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Clinicopathologic features and risk factors for hepatocellular carcinoma: Results from a single center in southern Turkey

Hepatosellüler karsinomun klinikopatolojik özellikleri ve risk faktörleri: Türkiye'nin güney bölümünde tek merkez sonuçları

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Background/aims: *The aim of this study was to determine the characteristics of hepatocellular carcinoma at a major health center in southern Turkey. Computed tomography was compared to the combination of ultrasonography and serum alpha-fetoprotein determination in the diagnosis of hepatocellular carcinoma.* ***Methods:*** *Of 226 patients with liver cirrhosis, 35 were diagnosed with hepatocellular carcinoma on first admission or during follow-up in the period between 1999 and 2002. The features investigated were, age at time of hepatocellular carcinoma diagnosis, etiology of cirrhosis, severity of cirrhosis at presentation, tumor pattern, stage of hepatocellular carcinoma, serum alpha-fetoprotein level, and dynamic computed tomography findings. Results were compared to previous findings in Turkey and elsewhere.* ***Results:*** *In the hepatocellular carcinoma patients, the male:female ratio was 4:1 and the mean age at presentation was 61 years. Chronic hepatitis B virus infection (65.7%) and chronic hepatitis C virus infection (28.6%) were the most frequently identified risk factors for hepatocellular carcinoma. Forty percent of the patients had Child-Pugh A cirrhosis when they were diagnosed with hepatocellular carcinoma. Sixty-seven percent of patients had fewer than three hepatocellular carcinoma nodules in the liver at the time of diagnosis. Only three of the hepatocellular carcinoma cases were Okuda stage I. The combination of ultrasonography and serum alpha-fetoprotein >20 ng/ml identified hepatocellular carcinoma in 32 of the 35 total cases.* ***Conclusions:*** *The results indicate that hepatitis B virus infection in patients with cirrhosis is still the leading risk factor for the development of hepatocellular carcinoma. Also, early-stage hepatocellular carcinoma is rarely diagnosed in cirrhosis patients from this region of Turkey. Surveillance with computed tomography for early diagnosis of hepatocellular carcinoma seems not to be mandatory.*

Key words: Hepatocellular carcinoma, alpha-fetoprotein, computed tomography, ultrasonography, clinicopathological features, hepatitis B virus, hepatitis C virus.

Amaç: *Bu çalışmanın amacı Güney Türkiye'de büyük bir sağlık merkezindeki hepatosellüler karsinomu karekteristiklerini belirlemekti. Hepatosellüler karsinom tanısında, ultrasonografi ve serum alfa-fetoprotein kombinasyonu ile bilgisayarlı tomografinin etkinliği karşılaştırıldı.* ***Yöntem:*** *1999-2002 yılları arasında karaciğer sirozu nedeniyle takip edilen 226 hastanın 35'ine ilk başvuru veya takipler sırasında hepatosellüler karsinom tanısı kondu. Hepatosellüler karsinom tanısı anındaki yaş, sirozun etyolojisi, sirozun şiddeti, tümör paterni, hepatosellüler karsinom evresi, serum alfa-fetoprotein düzeyi ve dinamik bilgisayarlı tomografi bulguları araştırıldı. Sonuçlar Türkiye ve başka yerlerdeki önceki bulgularla karşılaştırıldı.* ***Bulgular:*** *Hepatosellüler karsinom'h hastalarda erkek: kadın oranı 4:1 ve tanı anındaki ortalama yaş 61 idi. Kronik hepatit B virüs hepatosellüler karsinom infeksiyonu (%65.7) ve kronik hepatit C virüs hepatosüller karsinoma infeksiyonu (%28.6), hepatosellüler karsinom için en sık saptanan risk faktörüydü. Hepatosellüler karsinom tanısı konduğu anda hastaların %40'ı Child-Pugh A evresinde idi. Vakaların %67'sinde hepatosellüler karsinom tanısı anında karaciğerde 3'den az hepatosellüler karsinom nodulu vardı, hepatosellüler karsinom vakalarının yalnızca 3 tanesi Okuda evre l idi. 35 hastanın 32'sinde hepatosellüler karsinom tanısı serum AFP>200 nglml ve ultrasonografi kombinasyonu ile konuldu.* ***Sonuç:*** *Bu sonuçlar sirozlu hastalarda hepatosellüler karsinom infeksiyonun hepatosellüler karsinom gelişiminde halen önde gelen risk faktörü olduğunu göstermiştir. Türkiye'nin bu bölgesindeki sirozlu hastalarda erken evrede hepatosellüler karsinom nadiren saptanmıştır. Hepatosellüler karsinom'nın erken tanısında bilgisayarlı tomografi ile takip zorunlu gibi görünmemektedir.*

Anahtar kelimeler: Hepatosellüler karsinom, alfa-fetoprotein, bilgisayarlı tomografi, ultrasonografi, klinikopatolojik görünüm, hepatit B virüsü, hepatit C virüsü

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common and important cancers in the world, and is associated with poor prognosis. It is the seventh most frequent cause of cancer-related death in men, and the ninth most frequent cause in women. The incidence of HCC varies widely

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according to geographic location. Sub-Saharan Africa and eastern Asia are two high-incidence regions (1). More than 80% of HCC cases occur in individuals with cirrhosis of the liver (2), and the annual incidence of HCC in cirrhotic patients is 1-6% (3). These rates suggest that cirrhosis is the main risk factor for this tumor; however, a number of other important risk factors for the development of HCC have also been identified. They include hepatitis B virus (HBV) carrier state, environmental toxins, chronic hepatitis C virus (HCV) infection, and hereditary hemochromatosis. HCC also occurs in patients who have no known risk factors (4).

Hepatitis B virus is endemic to Turkey. The seropositivity rate for hepatitis B surface antigen (HBsAg) in the general population is 6.8%, and that for anti-HBs antibody is 29.7% (5). The seropositivity rate for HCV in Turkey is reportedly between 0% and 1.7% (5). When Turkey's geographical proximity to European countries and the similarity of HBV carrier rates to those in neighboring countries are considered, the age-adjusted incidence rate for HCC in our country is in the intermediate range compared to other nations (6, 7).

In this study, our aim was to determine the rate and characteristics of HCC in cirrhotic patients at one of the main health service centers serving southern Turkey. We were interested to learn whether the rate of HCC had changed from the rate reported in a multicenter study from Turkey that was conducted three years ago. We also sought to compare the value of dynamic computed tomography (CT) to that of ultrasonography (US) plus serum alpha-fetoprotein (AFP) measurement for diagnosing HCC.

MATERIALS AND METHODS

This study involved 226 patients with liver cirrhosis (144 men and 82 women; mean age 57.3±12.8 years) (Table 1) who had been in regular follow-up at Başkent University Adana Teaching and Medical Research Center between July 1999 and May 2002.

Cirrhosis was diagnosed histologically in most cases. In the remaining individuals, the diagnosis was based on patterns of clinical and laboratory findings associated with signs of portal hypertension on endoscopy and/or US, and/or the finding of an irregular liver margin on US. All patients were screened twice yearly for HCC with the combination of a US scan and serum AFP measurement. Dynamic CT was performed as well at least once during follow-up in each case.

Table 1. Demographic, clinical, and laboratory characteristics of the 226 cirrhosis patients who were studied

Characteristics	
Age (yrs, mean±SD)	57.3±12.8
Sex [No.(%)]	
Males	144 (63.7)
Females	82 (36.3)
Child-Pugh Class [No.(%)]	
A	83 (36.7)
B	54 (23.9)
C	89 (39.4)
Etiology [No.(%)]	
*HBV	80 (35.4)
+HCV	83 (36.7)
HCV + Alcohol	1 (0.4)
HBV + Alcohol	1 (0.4)
HBV+ HCV	2 (0.9)
Hemochromatosis	1 (0.4)
Alcohol	12 (5.3)
Unknown	46 (20.5)

*Hepatitis B virus
+ Hepatitis Cvirus

A total of 35 cases of HCC were identified during the three-year period. The diagnosis of HCC was based on histological or cytological characteristics in 14 patients (40%), and on positive imaging findings (US, dynamic CT, and angiography with or without lipiodol) and serum AFP levels in 21 patients (60%). The upper normal limit for serum AFP in this study was 20 ng/ml. Diagnosis of HBV infection was based on positive serology for HBsAg using a microparticle enzyme immunoassay (MEIA) (Abbott Laboratories, AXSYM, USA). Diagnosis of HCV infection was based on positivity for anti-HCV antibodies, as determined by third-generation enzyme immunoassay (Abbott Laboratories). Serum AFP concentration was measured by MEIA (Abbott Laboratories, AXSYM, USA). "Heavy alcohol intake" was defined as a daily minimum consumption of 160 g alcohol for at least eight years.

The following parameters were retrospectively analyzed based on data from medical records: sex, age, etiology of cirrhosis, risk factors for HCC, Child-Pugh classification of stage of cirrhosis (8), Okuda stage of HCC (1), CT features, and serum AFP level at the time of HCC diagnosis.

Statistical Analysis

Data were analyzed using the Students t- and chi-square tests, and are presented as mean±SD. A p value of <0.05 was considered to indicate statistical significance.

RESULTS

The 35 patients with HCC included 28 men and seven women of mean age 61±10 years (Table 2). Regarding stage of cirrhosis, 14 (40%) cases were Child-Pugh class A, 10 (28.6%) were class B, and 11 (31.4%) were class C (Figure 1).

Serum AFP levels were above 20 ng/ml in 26 (74.3%) of the patients. Eighteen patients (51.4%) had AFP levels above 200 ng/ml, the level considered diagnostic for HCC (Table 2). A patient with chronic HBV infection had the highest serum AFP level (357023 ng/ml). The frequency of AFP >200 ng/ml was higher in the HBV-positive patients than in the HCV-positive patients (13/23 [56.5%] vs 4/10 [40%], respectively), but this difference was not statistically significant.

The etiology of chronic liver disease was known in all 35 HCC cases (Figure 2). Twenty-three (65.7%) of these patients had HBV, 10 (28.6%) had HCV, one (2.9%) had both HBV and HCV, and one (2.9%) had a history of heavy alcohol intake.

Solitary and paucifocal (two or three nodules) were the dominant tumor patterns, and the frequencies of the different forms were solitary 42.9%, paucifocal 22.8%, multifocal 31.4%, and diffuse 2.9% (Table 3). According to Okuda classification, more than half of the patients were stage II (stage I 8.6%, stage II 57.1%, stage III 34.3%) (Figure 3). All three of the Okuda stage I patients had Child-Pugh A cirrhosis.

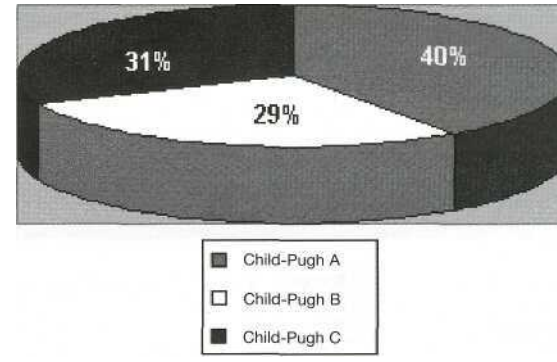


Figure 1. The distribution of Child-Pugh class in the hepatocellular carcinoma patients in the series.

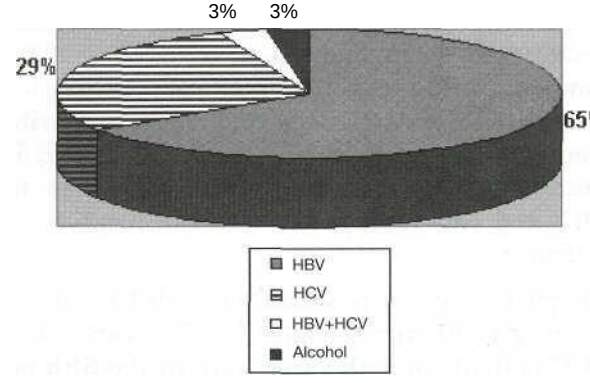


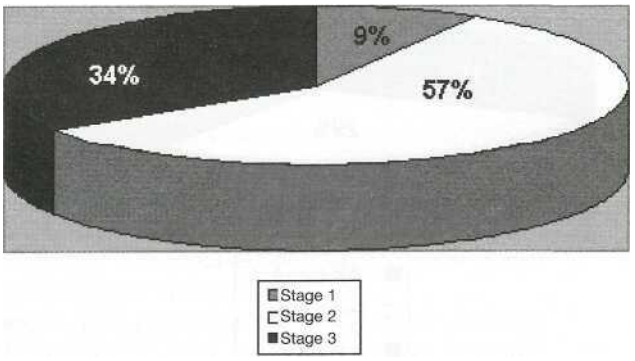
Figure 2. Distribution of the etiologies of hepatocellular carcinoma
HBV: hepatitis B virus; HCV: hepatitis C virus

Table 2. Demographic, clinical, and laboratory characteristics of the 35 patients with hepatocellular carcinoma

Characteristics	
Age (yrs, mean±SD)	61±10
Sex [No.(%)]	
Males	28 (80)
Females	7(20)
Child-Pugh Class [No.(%)]	
A	14(40)
B	10 (28.6)
C	11 (31.4)
Alpha-fetoprotein [No.(%)]	
<20 ng/ml	9 (25.7)
21-200 ng/ml	8 (22.9)
>200 ng/ml	18 (51.4)

Table 3. Macroscopic features and stage of cancer in the 35 patients with hepatocellular carcinoma (HCC)

HCC type	[No.(%)]
Solitary	15 (42.9)
Paucifocal (two or three nodes)	8 (22.8)
Multifocal (>3 nodes)	11 (31.4)
Diffuse	1(2.9)
Solitary HCC	
<3 cm	6 (40)
3.1-5 cm	3 (20)
>5 cm	6 (40)
Okuda stage	
I	3 (8.6)
II	20 (57.1)
III	12 (34.3)



Figüre 3. The distribution of Okuda stages of hepatocellular carcinoma.

The HCC group included significantly more males (n=28; 80%) than females (n=7; 20%) ($p<0.01$). However, when the patients were categorized according to viral etiology and the sex distributions were compared, there were no significant differences between the male:female ratios in the HBV and HCV groups (19:4 vs 7:3, respectively; $p>0.05$).

The median age at presentation with HCC in this series was 61 years (range, 31-77 years). Most HCC patients of both sexes were in the fifth and

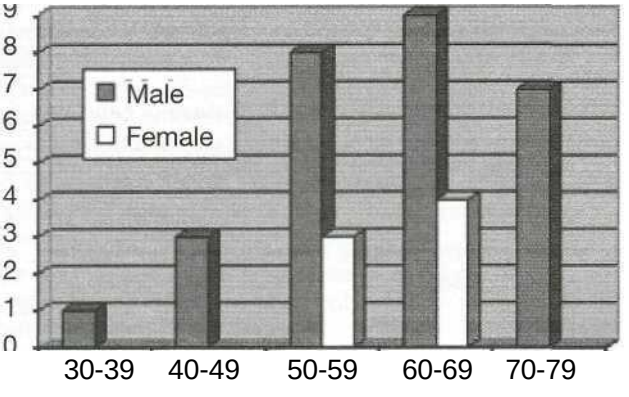


Figure 4. The sex and age distributions for the patients with hepatocellular carcinoma

the sixth decades of life (Figure 4). Patients with HBV-associated HCC tended to present at a younger age than those with HCV-associated HCC (mean ages 59.7 and 63.4 years, respectively; $p>0.05$).

Of the 35 cases in which typical HCC nodules were shown by dynamic CT, US demonstrated HCC nodules in 29 cases, and the combination of US and serum AFP >20 ng/ml detected HCC in 32 cases ($p<0.05$).

DISCUSSION

Compared to rates of HBV and HCV infection in other parts of the world, the incidence rates in Turkey's southern Anatolia region are in the middle range (5). As noted above, the worldwide incidence of HCC in patients with cirrhosis is 1-6% per year (3). The annual incidence of HCC in the 226 cirrhotic patients in our study was 5.6%, which is among the highest national rates globally. There is considerable variation in the annual rates of HCC development observed in populations from different geographic regions that have similar rates of chronic HBV or HCV infection. This may be related to differences in diagnostic approaches and levels of exposure to other carcinogenic or mutagenic environmental agents, such as aflatoxin (9, 10).

In many respects, our findings were similar to those of a previous multicenter study that was conducted in Turkey in the mid-1990s (11). The distribution of etiological factors, the noted sex differences, and the mean ages of the HCC patients were similar; however, we observed a significantly higher rate of HCV-associated HCC than was reported for the same region in the above-mentioned study (28.6% vs 10.3%). The higher rate of HCV-associated HCC in southern Anatolia compared to other parts of Turkey may be linked to differences in treatment and diagnostic methods. Also, the fact that patients with chronic HBV infection respond better to interferon treatment than those with chronic HCV infection may partially explain the higher frequencies of advanced liver disease and HCC in the latter group.

In our series, the majority of patients with HCC were male. Although the differences in sex distribution were insignificant when the cases were categorized according to viral etiology, males were more predominant in the HCC patients with HBV than in the HCC patients with HCV (male:female sex ratios 4.7:1 vs 2.3:1, respectively). We also noted a tendency for patients with HBV-associa ted HCC to present at a younger age than those with HCV-associated HCC, which is in line with previous observations (12-14).

In order to detect HCC as early as possible, it has become common practice to monitor cirrhotic patients with serial US scans and serum AFP

determinations. This type of combination screening can detect small asymptomatic HCC nodules, but it is not known whether finding such lesions actually extends life expectancy. Indeed, disease surveillance can improve survival if effective treatment for the target condition is available, and if the diagnosis is made when the disease is still treatable. In HCC, however, mortality remains high for patients who have small tumors treated with hepatic resection and percutaneous ethanol injection (PEI). Of the various rates reported in the literature, the best five-year survival rate in this group is close to 50% (15, 16). Recently, much better outcomes have been reported with orthotopic liver transplantation (17).

The ultimate objective of surveillance for lethal diseases is to reduce mortality in the target population. Many centers use the combination of US and AFP monitoring as a sensitive and standard approach for detecting HCC nodules during the follow-up of cirrhotic patients (18, 19). CT of the liver is frequently performed to evaluate abnormalities detected on US. Some centers use CT as the primary screening modality for HCC in patients with cirrhosis. The introduction of helical CT technology has increased the sensitivity of CT for detecting HCC, with estimates now as high as 90% (20). This technique involves rapid administration of contrast material in combination with extremely fast imaging. The arterial phase of enhancement allows for detection of hypervascular HCCs as small as 3mm diameter. In line with other reports, our results indicate that helical CT is more sensitive than US for detecting HCC nodules (21, 22); however, CT was not statistically superior to the combination of US and serum AFP in the diagnosis of HCC.

Despite the fact that 74.3% of our Turkish patients with HCC had above-normal serum AFP levels, only 51.4% had AFP levels above 200 ng/ml. In contrast, investigations of the Caucasian population with HCC (19, 23-25) have revealed considerably lower frequencies of AFP >200 ng/ml. Our findings and those of some recent studies indicate that surveillance with the US plus serum AFP level combination may miss some HCC nodules (19); however, it is not cost-effective to use dynamic CT to follow every patient with liver cirrhosis. Surveillance with imaging or serum testing is not recommended for individuals with advanced cirrhosis (Child-Pugh class B or C) who are not candidates for liver transplantation (26, 27). Thus, diagnosing HCC in this patient group is of no therapeutic value. On the other hand, early diagnosis of HCC nodules in Child-Pugh class A patients is important, as these individuals can benefit from surgery and other types of treatment, such as transarterial chemoembolization or PEI. In our study, the number of HCC patients classed as Child-Pugh A was greater than the number with advanced cirrhosis, and all the patients with Okuda stage I HCC had early-stage cirrhosis. These large proportions validate the suggestion that maximum effort should be made to diagnose early-stage HCC in patients with early-stage cirrhosis. In this subgroup, dynamic CT can offer considerable benefits, particularly in centers where CT is more sensitive than the US plus serum AFP combination for diagnosing HCC. CT could offer earlier diagnosis and also assist with planning optimal treatment in this patient group.

This retrospective study analyzed HCC-related data from the years 1999-2002 that was collected from one of the main health centers in southern Anatolia. Some results were in line with a recent 1994-1997 analysis that involved multiple centers in Turkey, and some results differed. Our results revealed a different distribution of HCC etiologies, in particular a higher rate of anti-HCV seropositivity, compared to this previous Turkish study. We believe that these changes may reflect multiple factors, such as response to specific treatments and different methods aimed at earlier diagnosis.

REFERENCES

1. Okuda K, Okuda H. Primary liver cell carcinoma. In: Benhamou J-P, McAntyre N, Rizzetto M, Rodes J, eds. Oxford Textbook of Clinical Hepatology, 2nd ed. Vol. 2. New York: Oxford University Press; 1999: 1491-530.
2. Collier J, Sherman M. Screening for hepatocellular carcinoma. Hepatology 1998; 27: 273-78.
3. Simonetti RG, Gamma C, Fiorello F, et al. Hepatocellular carcinoma. A worldwide problem and the major risk factors. Dig Dis Sci 1991; 36: 862-72.
4. Bralet MP, Regimbeau JM, Pineau P, et al. Hepatocellular carrcinoma occurring in nonfibrotic liver: epidemiologic and histopathologic analysis of 80 French cases. Hepatology 2000; 32: 200.
5. Mistik R, Balik I. Türkiye'de viral hepatitlerin epidemi olojisi. Bir metaanaliz. In: Kilicturgay K, Badur S (ed). Viral Hepatit 2001; 9-57.
6. Psiani P, Pakin DM, Bray F, Ferlay J. Estimates of the worldwide mortality from 25 cancers in 1990. Int J Cancer 1999; 83: 18-29.

7. Johnson PJ. The epidemiology of hepatocellular carcinoma. Eur J Gastroenterol Hepatol 1996; 8: 845-49.
8. Pugh NH, Murray-Lyon İM, Dawson JL, et al. Transection of the esophagus for bleeding esophageal varices. Br J Surg 1973; 60: 646-49.
9. Bergsland EK. Molecular mechanisms underlying the development of hepatocellular carcinoma. Semin Oncol 2001; 28: 521-31.
10. Bressac B, Kew M, Wands J, Ozturk M. Selective G to T mutations of p53 gene in hepatocellular carcinoma from southern Africa. Nature 1991; 350: 429-34.
II. Uzunalimoglu O, Yurdaydin C, Cetinkaya H, et al. Risk factors for hepatocellular carcinoma in Turkey. Dig Dis Sci 2001; 46: 1022-28.
12. Stroffolini T, Andreone P, Andriulli A, et al. Characteristics of hepatocellular carcinoma in Italy. J Hepatol 1998; 29: 944-52.
13. Di Bisceglie AM, Simpson LH, Lotze MT, Hoofnagle JH. Development of hepatocellular carcinoma among patients with chronic liver disease due to hepatitis C infection. J Clin Gastroenterol 1994; 19: 222-26.
14. Shiratori Y, Shiina Si Imamura M, et al. Characteristic difference of hepatocellular carcinoma between hepatitis B and C viral infection in Japan. Hepatology 1995; 22: 1027-33.
15. Kosuge T, Makuuchi M, Takayama T, et al. Long-term results after resection of hepatocellular carcinoma: experience of 480 cases. Hepatogastroenterology 1993; 40: 328-32.
16. Livraghi T, Giorgio A, Marin G, et al. Hepatocellular carcinoma and cirrhosis in 746 patients: long-term results of percutaneous ethanol injection. Radiology 1995; 97: 101-08.
17. Mazzaferro V, Regelia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996; 334: 693-99.
18. Yuen MF, Cheng CC, Lauder U, et al. Early detection of hepatocellular carcinoma increases the chance of treatment: Hong Kong experience. Hepatology 2000; 31: 330-35.
19. Pateron D, Ganne N, Trinchet JC, et al. Prospective study of screening for hepatocellular carcinoma in Caucasian patients with cirrhosis. J Hepatol 1994; 20: 65-71.
20. Hollett MD, Jeffrey RB Jr, Nino-Murcia M, et al. Dual-phase helical CT of the liver: value of arterial-phase scans in the detection of small (<1.5 cm) malignant hepatic neoplasms. Am J Roentgenol 1995; 164: 879-84.
21. Oi H, Murakami T, Kim T, et al. MR imaging and early-phase helical CT for detecting small intrahepatic metastases of hepatocellular carcinoma. AJR 1996; 166: 369-74.
22. Saada J, Bhattacharya S, Dhillon AP, et al. Detection of small hepatocellular carcinomas in cirrhotic livers using iodised oil computed tomography. Gut 1997; 41: 404-07.
23. Trevisani F, D'Intino PE, Bernard! M. Prospective screening for hepatocellular carcinoma: a debated issue. J Hepatol 1995; 22: 708-09.
24. Taketa K. Alpha-fetoprotein: reevaluation in hepatology. Hepatology 1990; 12: 1420-32.
25. Caturelli E, Bartolucci F, Biasini E, et al. Diagnosis of liver nodules observed in chronic liver disease patients during ultrasound screening for early detection of hepatocellular carcinomas. Am J Gastroenterol2002; 97: 397-405.
26. Trevisani F, De NS, Rappacini G, et al. Semiannual and annual surveillance of cirrhotic patients for hepatocellular carcinoma: effects on cancer stage and patient survival (Italian experience). Am J Gastroenterol 2002; 97: 734-44.
27. Sangro B, Herraiz M, Martinez-Gonzalez MA, et al. Prognosis of hepatocellular carcinoma in relation to treatment: a multivariate analysis of 178 patients from a single European institution. Surgery 1998; 124: 575-83.