Prognostic factors, treatment methods and survival times in hepatocellular carcinoma: Single-center experience in a decade

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ABSTRACT

Background and Aim: We aimed to investigate etiology, prognostic factors, treatment methods and the effects of these treatments on survival in HCC.

Materials and Methods: This is a retrospective study including 158 patients diagnosed with HCC in our hospital between the years 2000 and 2010.

Results: Etiological factors were HBV in 53.2% of cases, HCV in 21.5%, alcohol in 6.3%, HBV+alcohol in 5.7%, HCV+Alcohol in 1.9%, HBV+HCV in 1.9%, and the etiology was unknown in 9.5%. Of the 158 patients, 120 were treated, of which 81 had follow-up data. The mean follow-up period was 17.9 months (0.6-124 months). According to multivariate analysis, lesion size greater than 5 cm, Child class C, higher creatinine levels, and distant metastasis were prognostic factors for survival.

Conclusion: In our study, hepatitis B virus was the most frequent cause of HCC, while hepatitis C virus was the second. The most effective treatment methods on survival in HCC were liver transplantation and hepatic resection in eligible patients. Lesion size greater than 5 cm, Child class C, higher creatinine levels, and distant metastasis were determined as independent prognostic factors for survival.

Keywords: Hepatocellular carcinoma; Hepatitis B virus; Liver transplantation.

Introduction

Liver cancer is the fifth most common malignancy in males and the ninth in females. It is the sixth most common cancer and the fourth leading cause of cancer-related death worldwide.[1] More than 80% of the presenting HCC cases develop in cirrhotic liver and HCC accounts for 75-85% of primary liver cancers.[1-3] The most common cause of HCC cases worldwide is HBV infection with a 54% incidence rate, HCV infection comes second with a 31% rate and the remaining 15% develops due to other causes.[4] The total prevalence of HBV and HCV in HCC cases is above 60% in most countries.[5]

Although hepatic resection and liver transplantation are still considered the gold standard in the treatment of hepatic tumors, most tumors are not surgically resectable at the time of diagnosis. The factors to prevent resection include the number of lesions, proximity with large vascular and biliary structures, residual functional parenchymal insufficiency, and medical co-morbidities.[6]

Currently, curative therapies in HCC treatment include resection, liver transplantation, and ablative techniques. Non-curative treatments include transarterial chemoembolization (TACE), transarterial radioembolization, radiation therapy, and systemic chemotherapy.[7]

In this study, we aimed to determine the risk factors, tumor characteristics and prognostic factors of the patients followed with HCC diagnosis in our hospital and also to investigate the treatment methods and the effect of these treatments on survival time.

Materials and Methods

This was a retrospective study including patients diagnosed as HCC with laboratory, radiological and pathological findings according to the AASLD guideline, between January

2000 and August 2010 at Baskent University Department of Gastroenterology and General Surgery. A total of 158 patients were included in the study. The diagnosis of HCC was made in 117 patients by liver biopsy, and 41 patients were diagnosed according to radiological findings and alpha-fetoprotein (AFP) values. The presence of another malignant disease was considered as an exclusion criterion. Patient data was obtained by reviewing patient records. In our hospital, 120 of 158 patients diagnosed with HCC were treated. Of these, 81 patients had follow-up and survival data.

Treatment methods of our patients included resection, transplantation, radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), TACE, systemic chemotherapy, palliative care, and combinations of these modalities. To evaluate the effects of treatment groups on survival, due to the small number of patients, TACE+RFA, TACE+PEI, TACE+PEI+RFA groups were accepted as the combined treatment group, and RFA, PEI, RFA+PEI groups were accepted as percutaneous ablation group.

Portal vein thrombosis was defined as the detection of thrombus in the main portal vein, right portal vein, or left portal vein branch. The invasion of the main portal vein, hepatic vein, vena cava inferior, or main hepatic artery was accepted as macrovascular invasion. Follow-up time was considered the time from diagnosis until the patient's death or the end of the follow-up period. This study was approved by Baskent University Institutional Review Board (Approval date: 04 May 2010, Project no: KA10/69).

Statistical analyses

Analysis of the data was performed with SPSS for Windows version 11.5 package program. Descriptive statistics were expressed as mean±standard deviation or median (minimum-maximum) for continuous variables, and the number of cases or percentage (%) for categorical variables.

Whether categorical variables have statistically significant effects on survival rates and life expectancy or not was determined with Kaplan Meier survival analysis by using the log-rank test. The 1, 3, and 5-year survival rates, mean survival time, and 95% confidence interval (CI) were calculated for each variable. Whether there was a statistically significant effect of continuous variables on survival rate or not was assessed by using proportional hazard regression analysis of univariate Cox. The hazard ratio and 95% CI for each variable were calculated.

Multivariate Cox proportional hazard regression analysis was used to examine the effects of variables found to be effective on survival as a result of univariate analysis and risk factors thought to be clinically effective. Variables determined as $p < 0.25$ in univariate analysis were included in the multivariate model as candidate risk factors. P-value less than 0.05 was considered statistically significant.

Results

A total of 158 patients were enrolled in the study. The mean age of our patients was 59.9±11.3 years, 84.8% of them were male and 15.2% were female. When we classified patients according to etiology, 53.2% were HBV, 21.5% were HCV, 6.3% were alcohol, 5.7% were HBV+alcohol, 1.9% were HCV+Alcohol, 1.9% were HBV+HCV, and 9.5% were of unknown etiology. The median follow-up time of the 81 follow-up patients was 17.9 months. Patient with the shortest follow-up period was followed for 0.6 months and was in the palliative care group. The patient with the longest follow-up period was followed for 124 months and was in the resection group (Table 1).

Totally 43.9% of the patients were Child A, 31.2% were Child B, 24.8% were Child C. Portal venous thrombosis detected in 30 patients, macrovascular invasion in 20 patients, and distant

metastasis in 11 patients. Since the computed tomography (CT) and MRI results of one patient could not be obtained, these evaluations were made to the remaining 157 patients. Twenty of the 81 patients died during the follow-up period. Other data of the patients are given in Table 1.

Of the 158 patients, 120 were treated, follow-up data was present in only 81 patients. Liver transplantation was performed in 35 patients, resection in 9 patients, TACE in 25 patients, TACE+RFA in 7 patients, TACE+PEI in 12 patients, TACE+PEI+RFA in 1 patient, only RFA in 7 patients, PEI in 4 patients, RFA+PEI in 1 patient, chemotherapy in 2 patients, and palliative care in 17 patients. One patient in the systemic chemotherapy group received 5-fluorouracil (5-FU) and the other patient received doxorubicin, followed by sorafenib.

Survival rate and mean survival time analysis were performed in 81 patients having follow-up data. When evaluated according to univariate analysis, it was determined that the largest lesion size, macrovascular invasion, and distant metastasis had significant effects on overall survival ($p<0.001$, $p<0.001$, and $p<0.001$, respectively, Table 2). The mean survival time of the group with lesion size 5 cm or more was significantly lower than groups with lesion size ≤3 cm and 3.1-5.0 cm ($p<0.001$, $p=0.027$, respectively). There was no significant difference in survival rates between groups with lesion size ≤3 cm and 3.1-5.0 cm ($p=0.422$).

When the effects of age, prothrombin time (PT), total bilirubin, ALT, creatinine and, platelet levels on overall survival were investigated, a statistically significant relationship was found only between creatinine levels and the survival rate (95% CI: 5.857-131.018, $p<0.001$, Table 3).

Among 81 patients in follow-up; 20 patients were in the liver transplantation group, 6 patients were in the resection group, 16 patients in the TACE group, 18 patients in the combined treatment, 9 patients in the percutaneous ablation group, 2 patients in the

chemotherapy group, and 10 patients in the palliative care group. The distribution of these patients according to Child classification is shown in Table 4.

The 1, 3, and 5-year survival rates of patients with liver transplantation were 95.0%, 85.0%, 79.7%, respectively, and the mean survival time was 65.8 months. The 1, 3, and 5-year survival rates of patients with resection were 100% for all. Since there was no mortality in the resection group, the mean survival time was not calculated. The 1 and 3-year survival rates of patients in whom TACE was applied were 61.8% and 0%, respectively, and the mean survival time was 22.3 months. 1, 3, and 5-year survival rates of the combined treatment group were 100%, 66.7%, and 66.7%, respectively, and the mean survival time was 54 months. One year survival rate of the percutaneous ablation group was 66.7% and the mean survival time was 19.6 months. One year survival rate of the palliative care group was 65.6%, and the mean survival time was 17.2 months (Tablo 4).

In univariate statistical analysis, the largest lesion size, macrovascular invasion, distant metastasis, and higher creatinine levels had significant effects on overall survival. Portal venous thrombosis and platelet counts had p values less than 0.25, and Child classification p = 0.253 with borderline probability values, so they were considered candidate risk factors for multivariate analysis. As a result of the multivariate Cox proportional hazards regression analysis, the factors that had the greatest impact on overall survival were, in order of importance, lesion size greater than 5 cm, Child class C, higher creatinine levels, and distant metastasis (p=0.002, p=0.008, p=0.014, and p=0.036, Table 5).

Discussion

HBV was responsible for the etiology of HCC in 53.2% of our patients. HBV positivity in HCC patients was reported as ranging from 44.4% to 65.7% in studies from Turkey.[8-10] The HCV positivity rate was 21.5% in our patients. In studies from our country, the incidence of

HCV in HCC was reported to vary between 21.3-28.6%.[8-11] Except for Russia and Greece where HBV is more prevalent, in European countries HCV is more common than HBV. The same predominance of HCV can be traced in most of the South American countries and in the United States, where HBV is seen at a very low rate (8%). HBV infection is predominant in East Asia countries. In Western Asia, while HBV and HCV rates in Saudi Arabia and Yemen are similar, HBV infection is predominant in Turkey.[5]

The etiologic agent was alcohol in 6.3% of our patients. In other studies from Turkey, the alcohol-induced HCC rate was found to be 5.1%, 5.9%, and 7.2% which were similar to our ratio.[8,10,11] Our HBV+alcohol ratio was 5.7%. In some studies, HBV+alcohol was evaluated within the HBV group while HCV+alcohol was dealt with in the HCV group.[8] HCV+alcohol ratio was 1.9% in our patients. HBV+HCV coinfection was detected at a ratio of 1.9%. In other studies from Turkey, HBV+HCV coinfection ranged between 2-5%.[8-10] The ratio of patients grouped as unknown etiology was 9.5%. In other studies from our country, the rate of patients with unknown etiology ranged from 5.1% to 19.5%.[8,10] The results of our study were compatible with the literature in terms of etiology. Moreover, HBV was the most common cause for the etiology of HCC in Turkey, while HCV was the second. In Turkey was reported that the incidence of hepatitis B decreased from 8.26 per 100,000 people in 2002 to 4.26 per 100,000 people in 2010, explained by HBV vaccination to the newborn since 1998.[12] Turkey's HBV-3 vaccination rate has increased from 72% in 2002 to 98% in 2016.[13]

The male-to-female ratio in our study was 5.5/1. HCC is reported 2 to 3 times more in men than women in most regions of the world and the ratio of male to female in published articles ranges from 2/1-8/1.[1,14] Gender differences in HBV and HCV may explain the higher prevalence of HCC in males. However, environmental differences, geographical differences, hormonal changes, behavioral risk factors (alcohol, smoking), and compliance with antiviral

treatments may further affect these differences.[15] In other studies performed in Turkey, male/female ratios of 3.3/1, 3.7/1, 4/1, and 7/1 have been reported.[8-11]

According to the univariate analysis performed in our study, the survival rate in patients with macrovascular invasion was significantly lower when compared to those without macrovascular invasion. Most studies in the literature have identified macrovascular invasion as an independent prognostic factor in terms of survival.[16-18]

The survival rates at 1, 3, and 5 years were 95%, 85%, and 79.7% respectively, in our liver transplantation patients. Liver transplantation was performed in 10 patients according to the Milan criteria and in other 10 patients according to the expanded criteria.[19] Regardless of the number and size of the tumors, patients without macrovascular invasion and extrahepatic metastasis were included in the expanded group.[19,20] Mean survival time was 68.6 months in our patients who met the criteria of Milan, and 60.3 months in the group of patients beyond Milan criteria. When comparing these two groups according to univariate analysis, there was no significant difference in mean survival time. Poon and colleagues conducted 43 liver transplantations based on the Milan criteria and found that 1, 3, and 5-year survival rates were 98%, 92%, and 81%, respectively. In a liver transplantation study of Yao et al. including 70 patients, 1 and 5-year survival rates in ≤pT2 HCC were 91,3% and 72,4%, respectively, while 82.4% and 74.1% in pT3 tumors.[21,22] Our survival rates were similar to the results of these studies.

The 5-year survival rate in our resection group was 100%. Survival rates after resection were as follows in the literature, 58-100% for 1-year survival, 28-88% for 3-year survival, 11-75% for 5-year survival, and 19-26% for 10-year survival.[23] The higher 5-year survival rate observed in our study may be due to the small number of patients included.

TACE, RFA, PEI, the combination of these treatments or chemotherapy was applied to patients who were unresectable, liver transplantation was contraindicated, or was not

convenient for transplantation. The benefit of combined treatment of TACE+PEI was first demonstrated by Tanaka et al.[24] The rationale of combined treatment is to reduce the tumor density after TACE and to dissolve intratumoral septa thus increasing ethanol diffusion into the tumor.[25] PEI addition after TACE was expected to increase complete necrosis.[26] In subsequent studies, this also proved valid for RFA.

When we evaluated by multivariate analysis, independent poor prognostic factors on survival included tumor size greater than 5 cm, Child class C, higher creatinine levels, and distant metastasis. In their study of 1569 HCC patients, Shi et al. reported Child-Pugh classification, macrovascular invasion and largest tumor size as independent prognostic factors.[18] Schwarz et al. also noted distant metastasis, largest tumor size, and macrovascular invasion as independent prognostic factors in HCC.[17] The creatinine level was not assessed in the above studies. In studies evaluating creatinine level, it was detected to be an effective prognostic factor on survival.[27-29]

In conclusion, our study shows that hepatitis B virus was the most common causative agent of HCC etiology, followed by hepatitis C virus infection. Hepatitis B vaccination in newborns should be continued, and the vaccination rate should be kept at the highest level. Vaccination of high-risk groups should be given importance. The most effective treatment methods on survival were liver transplantation and hepatic resection in eligible patients with HCC. Tumor size greater than 5 cm, Child class C, higher creatinine levels, and distant metastasis were found to be independent prognostic factors on survival.

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Table 1. Baseline Characteristics of Patients

Variables	**n=158**
Age (year) [mean±sd (min-max)]	59,9±11,3 (17-90)
Gender	[n (%)]
Male	134 (84,8%)
Female	24 (15,2%)
Etiology	[n (%)]
HBV	84 (53,2%)
HCV	34 (21,5%)
Alcohol	10 (6,3%)
HBV+Alcohol	9 (5,7%)
HCV+Alcohol	3 (1,9%)
HBV+HCV	3 (1,9%)
Unknown etiology	15 (9,5%)
Number of lesions [median (min-max)]	2 (1-5)

Single nodule [n (%)]	73 (46,5%)
Two nodules [n (%)]	23 (14,6%)
Three nodules [n (%)]	18 (11.5%)
More than three nodules [n (%)]	39 (24.8%)
Diffuse [n (%)]	4 (2,5%)
Largest lesion size (cm) [median (min-max)]	3,75 (1,2-29)
Largest lesion size (cm)	[n (%)]
≤3 cm	57 (36,1%)
3.1-5.0 cm	41 (25,9%)
>5.0 cm	54 (34,2%)
Child classification	[n (%)]
Child A	69 (43,9%)
Child B	49 (31,2%)
Child C	39 (24,8%)
Albumin (g/dl) [median (min-max)]	3,4 (2,1-4,8)
PT (second) [median (min-max)]	15,8 (12,0-33,0)
Total bilirubin (mg/dl) [median (min-max)]	1,5 (0,2-32,9)
ALT (u/l) [median (min-max)]	43,0 (6,0-962,0)

Creatinine (mg/dl) [median (min-max)]	0,8 (0,4-3,3)
Platelet (x10^3/µl) [median (min-max)]	111,5 (27,0-451,0)
AFP (ng/ml) [median (min-max)]	26,7 (1,85-1168789,0)
AFP level (ng/ml)	[n (%)]
≤20.0	64 (46,7%)
20.1-200.0	33 (24,1%)
>200.0	40 (29,2%)
Portal venous thrombosis*	30 (19,1%)
Macrovascular invasion*	20 (12,7%)
Distant metastasis*	11 (7,0%)
Exitus#	20 (24,7%)
Follow-up time (month) [median (min-max)]	17,9 (0,6-124)

sd: Standard deviation; min: Minimum; max: Maximum; HBV: Hepatitis B virus; HCV: Hepatitis C virus; PT: Prothrombin time; ALT: Alanine aminotransferases; AFP: Alpha-fetoprotein.
*The calculation was made on 157 subjects, #The calculation was made on 81 subjects.

Table 2. Univariate Analysis Results

Variables	Survival Rates (%)			Mean survival time (month) (95% CI)	P*
	1 Year	3 Years	5 Years		
Gender					0,656
Male (n=68)	83,1	69,3	65,9	83,8 (68,0-99,6)	
Female (n=13)	83,3	83,3	83,3	60,0 (45,9-74,2)	
Etiology					0,513
HBV (n=44)	80,9	73,8	73,8	94,0 (77,5-110,4)	
HCV (n=19)	82,4	54,1	36,1	43,2 (27,7-58,7)	
Alcohol (n=2)	50,0	na	na	10,5 (0,0-23,1)	
HBV+Alcohol (n=6)	83,3	83,3	83,3	53,1 (35,0-71,3)	
HCV+Alcohol (n=2)	100,0	-	-	29,5 (29,5-29,5)	
Unknown etiology (n=8)	100,0	100,0	100,0	70,5 (64,5-76,5)	
Child classification					0,253
Child A (n=41)	88,1	71,7	71,7	88,2 (66,8-109,6)	
Child B (n=22)	85,4	85,4	56,9	49,9 (36,1-63,8)	
Child C (n=18)	61,1	54,3	54,3	43,8 (27,8-59,8)	
Number of lesions					0,722

Single nodule (n=40)	84,3	60,2	45,2	52,0 (40,3-63,7)	
Two nodules (n=10)	88,9	88,9	88,9	111,2 (86,7-135,4)	
Three nodules (n=11)	81,8	81,8	81,8	58,7 (43,0-74,3)	
More than three nodules (n=18)	80,5	71,6	61,3	54,1 (37,8-70,4)	
Diffuse (n=2)	50,0	50,0	50,0	38,6 (0,0-88,8)	
Largest lesion					<0,001
≤3.0 cm (n=36)	94,2	85,6	85,6	102,3 (84,5-120,0)	
3.1-5.0 cm (n=18)	88,9	67,7	67,7	56,6 (41,9-71,3)	
>5.0 cm (n=25)	63,7	31,9	-	25,5 (17,0-33,9)	
Portal venous thrombosis					0,197
No (n=69)	85,1	74,5	70,8	88,6 (73,1-104,0)	
Yes (n=12)	70,1	35,1	35,1	38,1 (15,3-61,0)	
Macrovascular invasion					<0,001
No (n=76)	86,6	73,5	70,0	88,7 (73,8-103,6)	
Yes (n=5)	0,0	-	-	4,7 (2,1-7,3)	
Distant metastasis					<0,001
No (n=76)	85,1	72,2	68,8	87,4 (72,5-102,3)	
Yes (n=5)	na	na	na	3,5 (2,0-5,0)	
AFP					0,520
≤20.0 (n=39)	92,3	78,2	78,2	62,0 (53,4-70,5)	
20.1-200.0 (n=13)	90,9	75,8	75,8	61,4 (42,3-80,5)	
>200 (n=19)	81,4	69,8	55,8	79,2 (47,4-110,9)	

Albumin					0,379
≤3.5 (n=44)	81,3	66,5	59,1	51,9 (41,1-62,6)	
>3.5 (n=37)	85,4	75,5	75,5	91,0 (70,9-111,1)	
General	83,1	70,5	67,2	85,4 (70,6-100,2)	-

CI: Confidence interval; HBV: Hepatitis B virus; HCV: Hepatitis C virus; na: Not analyzed; AFP: Alpha-fetoprotein.
*Kaplan-Meier survival analysis by using the log-rank test.

Table 3. Univariate Analysis Results

Variables	HR	95% CI	P-Value*
Age	1,003	0,961-1,047	0,883
PT	0,977	0,855-1,117	0,737
Total bilirubin	0,982	0,829-1,162	0,830
ALT	1,000	0,991-1,010	0,959
Creatinine	27,702	5,857-131,018	<0,001
Platelet	1,004	0,999-1,009	0,083

HR: Hazard ratio; CI: Confidence interval;
PT: Prothrombin time; ALT: Alanine aminotransferases.
*Cox proportional hazards regression analysis

Table 4. Evaluation of Survival Rates and Mean Survival Time According to Treatment Groups

	Child A	Child B	Child C	Survival Rates (%)			Mean survival time* (month) (95% CI)
	n	n	n	1 Year	3 Years	5 Years	
Liver transplantation (n=20)	6	4	10	95,0	85,0	79,7	65,8 (55,8-75,7)
Resection (n=6)	5	1	0	100,0	100,0	100,0	na
TACE (n=16)	12	1	3	61,8	0,0	-	22,3 (14,5-30,0)
Combined treatment (n=18)	12	6	0	100,0	66,7	66,7	54,0 (26,3-81,6)
Percutaneous ablation (n=9)	2	3	4	66,7	-	-	19,6 (12,8-26,3)
Chemotherapy (n=2)	1	1	0	-	-	-	-
Palliative care (n=10)	3	6	1	65,6	-	-	17,2 (8,7-25,7)

CI: Confidence interval; na: Not analyzed; TACE: Transarterial chemoembolization.
*Kaplan-Meier survival analysis

Table 5. Multivariate Analysis of All Possible Risk Factors

Variables	HR	95% CI	P-Value
Child B	1,973	0,376-10,363	0,422
Child C	7,054	1,647-30,215	0,008
Lesion size 3.1-5.0 cm	3,682	0,736-18,418	0,113
Lesion size >5.0 cm	13,707	2,680-70,118	0,002
Portal venous thrombosis	1,670	0,409-6,830	0,475
Macrovascular invasion	1,445	0,191-10,938	0,722
Distant metastasis	12,237	1,177-127,208	0,036
Creatinine	19,477	1,840-206,129	0,014
Platelet	1,004	0,997-1,011	0,265

HR: Hazard ratio; CI: Confidence interval.