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Hepatosellüler Karsinomlu Hastaların Geriye-Dönük Değerlendirilmesi-Tek Merkez Deneyimi

ÖZET

Amaç: Primer karaciğer kanserleri, dünyada en sık ve en ölümcül tümörlerden birisidir. Hepatosellüler formları tüm primer karaciğer tümörlerinin yaklaşık %80'idir. Bu çalışmada amacımız kliniğimize başvuran hepatosellüler kanserli olguların retrospektif değerlendirmesini yapmaktır.

Yöntem: Öncelikle hepatosellüler karsinomalı her birey, tanı koyma aşamasında ve hepatosellüler karsinoma gelişimi döneminde var olan viral hepatit serolojisi yönünden ve antiviral tedavi alıp almadıkları yönünden incelendi. Sirotik hastalarda Child-Pugh evresi, non-sirotik vakalarda viral hepatitin evresi ve yaşam beklentisi bilinen hastalarda ortalama yaşam beklentisi değerlendirildi. Alfa-feto protein, kompüterize tomografi, ultrason ve manyetik rezonans görüntüleme bulguları retrospektif olarak değerlendirildi. Alfa-feto Protein seviyeleri ve tümör sayıları arasında ki ilişki istatistiksel olarak araştırıldı.

Bulgular: Toplam 69 hasta değerlendirildi. Başvurudaki ortalama yaş değerleri 62,8 (25-80 yaş) yıldı. Ortalama yaşam beklentisi tüm hastalar için 7,0 ay (0-145 ay) olarak hesaplandı. 18 hasta (%41,9) Child-Pugh sınıf A, 12 (%27,9) hasta Child-Pugh sınıf B ve 13 hasta (%30,2) Child-Pugh sınıf C olarak değerlendirildi. Aşırı alfa-feto protein seviyesi (>200 ng/ml) olan hastalarda multipl karaciğer kitlesine rastlanma riski 4 kat (OR: 4,05, %95 CI: 1,22-13,42) daha yüksek bulundu. Karaciğer kitlesini hepatosellüler karsinom olarak tanımlamada ki etkilerine bakıldığında tanısal etkinlik kompüterize tomografide %54,3, manyetik rezonans görüntülemede ise %55,8 olarak bulundu.

Sonuç: Sonuç olarak hepatosellüler karsinom tanısı laboratuvar ve görüntüleme teknikleri ile konur. Alfa-feto protein seviyeleri bu hastaların takibinde ve çoklu kitleleri tanımlamada önemlidir.

Anahtar Kelimeler: Hepatosellüler Karsinom, Alfa-Feto Protein, Görüntüleme, Retrospektif.

Retrospective Evaluation of Patients with Hepatocellular Carcinoma: Single-Center Experience

ABSTRACT

Objective: Primary liver cancer is one of the most common and lethal type of tumors in the world. Hepatocellular forms compose about 80% of all primary liver tumors. Our aim is to evaluate the patients with hepatocellular carcinoma admitted to our clinic retrospectively.

Methods: First we identified viral hepatitis serology and whether antiviral treatment was administered before the diagnosis and the period until the development of hepatocellular carcinoma for each case with hepatocellular carcinoma. Child-Pugh stage in cirrhotic cases, the stage of viral hepatitis in non-cirrhotic cases, and the treatment method suggested for hepatocellular carcinoma and the average life expectancy (for the patients whose life expectancy is known) were evaluated. Alpha-feto protein levels and computerized tomography, ultrasound, magnetic resonance imaging findings were evaluated retrospectively. Correlation between alpha-feto protein levels and tumor numbers were evaluated statistically.

Results: Total of 69 patients were evaluated. The median age at presentation was 62.8 (ranging from 25 to 80) years. Median (overall survival) OS was 7.0 (ranging from 0 to 145) months in all patients. 18 patients (41.9%) were Child-Pugh Class A, 12 (27.9%) patients were Child-Pugh Class B and 13 (30.2%) patients were Child-Pugh Class C. It was found that patients with severely high alpha-feto protein levels (>200 ng/ml), have 4 fold risk of multiple liver masses (OR: 4.05, 95% CI: 1.22-13.42). For the characterization of a liver mass as hepatocellular carcinoma, the diagnostic effectiveness of computerized tomography was 54.3%, and that of magnetic resonance imaging was 55.8%.

Conclusion: As a result the patients with hepatocellular carcinoma can be diagnosed with combination of laboratory findings and imaging techniques. Alpha-feto protein levels are important for follow up of such patients and identifying the multiple mass presences.

Keywords: Hepatocellular Carcinoma, Alpha-Feto Protein, Imaging, Retrospective

INTRODUCTION

Primary liver cancer is one of the most common and lethal type of tumors in the world. Hepatocellular forms are about 80% of all primary liver tumors (1), and the most common primary malign tumors in the liver. Hepatocellular carcinoma (HCC) is the fifth most common malign disease among men and eighth among women. It ranks the fourth in the list of causes of death associated with cancer. The incidence of HCC is three or four times higher in developing countries compared to the western countries. Men are under higher risk compared to women. Its incidence increases together with aging. The average age of diagnosis is 65 among men and 60 among women (2).

The incidence and etiology of HCC vary from one geographical region to another. The incidence is high in the East Asia and Southeast Africa (3). Hepatitis B is endemic in Turkey, and the rate of hepatitis carriers is 5 to 10%. The prevalence of hepatitis C is 1.5%. According to the records of the Ministry of Health, the incidence of HCC is 0.83% (4). The most significant factors that play a role in the development of HCC are cirrhosis, viral hepatitis, alcohol, and metabolic and autoimmune liver diseases. Independent of etiological factors, cirrhosis is the main risk factor for the development of HCC. Annual HCC incidence is 3% among patients with compensate cirrhosis (5).

Hepatitis B is one of the most important epidemiological factors associated with HCC particularly in developing countries. The most critical factor that determines the development risk of HCC in hepatitis B patients is the activity of the disease. The annual HCC incidence is 0.5% in chronic inactive hepatitis B infections, 0.8% in histologically active hepatic individuals, and 2.7% in cirrhotic patients. The other two significant factors associated with the development of HCC in hepatitis B patients are race and the age of catching the infection (6,7).

In the western countries and in Japan, hepatitis C has been the most important risk factor for the development of HCC. Individuals with chronic hepatitis C have 17.5 fold risk compared to those who do not have chronic hepatitis C (8). The annual HCC incidence is 1.8% among individuals with non-cirrhotic chronic hepatitis C and 7.1% among the cirrhotic individuals (9). Excessive alcohol consumption, hemochromatosis and Wilson's disease are the other major factors causing HCC (10-13).

The classic symptoms of HCC are right upper quadrant pain and loss of appetite. In stabile cirrhotic patients, the presence of sudden deterioration in liver functions, new ascites, hepatic encephalopathy and intra-abdominal bleeding should raise suspicion of HCC. Findings in an examination vary according to the stage of the disease. The main findings in physical examination are hepatomegaly, a palpable mass in the liver, a murmur on the liver, and ascites associated with the underlying cirrhosis or rarely with peritoneal metastasis. The major paraneoplastic syndromes related to HCC are hypoglycemia in 5% and polycythemia in 10% of the patients (14).

Focal liver lesions can be diagnosed by using clinical findings, laboratory data, imaging techniques, and mostly histopathological evaluation (2,15). In asymptomatic patients; incidental lesions are usually benign. Although cysts, hemangiomas and focal nodular hyperplasia (FNH) are the mostly diagnosed lesions, HCC should be excluded (16-18). Histopathological evaluation sometimes should be performed to diagnose the certain lesion because of establishing the characteristics and origin of metastatic lesions, and identifying the dysplastic lesions from hepatocellular carcinoma (19). HCCs can be diagnosed by invasive methods, such as biopsy, and non-invasive methods including magnetic resonance imaging (MRI), computed tomography (CT) imagines, ultrasonography (USG) and tumor markers such as alpha-feto-protein (20,21). Alpha-fetoprotein (AFP) is the most common used markers for the early diagnosis of HCC in cirrhotic patients, and also it has been considered as the gold-standard serum marker for screening patients at high risk for HCC. AFP can be used for the diagnosis and monitoring of responses to HCC treatment (22-24).

The purpose of this study is to determine the characteristics of and risk factors for HCC in patients admitted to our clinic.

MATERIALS AND METHOD

The participants of this study were 69 patients (21 women, 48 men) that admitted with HCC to the gastroenterology clinic of the Faculty of Medicine at Eskişehir Osmangazi University, Turkey, between 2000 and 2012. The patients were diagnosed with HCC by histopathology or characteristic radiological imaging. The demographic data as well as the size, grade and stage of tumors were examined retrospectively. Alcohol abuse was >80 gr among men and >60 gr among women per day during a period of over 10 years. First we identified viral hepatitis serology, whether antiviral treatment was administered before the diagnosis and the period until the development of hepatocellular carcinoma for each case with hepatocellular carcinoma. We further determined the Child-Pugh stage in cirrhotic cases, the stage of viral hepatitis in non-cirrhotic cases, the treatment method suggested for hepatocellular carcinoma and the average life expectancy (for the patients whose life expectancy is known). AFP levels and CT, USG, MRI findings were evaluated retrospectively.

SPSS 16.0 for windows was used for the statistical analysis. Correlation between AFP levels and tumor numbers were evaluated statistically. The

Kendall's tau b test to evaluate the effectiveness of imaging methods, and Odd's ratios were calculated.

RESULTS

Total of 69 patients were evaluated. The median age at presentation was 62.8 (range: 25 to 80) years. Median OS was 7.0 (range 0 to 145) months in all patients. Twenty one (30.4%) patients were female and 48 (69.6%) were male. Thirty four (49.3%) patients were infected by HBV. Twenty eight (40.6%) patients were infected by HCV. Six (8.7%) patients were alcohol abuser.

43 patients were evaluated for Child-Pugh classification and in these 43 patients; 18 patients (41.9%) were Child-Pugh Class A, 12 (27.9%) patients were Child-Pugh Class B and 13 (30.2%) patients were Child-Pugh Class C. Fifty seven patients were evaluated for AFP levels and it was found that 16 (28.1%) patients had mild (<20 ng/ml) elevation, 7 (12.3%) patients had moderate (20-200 ng/ml) elevation and 34 (59.6%) patients had severe (>200 ng/ml) elevation. When the AFP levels were divided into two groups, moderate-mild AFP levels (<200 ng/ml) and severe AFP level (>200 ng/ml), it was found that patients with severe AFP level have 4 fold risk of multiple liver masses (OR:4.05, 95% CI: 1.22-13.42)

For the characterization of a liver mass as HCC, the diagnostic effectiveness of BT was 54.3%, and that of MRI was 55.8%.

DISCUSSION

The literature has shown that there is a significant relationship between HBV DNA levels and the risk of developing HCC. The risk of developing HCC has increased in presence of precore/core promoter mutation and in individuals with genotype B, C and D (25). In our study, in all patients diagnosed with chronic hepatitis B infection, anti HBe was positive. The level of HBV DNA was $>10^4$ copies/ml in 62.5 % (10/16), $<10^4$ copies/ml in 31.2% (5/16), and negative in 6.3% (1/16) of the individuals with chronic hepatitis B. Of five cases receiving antiviral treatment before being diagnosed with HCC, the HBV DNA was negative in one patient, $<10^4$ copies/ml in one patient, and $>10^4$ copies/ml in three patients. We have not conducted genotyping for the cases in our study. However, when considered together with the information in the literature, the fact that the patients with chronic hepatitis B infection have precore/core promoter mutation, that active viral replication was high at the time of diagnosis even in patients that received antiviral treatment, and that the majority of the cases were diagnosed with chronic viral hepatitis infection simultaneously with HCC reveal the importance of public health methods to be used to prevent HCC development such as screening, vaccination, effective treatment of infected individuals and prevention of contagion (26).

The AFP level at 400ng/ml and over is considered diagnostic predictor of HCC in cirrhotic patients. CT and MRI are the imaging methods used with high sensitivity and specificity for the diagnosis of HCC (27). The follow-up procedure suggested for risk groups is the measurement of AFP level and liver imaging with USG in intervals of six months (28).In the present study, we found that AFP levels of HCC patients were significantly higher compared to those of non-HCC patients with a liver mass ($p<0.001$). However, in only 56.1% (32/57) of the HCC patients, the AFP level was over 400 ng/ml, which is considered significant diagnostically; and in 28.1% (16/57) of the patients, the AFP level was in the normal range. For the characterization of a liver mass as HCC, the diagnostic effectiveness of CT was 54.3%, and that of MRI was 55.8%. In cirrhotic cases where the AFP level was over 400 ng/ml, the liver mass could not be detected with USG in 8.6% of the patients and with CT in 8.1% of the patients. Also we found that severe AFP level (>200 ng/ml), it was found that patients with severe AFP level have 4 fold risk of multiple liver masses (OR: 4.05, 95% CI: 1.22-13.42).

In the cases where the imaging tests failed to detect the liver mass, the average size of the mass was 1.75 cm. There was no patient whose liver mass could not be detected by MRI. In three cirrhotic patients, we detected hyperechoic liver mass by USG and their level of AFP was over 400ng/ml. We administered liver blood pool scintigraphy with Technetium-99 m to these patients. For these three patients, the scintigraphy result was reported as hemangioma. But these patients were diagnosed with HCC in the biopsy performed after suspicion of HCC on CT or MRI. The data has shown that AFP measurement and imaging methods are not enough individually to diagnose HCC, and that they should be combined. In individuals whose AFP level is over the value that is diagnostically significant for HCC, even if one imaging method does not show any liver mass, other imaging methods should be used in order not to disregard the risk of HCC. MRI stands as the first imaging option in the characterization of a lesion.

HCC is a type of cancer with poor prognosis. The annual rate of mortality due to HCC is equal to the incidence of HCC. HCC causes the death of 598.000 people every year across the world. One-year life expectancy is 66.1%, three-year life expectancy is 39.7%, and five-year life expectancy is 32.52%. The most important factors that increase the life expectancy are early diagnosis of the disease, and surgical resection or liver transplantation (29,30). In our study, 56.9% of the participants were newly diagnosed patients and 43.1% of the participants were diagnosed chronic liver parenchyma patients. We found that only 31% of the patients with HCC were diagnosed in a stage that is suitable for surgical resection and transplantation, which are effective treatment methods. The average life expectancy was calculated as 22.8±4.6 months for 15 patients that were followed and treated in our clinic after the diagnosis of HCC and whose life expectancy was known. The low numbers of patients were suitable

for an effective treatment and the average life expectancy was low, which is probably because the patients were diagnosed in an advanced stage of the disease. As a result the patients with HCC can be diagnosed with combination of laboratory findings and imaging techniques. AFP levels are important for follow up of such patients and identifying the multiple mass presences.

REFERENCES

1. Dogan E, Yalcin S, Koca D, Olmez A. Clinicopathological characteristics of hepatocellular carcinoma in Turkey. Asian Pac J Cancer Prev 2012;13(6):2985-90.
2. Bosch FX, Ribes J. Epidemiology of primary liver cancer. Global epidemiology. In: Tabor E. editors. Vıruses and Liver Cancer. Netherlands: Elsevier Science B.V; 2002:1-16.
3. Sewart BW, Kleihues P. World Cancer Report. Lyon: IARC Pres 2003:11–9.
4. Uzunalimoglu O, Yurdaydin C, Cetinkaya H, et al. Risk factors for hepatocellular carcinoma in Turkey. Dig Dis Sci 2001;46:1022–8.
5. Colombo M, de Franchis R, Del Ninno E, et al. Hepatocellular carcinoma in Italian patients with cirrhosis. N Engl J Med 1991;325(10):675-80.
6. Abdo AA, Karim HA, Al Fuhaid T, et al. Diagnosis and management of hepatocellular carcinoma. The Saudi Journal of Gastroenterology 2007;13 (suppl):S1-24.
7. Gomaa AI, Khan SA, Toledano MB, Waked I, Taylor-Robinson SD. Hepatocellular carcinoma: epidemiology, risk factors and pathogenesis. World J Gastroenterol 2008; 14(27): 4300-8.
8. Donato F, Boffetta P, Puoti M. A meta-analysis of epidemiological studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma. Int J Cancer 1998;75(3):347-54.
9. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. Gastroenterology 2004;127(5 Suppl 1):S35-50.
10. Cottone M, Turri M, Caltagirone M, et al. Screening for hepatocellular carcinoma in patients with Child's A cirrhosis: an 8-year prospective study by ultrasound and alphafetoprotein. J Hepatol 1994;21(6):1029-34.
11. Niederau C, Fischer R, Sonnenberg A, Stremmel W, Trampisch HJ, Strohmeyer G. Survival and causes of death in cirrhotic and in noncirrhotic patients with primary hemochromatosis. N Engl J Med 1985;313(20):1256-62.
12. Fargion S, Fracanzani AL, Piperno A, et al. Prognostic factors for hepatocellular carcinoma in genetic hemochromatosis. Hepatology 1994 20(6):1426-31.
13. Polio J, Enriquez RE, Chow A, Wood WM, Atterbury CE. Hepatocellular carcinoma in Wilson's disease. Case report and review of the literature. J Clin Gastroenterol 1989;11(2):220-4.
14. Kew M. Hepatic tumors and cysts. In: Feldman M, Frıedman SL, Brandt LJ editors. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. Philadelphia: Saunders, 2006:2007-33.
15. Pons F, Llovet JM. Approaching focal liver lesions. Rev Esp Enferm Dig 2004;96(8):567-73.
16. Reddy KR, Schiff E. Approach to a liver mass. Seminars in liver disease 1993; 13(4): 423-35.
17. Rubin RA, Mithchell DG. Evaluation of the solid hepatic mass. Med Clin North Am 1996;80(5): 907-28.
18. Ros PR, Davis GL. The incidental focal liver lesion: photon, proton, or needle? Hepatology 1998;27(5): 1183-90.
19. Pons F, Llovet JM. Approaching focal liver lesions. Rev Esp Enferm Dig 2004;96(8):567-77.
20. Song do S, Bae SH. Changes of guidelines diagnosing hepatocellular carcinoma during the last ten-year period. Clin Mol Hepatol 2012;18(3):258-67.
21. Stigliano R, Marelli L, Yu D, Davies N, Patch D, Burroughs AK. Seeding following percutaneous diagnostic and therapeutic approaches for hepatocellular carcinoma. What is the risk and the outcome? Seeding risk for percutaneous approach of HCC. Cancer Treat Rev 2007;33(5):437-47.
22. Oka H, Tamori A, Kuroki T, Kobayashi K, Yamamoto S: Prospective study of alpha-fetoprotein in cirrhotic patients monitored for development of hepatocellular carcinoma. Hepatology 1994, 19(1):61-7.
23. Pateron D, Ganne N, Trinchet JC, et al. Prospective study of screening for hepatocellular carcinoma in Caucasian patients with cirrhosis. J Hepatol 1994, 20(1):65-71.
24. Zoli M, Magalotti D, Bianchi G, Gueli C, Marchesini G, Pisi E. Efficacy of a surveillance program for early detection of hepatocellular carcinoma. Cancer 1996;78(5):977-83.
25. Nguyen VT, Law MG, Dore GJ. Hepatitis B-related hepatocellular carcinoma: epidemiological characteristics and disease burden. J Viral Hepat 2009;16(7):453-463.
26. Franceschi S, Raza SA. Epidemiology and prevention of hepatocellular carcinoma. Cancer Lett 2009;286(1):5-8.
27. Gomaa AI, Khan SA, Leen ELS, Waked I, Taylor-Robinson SD. Diagnosis of hepatocellular carcinoma. World J Gastroenterol 2009;15(11): 1301-14.
28. Franceschi S, Raza SA. Epidemiology and prevention of hepatocellular carcinoma. Cancer Lett 2009;286(1):5-8.
29. Leong TY, Leong AS. Epidemiology and carcinogenesis of hepatocellular carcinoma. HPB 2005;7(1):5-15.
30. But DY, Lai CL, Yuen MF. Natural history of hepatitis-related hepatocellular carcinoma. World J Gastroenterol 2008;14(11):1652-6.