RESEARCH COMMUNICATION

Clinicopathological Characteristics of Hepatocellular Carcinoma in Turkey

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Abstract

Background: Hepatocellular carcinoma (HCC), the main malignant tumor of the liver, is very common and highly lethal. The aim of this study was to determine its clinicopathologic characteristics and risk factors in Turkey. Materials and methods: In this study, patients who were diagnosed as suffering from HCC in the period between August 2004 and December 2011 were evaluated retrospectively. Results: A total of 98 patients were included, with a median age 61 (range: 16 to 82). Seventy nine (80.6%) were male 59 (60.2%) were infected with hepatitis B virus (HBV) and 15 (15.3%) with HCV, another 15 (15.3%) being alcohol abusers. Seventy two (73.5%) were at advanced stage and 54 (55.1%) had elevated serum alpha-fetoprotein (AFP). Surgery, chemoembolization, systemic chemotherapy and application of the tyrosine kinase inhibitor sorafenib were the major treatment options. Conclusions: According to our findings HCC is mostly diagnosed in advanced stage and age, being five times more common in males than females. Main risk factors of HCC are HBV infection, HCV infection and alcohol abuse. Elevation in AFP may facilitate early diagnosis of HCC in high risk groups.

Keywords: Hepatocellular carcinoma - etiologic factors - alpha-fetoprotein - early diagnosis - Turkey

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Introduction

Primary liver cancer is one of the most common, and highly lethal malignant tumors worldwide. Hepatocellular carcinoma (HCC) forms aproximately 80% of all primary tumors of liver. It has high incidence rate which is sixth most common cancer in males and ninth most common cancer in females (Jemal et al., 2009). The incidence of HCC shows geographical variability, it is most frequent in southeast Asia and subSahara Africa that have more than 15 cases per 100000 population per year, less frequent in western countries (Beasley et al., 1981; Parkin, 2000; DeVita et al., 2008). According to Ministry of Health report that was published in 2003, the HCC incidence of in Turkey was 0.83/100000 (Alacacioglu et al., 2008). In Asia and Africa, high incidence rate of HCC have been associated both high endemic hepatitis B carrier rates as well as mycotoxin contamination of foodstuffs, stored grains, drinking water, and soil (Yue, 1995; Ueno et al., 1996; Fattovich et al.,1997). Studies from western countries have shown rising incidence of HCC (Taylor-Robinson et al., 1997; El-Serag et al., 1999; Law et al., 2000; Remontet et al., 2003). The reasons of rising incidence predominantly attributed to the increasing prevelance of hepatitis B virus (HBV) and hepatitis C Virus (HCV) due to immigration from eastern countries to westhern countries. On the other hand increasing incidence is also related to improved care for individuals with cirrhosis has resulted in prolonged and a relatively greater opportunity for malignant changes to develop. HCC is the major cause of death in cirrhotic patients in Europe (Bosch et al., 2004; Trevisani et al., 2002; Calvet et al., 1990). Once cirrhosis is present, up to 20% of patients will develop HCC over 10 years (Di Bisceglie et al., 1997).

The distrubution of HCC also differs among ethnic groups, sex and age (1). There are many etiologic factors which play a role in development of HCC. The cirrhosis the most important risk factor for HCC. The main etiologic factors that lead to cirrhosis are chronic viral infections of liver (HBV and HCV). Other risk factors that related to development of HCC are chronic alcohol intake, autoimmune chronic active hepatitis, cryptogenic cirrhosis, nonalcoholic fatty liver disease, chronic metabolic diseases of liver such as hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency, tyrosinemia, porphiria cutanea tarda, orotic aciduria, Alagille's syndrome and environmental factors such as aflatoxin, thorotrast, androgenic steroids, cigarette smoking (DeVita et al., 2008; Bugianesi , 2007). Although the mechanisms by which these varied etiologies lead to HCC are not fully elucidates. It is accepted that development of HCC in a given individual is a multi-step process and the result of an accumulation of risks of

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multifactorial etiology.

The aims of this study were to define tumor characteristics of patients who were applied to our centers, to identify risk factors of HCC that have impact on survival, and to find out association between alpha-fetoprotein (AFP) levels and outcome of patients.

Materials and Methods

The 98 patients who were referred to medical oncology department of the Hacettepe University Institute of Oncology and Van Yüzüncü Yıl University Hospital in the period between Agust 2004 and December 2011, included in this study

The patients were defined as HCC which is either by histopathological confirmation or characteristic radiologic apperance which is an early hyperenhanced arterial vascularization, followed by enhanced hypoattenuation (wash-out) in the late phase of imaging plus elevated alpha-foetoprotein (AFP) level (>200 ng/ml).

Demographics and tumor characteristics included biologic markers, tumor size, grade, stage and nodal status of the patients were evaluated retrospectively. Tumor staging were done according to American Joint Committee on Cancer, TNM Staging on Liver Tumors.

The alcohol abuse is defined as daily alcohol intake was > 60 g for vomen and > 80 g for men more than 10 years.

The upper limit of AFP of normal on assay used is 5.8 ng/ml. Furthermore, the patients were grouped according to venous blood AFP level as normal (<5.8 ng/ml), mild (5.8-20 ng/ml), moderate (20-200 ng/ml) and severe (>200 ng/ml).

All statistical analyses were performed with SPSS for Window software (RE SPSS 13.0; SPSS Chicago, IL). Desciptive statistics of relevant demographic and clinical features were performed. We compared Kaplan-Meier curves for all time-to-event outcome measueres with the standard (non-stratified) log rank test. We defined overall survival (OS) as the time from diagnosis to death from any cause. A two tailed P value <0.05 was considered significant in all tests.

Results

A total of 98 patients were evaluated. The median age at presentation was 61 (range: 16 to 82) years. Median OS was 7.0 (range 0 to 145) months in all patients. Nineteen (18.4%) patients were female and seventy nine (81.6%) patients were male. Median OS was significantly longer in female patients than male patients (p<0.024; Figure 1). Forty five (45.9%) patients were smoker. Fifty nine (60.2%) patients were infected by HBV, fifteen (15.3%) patients were infected by HCV and two (2.0%) patients were infected by hepatitis D virus (HDV). Median OS was significantly shorter in patients who were infected with HBV (p<0.016; Figure 2).

Fifteen (15.3%) patients were alcohol abuser. Median OS was significantly shorter in alcohol abusers compare to non-alcohol abusers (p<0.002; Figure 3).

When patients were analyzed for Child-Pugh classification, fifty seven (58.2) patients were Child-Pugh Class A, seventeen (17.3%) patients were Clild-Pugh Class B and eleven (11.2%) patients were Child-Pugh Class C. Median OS was significantly longer in Child-Pugh Class A group (P=0.000; Figure 4).

When AFP levels were analysed we found out that thirty three (31.6%) patients had mild (<20 ng/ml) elevation, seventeen (17.3%) patients had moderate (20-200 ng/ml) elevation and thirty seven (37.8%) patients had severe (>200 ng/ml) elevation. Median OS was significantly longer in the patients who had low AFP level (p<0.038; Figure 5).

By the assessment of tumor size, nine (9.2%) patients

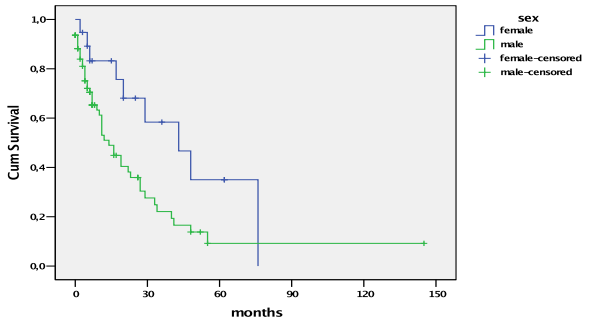

Figure 1. Survival of HCC Patients According to Sex

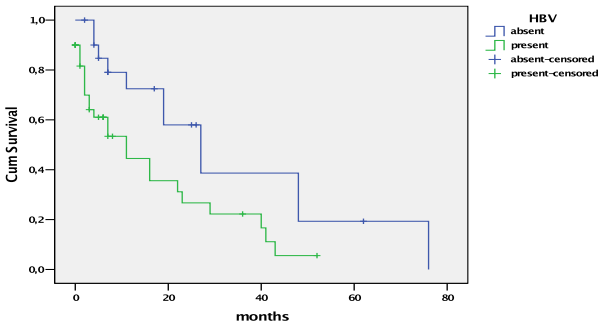

Figure 2. Survival of HCC Patients According to HBV

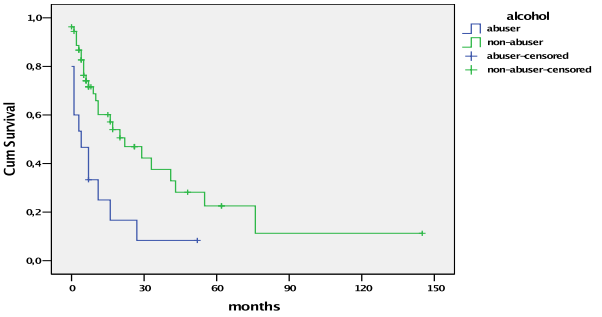

Figure 3. Survival of HCC Patients According to Alcohol Abuse

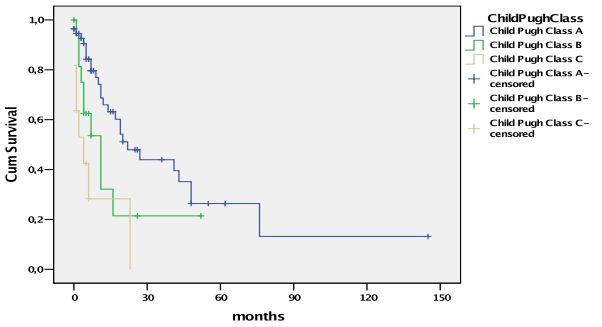

Figure 4. Survival of HCC Patients According to Child-Pugh Class

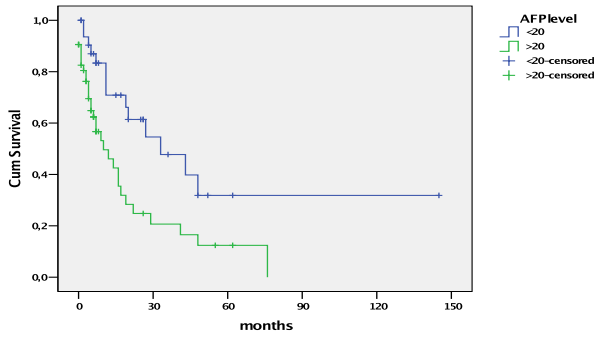

Figure 5. Survival of HCC Patients According to AFP Levels

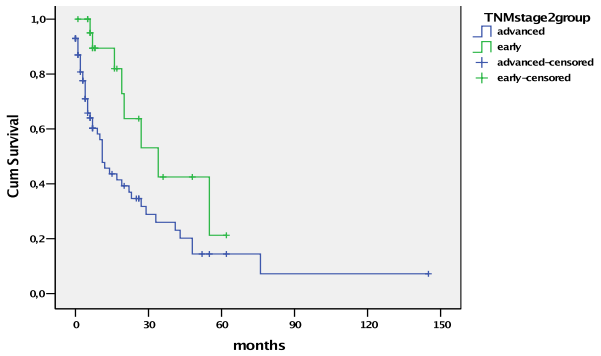

Figure 6. Survival of HCC Patients According to TNM Classification

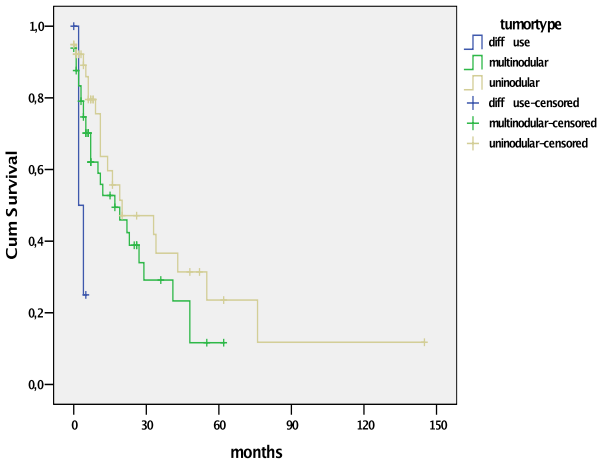

Figure 7. Survival of HCC Patients According to Tumor Type

had T1 tumors, sixteen (16.3%) patients had T2 tumors and sixty nine (70.4 %) patients had T3 tumors. When nodal status was examined, seventy seven (78.6%) patients had N0 and eighteen (18.4) patients had N1 node. Eighty (81.6%) patients had no metastasis and fifteen (15.3%) patients had metastasis. According to TNM staging, ten (10.2%) patients were at stage I, thirteen (13.3%) patients at stage II, fourty five (45.6%) patients at stage IIIA, twelve (12.2%) patients at stage IIIC and fifteen (15.3%) patients at stage IV. TNM stage of three (3.1%) patients were unknown. Median OS was significantly longer in early (stage I and II) stage compare to the advanced (stage III and IV) (P<0.015; Figure 6).

Among all patients, fourty (40.8%) patients had uni-nodular tumors and fourty seven (48%) patients had multinodular tumors and eight (8.2%) patients had diffuse tumors. Median OS was significantly longer in uninodular type tumors than multinodular and diffuse type tumors (P<0.020; Figure 7).

All patients were also evaulated for type of treatment that was performed. Nine (9.2%) patients had undergone to surgery. Chemoembolization is performed in fourteen (14.3%) patients. Twenty (20.4%) patients had cisplatin, interferon, adrimycin, 5-Fluorouracil combination chemotherapy protocol, eight (8.2%) patients had single agent adriamycin, five (5.1%) patient had 5-fluorouracil and folinic acid, four (4.1%) patients had UFT and six (6.1%) patients had treated with tyrosine inhibitor sorafenib. There was no any statistically significant difference between all treatment type for median OS.

All common characteristics of the patients are represented in Table 1.

Table 1. Clinical and Pathologic Characteristics of the 356 CRC Cases in this Study

		n (%)
N		98 (100)
Age (median; min-max)		61 (16-82)
Sex	Male	80 (81.6)
	Female	18 (18.4)
Hepatitis B serology:	Negative	28 (28.6)
	Positive	59 (60.2)
	Unknown	11 (11.2)
Hepatitis C serology:	Negative	72 (73.5)
	Positive	15 (15.3)
	Unknown	11 (11.2)
Hepatitis D serology:	Negative	85 (86.7)
	Positive	2 (02.0)
	Unknown	11 (11.2)
Alcohol intake:	Negative	54 (55.1)
	Positive	15 (15.3)
	Unknown	29 (29.6)
AFP level, ng/ml:	<20	33 (33.7)
	20-200	17 (17.3)
	>200	37 (37.8)
	Unknown	11 (11.2)
Child-Pugh classification:	Class A	57 (58.2)
	Class B	17 (17.3)
	Class C	11 (11.2)
	Unknown	13 (13.3)
Tumor type:	Uninodular	40 (40.8)
	Multinodular	47 (48.0)
	Diffuse	8 (08.2)
	Unknown	3 (03.1)
Tumor:	T1	9 (09.2)
	T2	16 (16.3)
	T3	69 (70.4)
	T4	0
	Unknown	4 (04.1)
Nodal Status:	N0	77 (78.6)
	N1	18 (18.4)
	Unknown	3 (03.1)
Metastasis:	M0	80 (81.6)
	M1	15 (15.3)
	Unknown	3 (03.1)
TNM:	Stage I	10 (10.2)
	Stage II	13 (13.3)
	Stage III A	45 (45.9)
	Stage IIIB	0
	Stage IIIC	12 (12.2)
	Stage IV	15 (15.3)
	Unknown	3 (03.1)

Discussion

HCC is malign epithelial liver tumor which is the fifth most frequent cancer and the third most common cause of cancer related mortality in the world (Kamangar et al., 2006). The life expectancy of patients with newly diagnosed HCC is classically been measured in weeks to months. Despite all avaliable treatment options the incidence and mortality rate are nearly equals to each other. In this present study, we aimed to investigate clinicopathological characteristics and risk factors of the 98 patients who refered to our medical oncology due to HCC.

According to our findings, HCC was mostly seen in elderly, male and advanced stage as seen in previous studies (Nagasue et al., 1985; Tsukuma et al., 1993; Jemal et al., 2009). The main risk factors were HBV, HCV and alcohol intake. More than half of the patients had elevated AFP.

HCC is more commonly seen in elderly patients, most probably due to long time of exposure to the underlying etiologic factor such as viral infection, chronic metabolic disorder of liver. According to a prospective Spanish study which had been done by Velázquez RF et al, there is a 4-fold greater risk for developing HCC in patients older than 54 years (Velázquez et al., 2003). In our study, median age was 61 years. Like studies that had been performed in westhern country, presentation of HCC was in older age. On the other hand, a mean age of presentation is decreasing in sub-Saharan Africa to a mean of 33 years (Prates et al., 1965).

The distrubution of HCC also differs among ethnic groups, regions within the same country, sex and age (Jemal et al., 2009). Men are at higher risk for HCC then vomen. In present study, HCC is approximately five times more common in the male than in female and overall median survival found to be significantly longer in female patients. Until now, it was not well understood why HCC is more common in male. Nagasue et al speculated that estrogens and androgens modulate hepatocarcinogenesis (Nagasue et al., 1985).

Hepatitis B virus has well known risk factor that play a role in development of HCC. The annual incidence of developing HCC in HBV infected patients at age 70 is 1%. HBV carriers were 100 times more likely to develop HCC than the uninfected patients, but HCC occurs more commonly in patients with established cirrhosis than in noncirrhotic patients (Beasley et al., 1981; Fattovich et al., 1991; Koike et al., 2002; Manno et al., 2004). It has been shown by Beasley at al that the annual incidence of HCC in HBV carriers was 0,5% (Beasley et al., 1981). HBV has eight genotypes (A-H) with distinc geopraphic distrubutions, separated by 8% sequence difference between genotypes and there had been shown significant differences in disease progression among this genotypes. Genotypes F and C are associated with HCC (Schaefer, 2005). Simonetti et al emphasizes that HCC can develop especially in chronic HBV-infected persons who remain HBsAg positive but it should be kept in mind that HCC can still occur in after clerance of HBsAg (Simonetti et al., 2010). Liaw YF and et al stated that in HBV-related cirhosis, antiviral therapy with lamuvudine is decreasing rate of HCC development (Liaw et al., 2004). Thus prevention of HBV-related HCC is best accomplished by vaccination program (Lok, 2004). In current study, we found that fifty nine (60,2%) patients who develop HCC had chronic HBV infection and HBV infected patients had short median overall survival time compare to the uninfected patients.

HCC incidence is also increased in patients infected by HCV especially in patients who have established cirrhosis (Degos et al., 2000; Fattovich et al., 2000). However, it is difficult clinically to determine the transition from bridging fibrosis to cirrhosis. Therefore surveilance may be offered to patients with HCV and cirhosis or with bridging fibrosis or transition to cirrhosis. In present study, hepatitis C infection was determined in fifteen (15,3%) patients. In some studies, it has been shown that regardless of liver function, low platelet count can be used as non-invasive marker to predict development HCC (Degos et al., 2000; Moriyama, 2003). In this study, we did not find any significant relationship between HCC and HCV and platelet count.

Alcoholic cirrhosis is a risk factor of development of HCC. Lee FI reported that the annual incidence of HCC in alcohol related cirrhosis is approximately 1-4% (Lee, 1966). In another study, it has been shown that alcoholic liver disease accounted for 32% of all HCC (Hassan et al., 2002). In our study we found that fifteen (15,3%) patients with HCC had alcohol history which is lower than rate of western countries (Schöniger-Hekele et al., 2000). Furthermore in our study, alcohol abusers had significantly shorter median overall survival time in compare to non-abusers. Low rate of alcohol related HCC is most probably due to the islamic population our country. Hajiani et al also found low rate of alcohol related HCC in Iran (Hajiani et al., 2005).

Tumor markers are useful tools in cancer diagnosis, staging, detecting prognostic pattern, monitoring therapeutic effectiveness, detection of recurrence, localization of tumor and screening the general population or groups at risk. Although alfa-feto protein is one of the good serologic marker that has been used in diagnosis of HCC. It has a poor sensitivity rate ranging from 39% to 65% and a specifity ranging from 76% to 97%. The value over 200 ng/ml is reliable as tumor marker and a consistent rise in AFP level may also reliable marker during the follow up (Giannelli, 2006). Xu J et al stated that high levels of AFP (>20 ng/ml) signify a highly malignant tumor and unfavorable prognosis (Xu et al, 2012). In our study fifty four (55.1%) patients had elevated AFP (>20 ng/ml) which is consistent with previous studies (Daniele et al., 2004; Marrero et al., 2004). The patients who had AFP level above 20 ng/ml had significantly worse prognosis compare to the patients who had normal level. In patients who had elevated AFP level, further diagnostic procedures can be performed. Therefore high level AFP in risk groups can be used early diagnostic parameter. There are some other biomarkers which had been investigated in HCC such as AFP-L3, des-gamma carboxy prothrombin, glypican-3 and squamous cell carcinoma antigen, but it was found that they have no superiority to AFP.

The prognosis of hepatocellular carcinoma primarly depends on stage at presentation which means large tumor. Tsujita E et al stated that larger tumor size is an independent and significant poor prognostic factor for HCC (Tsujita et al., 2012) and Ma C et al also found that early stage HCC were closely correlated with better prognosis (Ma et al., 2012). Number of tumor nodules in liver has impact on overall suvival, according to Chan KM et al the patients with multıple tumors (>three) had higher risk of recurrence after liver transplantation and shorter overall survival (Chan et al., 2011). Therefore, it should be kept in mind that small tumor has better prognosis. However, there are different staging systems such as TNM (Edge et al., 2010), Okuda (Okuda et al., 1985), Barcelona Clinic Liver Cancer (BCLC) (Llovet et al., 1999) (Cancer of the Liver Italian Program (CLIP) (The CLIP investigators, 1998) and there is no worldwide consensus on the use of one of the particular staging system. It is crucial to decide stage of HCC because of variable treatment options. In this present study, according to TNM classification, seventy two (73.5%) patients were at advanced stage (stage III and IV). This finding showed that diagnosis of HCC is usually at advanced stage which can be explain by the late symptomatic disease characteristic. Furthermore in current study, median overall survival time found to be significantly longer in early stage patients.

In conclusion, HCC is highly lethal tumor and generally diagnosed in advanced stage (stage III and IV) in Turkey. Therefore patients who diagnosed as HCC have very short life expectancy. Early diagnosis of the disease is very important because of having chance of curative treatment modalities such as surgery, radiofrequency ablation, percutaneous intratumoral ethanol injection, orthotopic liver transplantation. Determination of risk factors such as HBV and HCV infection and alcohol consumption is critical in risk groups. Close follow up with serial ultrasonography and serum AFP level in patients who have risks factors may provide early diagnosis of HCC.

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