis of HCC patients of history of alcoholism.**

Keywords: Hepatocellular carcinoma; alcoholism; curative resection; prognosis

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1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cause of cancer, and its incidence is increasing worldwide because of the dissemination of hepatitis B and C virus infection [1]. The most common histologic type of primary liver cancer, hepatocellular carcinoma (HCC), is a malignant tumor arising from hepatocytes, the liver's parenchymal cells [2]. The best principle to manage HCC is to make an early diagnosis and perform radical therapy. Surgical resection is the first line therapeutic option for early HCC [3]. Hepatic curative resection is widely accepted as the treatment of choice for HCC but the long-term survival is still not ideal [4]. Overall survival after resection of HCC has improved in recent years. However, the recurrence rate still remains high [5]. Chronic alcohol consumption is a major health issue worldwide, the most comprehensive estimates of death rates caused by alcohol come from the World Health Organization (WTO) Global Burden of Disease Project, which concluded that alcohol accounts for approximately 1.8 million deaths per year (3.2% of all death) [6]. Many reported in the literature that ethanol is one of the important factors of the development of HCC. But few reports about the history of alcoholism effect prognosis on HCC in patients after curative resection. This research through retrospective analysis of clinical data primary HCC curative resection on the prognosis of patients with alcoholism affects.

2. Methods

2.1 Patients

From January 2001 to December 2011, a total of 606 patients with HCC after curative resection visited in Affiliated Hospital of Medical College Qingdao University. The preoperative diagnosis of HCC was based on the diagnostic criteria for HCC used by the European Association for the Study of the Liver. All patients were diagnosed by at least 2 radiologic imaging and blood biochemical examination of HCC before resection. All patients had a chest X-ray, USG of abdomen, and contrast CT or MRI of abdomen. Laboratory blood tests including hepatitis B surface

antigen, antibodies to hepatitis C, serum AFP, carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), serum albumin, total bilirubin, aspartate minotransferase (AST), alanine aminotransferase (ALT), prothrombin time and so on were obtained. Progression profile of HCC (number of tumors, maximum tumor size, presence of macroscopic tumor thrombosis and presence of extra-hepatic invasion), treatments employed, and survival rates were recorded. The liver function status was valuated using the Child-Pugh grading. Stage of the HCC was performed according to the TNM staging system proposed by the American Joint Committee on Cancer [7]. Alcoholism according to the Blonski standard [8], the definition of alcoholism: every day drink alcohol 80g or more and continued more than five years. Formula: Alcohol(g)=drinking(ml)*ethanol concentration(%).

2.2 Follow-up

After curative resection, the patients were monitored, we have mainly adopted the outpatient follow-up and used of telephone and mail to help follow-up. The end of the follow-up to the 2010-12-31 or patient death. The median follow-up time were 35.8 months(2~126.8 months). Dynamic contrast-enhanced computer tomography (CT) and magnetic resonance imaging (MRI) along with serum tumor marker, such as AFP, was used for assessment during the follow-up every months. Recurrence was diagnosed on dynamic CT and MRI by contrast enhancement in the arterial phase and wash-out in the delayed phase. Recurrent tumor was confirmed by positive staining of the tumor during transarterial chemoembolization (TACE) or histological diagnosis in re-resection specimen. Local ablation therapy, chemotherapy, or radiotherapy was used to treat patients with recurrent HCC, if they had not been treated with TACE or re-resection .

2.3 Statistical analysis

The difference of clinical and pathological factors in the contrast group were evaluated by Chi-square test with Yates correction or the Fisher exact test where appropriate. Significant difference was set at P value<0.05. Overall survival and disease-free survival were measured from the date of surgery to the time of death and to the time when recurrent tumor was first diagnosed, respectively. Statistical analyses were performed using ANOVA to test for differences in variables with regard to survival. Factors associated with a $P < 0.05$ in the ANOVA analysis were sequentially entered into the Cox regression analysis to indicate the relatively independent risk factors. The closing date for the study was December 31, 2011. All statistical analyses were performed by the SPSS release version 20.0 for Windows (SPSS Inc., Chicago, IL).

Table1 Comparison the different years between DFS and OS.

	DFS-No alcoholism	DFS-Alcoholism	P	OS-No alcoholism	OS-Alcoholism	P
First	77.7%	70.6%	0.089	92.1%	90.4%	0.529
Second	59.6%	50.0%	0.047	81.7%	74.3%	0.056
Third	41.1%	30.9%	0.032	58.7%	47.8%	0.024
Fifth	23.6%	7.4%	0.000	33.0%	15.4%	0.000
Seventh	11.7%	3.7%	0.006	15.3%	5.1%	0.002
Tenth	3.4%	0.7%	0.097	4.5%	1.5%	0.107

3. Result

In 606 patients, 136 cases (22.4%)reached alcoholism standards, this was alcoholism group. All patients in this group were men. And this group after the operation had been temperance. Did not reach the alcoholism standard in 470 (77.6%) cases as non alcohol group. Comparison the difference in first，second，third，fifth，seventh and tenth years between DFS and OS is shown in table 1. The difference of DFS and OS in the contrast group were evaluated by

Chi-square test, the result showed that the disease-free survival rate have statistically significant difference between the two groups in second， third， fifth and seventh years, P<0.05; the overall survival rate have statistically significant difference between the two groups in third， fifth and seventh years, P<0.05(Table 1). Comparison of clinical and pathological factors between alcohol group and non alcohol group is shown in Table 2, 3 and 4. The following factors were statistically significant difference between the two groups: a high serum GGT level (P=0.000), a high alpha-fetoprotein level (P=0.021) and histopathological differentiation (P=0.007) .

Table 2 Comparison of baseline factors between alcoholism group and non alcoholism group.

Factors	alcoholism	No alcoholism	χ^2	P
Age（n）			1.109	0.292
＞55	57（41.9）	221（47.0）		
≤55	79（58.1）	249（53.0）		
Serum ALB（g/L）			0.045	0.832
＜35	15(78.6)	55(75.7)		
≥35	120(21.4)	412(24.3)		
Serum ALT(U/L)			0.148	0.700
≤60	102(75.0)	360(76.6)		
＞60	34(25.0)	110(23.4)		
Serum GGT（U/L）			12.351	**0.000**
≤64	67（51.1）	289（68.0）		
＞64	64(48.9)	136（32.0）		
HBsAg(positive)			0.358	0.550
positive	102（85.0）	345（87.1）		
negative	18（15.0）	51（12.9）		
Cirrhosis			0.207	0.649
No	11(8.1%)	44(9.4%)		
yes	125(91.9%)	426(90.6%)		
Preoperative TACE			3.634	0.057
no	125(91.9%)	401(85.7%)		
yes	11(8.1%)	67(14.3)		

Kaplan-Meier analysis (log rank test) showed that the OS of the non alcoholism group was significantly higher than that of the alcoholism group (P=0.045), and showed that although the DFS of the non alcoholism group was higher than that of the alcoholism group (medians: 43.0 and 31.0 months, respectively), there was no statistical significance(Table5 and Table 6). Cox regression analysis showed alcoholism to be an independent predictor of overall survival (P=0.047) (Table 7).

4. Discussion

Alcoholism is a social problem of the world, it's widely consumed in most parts of the world and has long been associated with various liver diseases accounting for about 4% of all deaths [9]. Excessive chronic causes hepatic steatosis, which can progress, if drinking continues , to more advanced form of alcoholic liver disease (ALD) such as alcoholic steatohepatitis (SH), hepatic fibrosis and cirrhosis and ultimately hepatocellular carcinoma [10]. Donato [11] reported that the risk of hepatocellular carcinoma in alcoholism (every day drink alcohol 80g or more and continued more than five years) was five times that of

the non alcoholism. The alcohol intake was proportionate to the increased risk of hepatocellular carcinoma. Mathurin P [12] et al .reported that if the patients with alcoholic liver cirrhosis insist on temperance without ascites and aurigo , there 's five -year survival rate was 89%,however if the patients continue to excessive drinking ,the five-year survival rate was 68%. In recent years, the domestic and foreign research reported that alcohol and other carcinogens have synergistic interaction.

Table 3 Comparison of Intraoperative factors between alcoholism group and non alcoholism group.

Factors	alcoholism	No alcoholism	χ^2	P
Liver resection range			0.076	0.783
≤2 segments	121（89%）	422(89.8%)		
＞2 segments	15（11.0%）	48（10.2%）		
surgical margin			1.156	0.282
＜0.5cm	49（36.6%）	148(31.6%)		
≥0.5cm	85（63.4%）	320(68.4%)		
Non-anatomical resection			0.136	0.712
no	98(72.1%)	331(70.4%)		
yes	38(27.9%)	139(29.6%)		
Interaoperative blood loss			0.020	0.887
≥1000ml	20(14.7%)	71(15.2%)		
<1000ml	116(85.3%)	396(84.8%)		
Liver blood occlusion			0.663	0.416
no	60（44.1%）	225(48.1%)		
yes	76（56.89%）	243（51.9%）		
transfusion			0.051	0.822
no	103（75.7%）	350（74.8%）		
yes	33（24.3%）	18（25.2%）		

Table 4 Comparison of Tumor factors between alcoholism group and non alcoholism group.

Factors	alcoholism	No alcoholism	χ^2	P
Serum AFP(ng/ml)			5.311	**0.021**
≥400	110(81.5%)	335(71.6%)		
＜400	25(18.5%)	133(28.4%)		
Histopathological differentiation			9.820	**0.007**
highly	27(19.9%)	53(11.4%)		
moderately and poorly	108(79.4%)	393(84.3)		
necrosis	1(0.7%)	20(4.3%)		
solitary HCC				
no	20(14.7%)	85(18.2)	0.895	0.344
yes	116(85.3%)	382(81.8)		
Tumor size(cm)				
≥5cm	67(49.3%)	232(49.4%)	0.000	0.984
＜5cm	69(50.7%)	238(50.6%)		

Table5 Univariate analysis of factors influencing overall survival .

Factors	Kaplan-Meier analysis median（months）	P
Sex（male/female）	37.0/16.0	0.476
Age（≤55/＞55）	78.2/55.0	**0.031**
HBV(pocitive/negative)	67.0/60.7	0.111
Serum ALB(<35/≥35g/L)	48.2/74.4	**0.045**
Serum ALT（≤60/＞60U/L）	74.6/56	**0.031**
Serum GGT(≤64/>64U/L)	105.0/43.0	**0.000**
Cirrhosis(no/yes)	64.0/66.0	0.078
Liver resection range(1/≥2 segments)	78.2/56.0	**0.003**
anatomical resection(no/yes)	63.0/111.9	0.161
surgical margin (<0.5/≥0.5cm)	61.8/68.0	0.079
Interaoperative blood loss（<1000/≥1000ml）	74.6/51	**0.007**
Transfusion(no/yes)	78.2/49	**0.001**
AFP(≤400/>400ng/ml)	58.0/95.0	**0.004**
Child-Pugh（A/B）	35.0/16.0	0.668
Tumor size (≤5/＞5cm)	81.0/44.0	**0.000**
Histopathological differentiation (highly/ moderately and poorly/ necrosis)	113.0/65.0/49.0	**0.021**
solitary HCC(no/yes)	42.0/79.0/	**0.000**
Alcoholism(no/yes)	74.0/54.0	**0.045**

A longitudinal study (mean, 6.2 y) of 341 hepatitis B surface antigen– positive healthy blood donors tested in Japan between 1972 and 1975 found that alcohol consumption of more than 27 g/day (duration of alcohol use not stated) was associated with more than a 5-fold increase in the relative risk for development of HCC [13].

In the past, ethanol was not considered a carcinogen, but rather a co-carcinogen and/or tumour promoter, as, on its own, ethanol administration to animals did not induce tumours. Detailed analysis of many of these studies by the IARC Working Group revealed that they were inadequately designed and performed [14]. However, Seitz [15] reported that the current evidence for a contributory role of chronic alcohol consumption to worldwide cancer burden and the mechanisms involved. Morgan [16] reported that HCC can occur in persons with alcohol-induced liver disease who do not have cirrhosis, it was suggested that ethanol and (or)its metabolites caused HCC by other ways without cirrhosis. Alcohol didn't caused cancer by itself ,but it caused cancer collaterally. The liver is the major site of ethanol metabolism, related basic research showed that the mechanisms of continuous ethanol stimulation leading to liver damage may include alcohol dehydrogenase (ethanol metabolite) forming complex antigen inducing immune res-ponse in the body and the ROS lead to lipid peroxidation and lipid peroxidation products such as 4-hydroxynonenal (4HNE), which binds to DNA to form mutagenic adduct [15]. Substantial research has been done, investigating the mechanisms by which excessive alcohol interferes with retinoid metabolism(alcohol acts as a competitive inhibitor of vitamin A oxidation to retinoic acid involving alcohol dehydrogenases and acetaldehyde dehydrogenases [17]. Faitha et al. [18] reported that a major role of mitochondria in alcohol induced hepatic fat accumulation. Alcohol consumption results in inhibition of PPAR-α and stimulation of SREBP-1C and the transformation of liver from an oxidizing to a fat-storing organ. Alcohol also induces reactive oxygen species levels and causes liver injury and apoptosis in part by regulating sirtuins

levels and enzymes of the antioxidant defense .

Table6 Univariate analysis of factors influencing disease free survival.

Factors	Kaplan-Meier analysis median（months）	P
Sex（male/female）	35.8/88.1	0.083
Age（≤55/＞55）	50.8/28	0.089
HBV(pocitive/negative)	43.0/26.0	0.789
Serum ALB(<35/≥35g/L)	37.0/43.0	0.954
Serum ALT（≤60/＞60U/L）	48.2/27.0	**0.034**
Serum GGT(≤64/>64U/L)	52.9/21.0	**0.000**
Cirrhosis(no/yes)	52.0/39.0	0.113
Liver resection range(1/≥2 segments)	50.8/20.4	**0.001**
anatomical resection(no/yes)	43.0/40.0	1.000
surgical margin (<0.5/≥0.5cm)	25.0/51.0	**0.003**
Interaoperative blood loss（<1000/≥1000ml）	49.2/21.0	**0.003**
Transfusion(no/yes)	50.8/24.0	**0.003**
AFP(≤400/>400ng/ml)	58.0/95.0	**0.004**
Child-Pugh（A/B）	43.0/22.0	0.319
Tumor size (≤5/＞5cm)	56.9/20.0	**0.000**
Histopathological differentiation(highly/ moderately and poorly/ necrosis)	61.6/34.0/55.0	0.068
solitary HCC(no/yes)	23.0/49.5	**0.000**
Alcoholism(no/yes)	43.0/31.0	0.261

Table 7 Multivariate analysis of factors influencing OS and DFS.

Factors	OS		DFS	
	RR（95%CI）	P	RR（95%CI）	P
solitary HCC	2.825(2.181-3.658)	0.000	0.623（0.482-0.807)	0.000
Tumor size >5cm	1.821(1.374-2.387)	0.000	1.759（1.418-2.182)	0.000
GGT>64 U/mL	1.976(1.574-2.524)	0.000	1.668 (1.336~2.082)	0.000
Alcoholism	1.328(1.004-1.757)	0.047		
Surgical margin <0.5cm			0.713（0.571-0.889)	0.003

Beier [19] and his colleagues reported that abstainers with Alcoholism history are more likely to suffer from HCC than alcoholics in past 10 years. In this study, all patients gave up alcohol postoperatively. However, preoperative alcoholism history may infect the prognosis of HCC patients after curative resection. Further analysis indicated that the crisis of relapse and survival in patients with Alcoholism history mainly come from the DFS and OS of mid-and-long term. Another research showed that, in patients abstained from drinking, hepatic cell proliferation still existing in hepatopathy or liver cirrhosis related to alcohol, including canceration [20]. Therefore, patients with alcoholism history are high risk population of HCC relapse and require frequent medical observation.

HCC patients were divide into solitary group and non- solitary group. Solitary HCC has a good prognosis due to no invasion of hepatic capsule. Non-isolate type HCC has poor tumor biologic characteristics, including vascular invasion, formation

of multifocal lesions and satellite lesions. Non-isolate type HCC has also been acted as an independent risk factor. Relative analysis indicates the less correlation between preoperative alcoholism history and non-isolate type HCC(r=0.048, P>0.05).

GGT is a mitochondrial enzyme Contains sulfhydryl, which exists in hepatocyte and endothelial cells of bile duct. Toshikuni's [21] study found GGT is a sensitive indicator to hepatocellular damage. When alcohol damage the hepatocyte, level of GGT increased earliest but decreased latest. Lu's [22] study suggest that alcohol and its metabolites activated by the Kupffer cells, releasing quantity of active oxygen, and then induce NF－κB to activate cytokines(likeTNF-α, IL-6). This could amplify inflammatory response through gene transcription. Alcoholic group in this study show a close relationship with GGT and non-anatomical hepatectomy. Alcoholism contribute to hepatic inflammatory state, affect liver function, transform hepatic stellate cell into fibroblast . Finally, cause liver cirrhosis happened, which may increase the difficulties to anatomical hepatectomy. Xin Yin's [23] results presented that patients in high GGT group had a much lower survival ratio to patients in normal GGT group(62.67% / 35.7%). Our work has similar results: OS in group with increased GGT were shorter than normal GGT group. We also found that serum levels of GGT greater than 64 U/ml was an independent risk factor of postoperative survival. These results suggest GGT is of great significance to postoperative survival.

The size of liver tumor reflects the level of tumor burden, it was reported that the size of liver tumor is the most important factor in recurrence free survival rate and it reflects the Severity and disease progression [24]. Moreover, the size of liver tumor is related to the presence of metastases [25]. This research shows a consistent result above that diameter of liver tumor less than 5cm is an independent risk factor in OS and DFS of HCC patients. Besides, incisal edge of tumor has significant correlation with the size of liver and the non-isolate type HCC(P<0.01). This study suggests that tumorous incisal edge is depend from its biological characteristics; anatomical hepatectomy does not affect prognosis.

5. Conclusion

In conclusion, alcoholism has seriously implications for prognosis of patient with HCC. These patients should have regular do radiological examination and liver function tests to find the recurrence and therpy in early stage and to improve of patients with alcohol liver disease (ALD). Consequently, alcoholism as an important factor influencing the prognosis of patients with HCC, it's clinical value should be sufficient attention.

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