1130-0108/2012/104/5/242-247
Revista Española de Enfermedades Digestivas

Rev Esp Enferm Dig (Madrid)
Vol. 104. N.° 5, pp. 242-247, 2012

ORIGINAL PAPERS

Factors related to survival in hepatocellular carcinoma in the geographic area of Sabadell (Catalonia, Spain)

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ABSTRACT

BAckground: hepatocellular carcinoma (HCC) is a very frequent tumor. Screening for the disease is effective, but the prognostic factors are difficult to evaluate.

Objectives: 1. To determine epidemiological data and the clinical course of HCC in our setting. 2. To compare patient survival according to whether screening is performed or not. 3. To evaluate survival prognostic factors.

Patients and methods: data on the epidemiology and clinical course of patients diagnosed with HCC were collected on a prospective basis (January 2004-December 2006). Two groups were considered according to whether screening had been performed (group A) or not (group B).

Results: a total of 110 patients were diagnosed with HCC (70% males). The most common etiology of cirrhosis was hepatitis C (56.1%), and 69% presented mild liver failure (Child-Pugh grade A). The median follow-up was 1.8 years. Fifty-one percent had been subjected to screening. The diagnosis of HCC was established by imaging techniques in 48.2% of the cases, and by histological criteria in 51.8%. The median tumor size was 23 mm in group A and 28 mm in group B (p = 0.005). Treatment with curative intent was provided in 72% of the cases in group A and in 48% in group B (p = 0.011). The median overall survival was 1.99 years -2.67 years in group A and 1.75 years in group B (p = 0.05).

The multivariate analysis of overall survival showed the type of treatment (OR = 2.82 95%CI: 1.3-6.12, p = 0.009) and liver function (OR = 1.71 95%CI: 1.1-2.68, p = 0.020) to be independent predictors of survival.

Conclusions: screening allows the diagnosis of smaller lesions and a higher percentage of curative treatments. The degree of liver function and the provision of curative treatment are independent predictors of survival.

Key words: Hepatocellular carcinoma. Cirrhosis. Screening. Survival predictive factors.

Received: 21-11-11.
Accepted: 14-02-12.

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Miquel M, Sopeña J, Vergara M, Gil M, Casas M, Sanchez-Delgado J, Puig J, Alguersuari A, Criado E, Dalmau B. Factors related to survival in hepatocellular carcinoma in the geographic area of Sabadell (Catalonia, Spain). Rev Esp Enferm Dig 2012; 104: 242-247.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common type of tumor in the world (1). However, its epidemiological characteristics, incidence and risk factors vary among different geographical settings (2-4). Chronic hepatitis B virus (HBV) infection is the main risk factor in Asia and Africa, while in Western countries (including Spain) and in Japan, chronic hepatitis C virus (HCV) infection is the main risk factor for HCC (5-10).

In over 80% of all cases, HCC develops in a cirrhotic liver. As a result, cirrhosis is considered a preneoplastic disease (11,12), and is the main predisposing factor for HCC (13,14). The incidence of HCC in these patients ranges from 1.5-6% annually (2,15,16), but tends to increase (17). An incidence of 8.6% has recently been reported (17,18). The characteristics of these patients are ideal for semestrial abdominal ultrasound screening protocols (13,19), since this is a well established target population in which noninvasive and low cost techniques allow us to offer potentially curative treatment (9,18,20). In the best series, the diagnosis of HCC in its early stages affords survival rates of up to 70% after 5 years (21). However, there are still patients who are diagnosed with cirrhosis after the detection of HCC.

A number of risk factors for HCC have been identified, such as age, the male sex, HBV infection, and altered alpha-fetoprotein (AFP) levels (6). In our setting, chronic hepatitis due to HCV infection is one of the main factors. However, the prognostic factors at the time of diagnosis

are difficult to evaluate, due to the usual presence of underlying cirrhosis.

The objectives of the present study are: a) to determine the epidemiological, clinical, therapeutic and evolutive factors of HCC in our setting; b) to compare survival among patients subjected to screening *versus* those without screening; and c) to assess the prognostic factors for survival in a cohort of patients diagnosed with HCC.

MATERIAL AND METHODS

Patients

We prospectively included all patients diagnosed with HCC between January 2004 and December 2006 in the Hepatology Unit (Corporació Sanitària Parc Taulí, Sabadell, Catalonia, Spain) (recruitment population 400,000), and subjected to follow-up until February 2011.

The patients were classified into two groups according to origin. Group A consisted of patients mainly derived from our outpatient clinic, diagnosed with cirrhosis and enrolled in a screening program involving semestrial hepatic ultrasound exploration and AFP determinations. Group B in turn comprised patients not enrolled in the screening program (underlying liver disease was not known, the patients had been lost to follow-up, or the latter had been irregular) and who were referred to our Unit from the primary care centers of our reference area for the study of liver lesions detected as a result of imaging explorations, following confirmation of the diagnosis of HCC.

Study variables

At the time of diagnosis and inclusion in the study, we collected epidemiological, clinical and laboratory test data, as well as information referred to the type of treatment provided. Follow-up was continued until the end of the study, loss to follow-up, or death (with registry of the cause of death).

The diagnosis of cirrhosis was established from the clinical, laboratory test, ultrasound and/or endoscopic data, or according to histological criteria. In all cases we investigated the etiology of the underlying liver disease, with serological testing for HBV and HCV, and the evaluation of iron metabolism, alpha-1-antitrypsin, ANA and AMA autoantibodies, and history of alcohol consumption (g/day). Baseline liver function was scored according to the classification of Child-Pugh (22) and the model for end-stage liver disease (MELD) developed by the Mayo Clinic (23).

The diagnostic criteria for HCC were those established by the European Association for the Study of the Liver (EASL) (24): compatible biopsy findings, two imaging methods with consistent findings in lesions < 2 cm in size, one imaging method with consistent findings in lesions ≥ 2 cm in size, and AFP > 200 ng/mL.

Once HCC was diagnosed, we determined whether the patient was enrolled in a screening program, and whether this conditioned differences in tumor size, treatment possibilities, prognosis and outcome.

Treatment for HCC in each patient was decided by the tumor committee according to the criteria proposed by the Barcelona Clinic Liver Cancer (BCLC) staging system (19). Two management groups were established: potentially curative (resective surgery, liver transplant or percutaneous treatment) and palliative (embolization or symptomatic treatment).

One month after percutaneous treatment, liver MRI and abdominal ultrasound were performed –tumor ablation being considered in the absence of signs of persistent tumor. Evidence of persistent tumor in any of the tests performed was taken to represent partial response. Lastly, disease progression was defined as the observation of lesion growth or the appearance of new lesions.

Statistical analysis

Data analysis was performed using the SPSS version 15.0 statistical package. Bivariate analysis was based on the Chi-square, Student t and Mann-Whitney U-tests, and Kaplan-Meyer survival and Cox multiple regression analyses were performed. Continuous variables are reported as the mean and standard deviation (SD). Variables showing a non-normal distribution are reported as the median and range.

RESULTS

Baseline demographic and clinical characteristics

A total of 110 patients were diagnosed with HCC, of which 77 were men (70%). All were cirrhotic. The mean patient age at the time of diagnosis of cirrhosis was 65.8 years (SD 11.2). The most common etiology was: chronic hepatitis due to HCV infection (56.1%), followed by alcohol abuse (25.1%) (Table I). At the time of diagnosis, 17 patients (15.45%) presented alcohol abuse (> 60 g/day), 4 had intakes of 20-40 g/day, and the rest consumed less than 20 g/day or were abstemious.

Characteristics of the patients diagnosed with HCC

Fifty-six patients were subjected to screening (51%). The mean age was 69.72 years (SD 10.3). Seventy-six patients (69%) suffered mild liver failure (Child-Pugh grade A), 30 (27.3%) presented moderate liver failure (Child-Pugh grade B), and 4 (3.6%) suffered severe liver failure (Child-Pugh grade C). The mean MELD score was 10.14 (SD 3.17). As regards the complications of cirrhosis, 74 patients (67.3%) had not suffered clinical decompensation. Among the decom-

Table I. Epidemiological characteristics of the global patients and by screening groups

	Global	*Screening*	*No screening*	*p*
No. patients	110	56 (50. 9%)	54 (49.1%)	
Sex (male/female)	77/33	39/17	38/16	
Age at diagnosis HCC (years)	69.7 (± 10.3)	69.6 ± 10.8	69.8 ± 9.89	0.7
Cause of cirrhosis (n)				0.236
HCV	55 (56.1%)	32 (64%)	23 (48.9%)	
Alcohol	25 (25.1%)	13 (26%)	12 (25%)	
HBV	2 (2%)	1 (2%)	1 (2%)	
HCV + Alcohol	11 (11.2%)	3 (6%)	8 (16.7%)	
Cryptogenic	5 (5.2%)	1 (2%)	4 (8.3%)	
Child-Pugh				0.456
A	76 (69.1%)	41 (73.5%)	35 (64.8%)	
B	30 (27.3%)	14 (25%)	16 (20.4%)	
C	4 (3.6%)	1 (0.9%)	3 (2.7%)	
MELD (SD) (score)	10.14 (3.17)	10.42 (3.55)	9.85 (2.73)	
Complications of cirrhosis				
Portal hypertension*	64 (58.2%)	41 (73.2%)	23 (42.6%)	0.001
Ascites	26 (23.6%)	15 (26.8%)	11 (20.4%)	0.286
UDB	12 (16.4%)	8 (14.3%)	4 (7.4%)	0.198
Hepatic encephalopathy	7 (10.9%)	3 (5.4%)	4 (7.4%)	0.480
Spontaneous bacterial peritonitis	5 (4.5%)	3 (5.4%)	2 (3.7%)	0.517
Alpha-fetoprotein (IU/l)	15.7	12.9	17.3	0.247
range (IU/l)	(0.5-99510)	(0.5-9930)	(1.4-99510)	

* Diagnosed by endoscopic and/or clinical criteria.

pensated patients (36 cases), the most frequent cause of decompensation was ascites (26 patients, 72.2%); of these, 5 (19.2%) had presented spontaneous bacterial peritonitis (SBP). In turn, upper digestive bleeding (UDB) secondary to portal hypertension was recorded in 12 patients (33.3%), and 7 subjects (19.4%) had suffered at least one episode of hepatic encephalopathy (HE). Sixty-four patients (58%) presented endoscopic and/or clinical criteria of portal hypertension. There were no statistically significant differences in baseline characteristics between the two groups, except as regards the presence of portal hypertension (Table I).

HCC was diagnosed in 57 patients (51.8%) based on histological criteria (group A = 29 and group B = 28), in 38 patients (34.5%) based on two imaging methods with consistent findings (group A = 24 and group B = 14), and in 15 patients (13.6%) based on one imaging method with consistent findings and alpha-fetoprotein > 200 IU/L (group A = 3 and group B = 12) (p = 0.03).

Characteristics of HCC at diagnosis

Seventy-six patients (69.1%) had a single lesion with median size of 25 mm. Ten patients (9.1%) had two lesions – the median size of the largest being 25 mm *versus* 17 mm for the smaller lesion. Of the remaining 24 patients, 20 (18.2%) suffered multifocal HCC, and 4 (3.6%) presented diffuse disease.

In reference to whether screening had been performed or not, 43 patients (76.8%) in group A had a single lesion, *versus* 33 patients (61.1%) in group B. Two lesions were detected in 5 patients (8.9%) in group A and in 5 patients (9.3%) in group B. In turn, multifocal HCC was observed in 7 patients (12.5%) in group A and in 13 patients (24.1%) in group B. Only one patient (1.8%) in group A suffered diffuse HCC *versus* 3 patients (5.6%) in group B. The difference in relation to the number of lesions was not statistically significant (p = 0.25) (Table II).

Based on the BCLC treatment criteria (17), we evaluated whether the malignancy met criteria for treatment with curative intent (defined as 3 lesions measuring under 1 cm in size or one lesion under 5 cm in size) or for palliative treatment. In group A, 40 patients (71.4%) were found to be candidates for curative therapy, *versus* 26 patients (48.1%) in group B (p = 0.011).

A total of 66 treatments (60%) were carried out with curative intent: radiofrequency ablation in 33 patients (30%) (69.7% in group A and 30.3% in group B), alcoholization in 23 patients (20.9%) (61% in group A and 39% in group B), proposed liver transplantation in 6 patients (5.5%) (33.3% in group A and 66.6% in group B), and surgical tumor resection in 4 patients (3.6%) (25% in group A and 75% in group B). In turn, 44 treatments were carried out with palliative intent: arterial embolization in 18 patients (16.4%) (38.8% in group A and 61.2% in group B) and symptomatic treatment in 26 patients (23.6%) (34.6% in group A and 65.4% in group B) –

Table II. Characteristics of HCC at the time of diagnosis

	Global	*Screening*	*No screening*	*p*
Patients according to number of lesions:				0.25
Single	76 (69.1%)	43 (76.8%)	33 (61.1%)	
Two	10 (9.1%)	5 (8.9%)	5 (9.3%)	
Multifocal	20 (18.2%)	7 (12.5%)	13 (24.1%)	
Diffuse	4 (3.6%)	1 (1.8%)	3 (5.6%)	
Median lesion size (mm)	25	23	28	
range (mm)	8-135	8-80	12-135	
Treatment provided				
Curative	*66 (60%)*	*40 (71.4%)*	*26 (48.1%)*	*0.011*
Resection	4	1	3	
Liver transplant	6	2	4	
Percutaneous (RF/OH)	56 (33/23)	37 (23/14)	19 (10/9)	
Palliative	*44 (40%)*	*16 (28.6%)*	*28 (51.9%)*	
TACE	18	7	11	
Symptomatic	26	9	17	

RF: radiofrequency ablation. OH: alcoholization. TACE: trans-arterial chemoembolization.

of which 13 suffered portal tumor thrombosis. Treatment with curative intent was provided in 71.4% of the patients subjected to screening (group A) and in 48.6% of the patients without screening (group B). In turn, palliative treatment was provided in 51.8% of the patients not subjected to screening and in 28.5% of the patients who had undergone screening.

In the 56 patients who underwent percutaneous treatment, controls were made after one month, based on two imaging techniques (abdominal ultrasound with contrast and liver MRI), showing evidence of tumor ablation in 43 cases (76.8%). Of the remaining 13 patients, 8 (14.3%) showed partial remission after the first percutaneous treatment, 3 (5.4%) suffered disease progression, and in two cases the response could not be evaluated.

Patient outcome

At the end of the follow-up period, 87 patients (82.1%) had died, 19 (17.9%) were still alive, and 4 (3.6%) had been lost to follow-up. In group A, the median survival was 2.67 years (1.07-4.28), *versus* 1.75 years (1.02-2.5) in group B.

The main cause of death was liver failure, recorded in 47 patients (54%), secondary to either HCC (34 patients, 39%) or advanced-stage cirrhosis (13 patients, 15%). Death was a consequence of the complications of cirrhosis (spontaneous bacterial peritonitis, upper digestive bleeding, hepatorenal syndrome, infections) in 24 cases (27.6%), of causes unrelated to the liver disease in 5 patients (5.7%), and secondary to the applied treatment in 3 cases (3.4%)(post-embolization liver failure in 2 patients, and postoperative complications in another). The precise cause of death could not be established in 8 patients (9.2%).

The median overall survival was 1.99 years (1.14-2.84), *versus* 3.48 years (1.79-5.17) and 0.9 years (0.66-1.14) among the patients subjected to curative and palliative treatment, respectively ($p < 0.0001$) (Fig. 1).

Tumor size at the time of diagnosis conditioned survival. Specifically, in patients with a tumor size of ″ 30 mm, the median survival was 2.98 years (95%CI: 1,9-4,1), while in the case of lesions measuring 30-50 mm, survival was 4.65 years (95%CI: 0.87-8,43). Lastly, in those tumors measuring ≥ 50 mm, the median survival was limited to 0.73 years (95%CI: 0.46-1) ($p = 0.000$).

On analyzing survival according to liver function, the patients with mild liver failure (Child-Pugh grade A) presented a median survival of 2.46 years (1.62-3.3), *versus* 1.22 years (0.74-1.71) and 0.15 years (0-2.21) in the patients with moderate (Child-Pugh grade B) and severe liver failure (Child-Pugh grade C), respectively ($p = 0.021$).

Regarding the complications associated to the liver disease, only ascites was found to be a significant factor for survival. The patients with ascites presented a median survival of 1.1 years (95%CI: 0.74-1.46), *versus* 2.37 years (95%CI: 1.78-2.96) in the rest of the subjects ($p = 0.015$). A history of other complications of cirrhosis (hepatic encephalopathy, UDB or SBP) did not modify survival.

Likewise, no statistically significant differences were found on analyzing other factors such as sex ($p = 0.36$), age under 65 years at the time of diagnosis ($p = 0.21$), or the cause of cirrhosis ($p = 0.53$).

The multivariate analysis considered those factors found to be statistically significant in the univariate analysis: degree of liver function, screening, tumor size, and the treatment provided (curative *versus* palliative). Ascites was not included, since clinical liver function as deter-

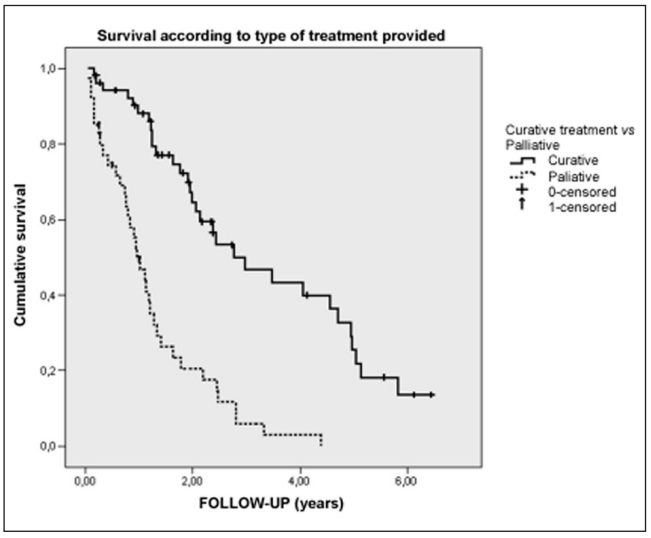

Fig. 1. Survival curve according to the treatment provided (curative intent *versus* palliative).

mined by the Child-Pugh score is more relevant and moreover contemplates ascites. In this analysis, only treatment intent (OR = 2.82; 95%CI: 1.3-6.12; p = 0.009) and liver function (OR = 1.71; 95%CI: 1.1-2.68; p = 0.02) were identified as independent predictors of survival, while screening (OR: 1.13; 95%CI: 0.64-2.01; p = 0.68) and tumor size (OR: 1.01; 95%CI: 0.99-1.03; p = 0.4) were not statistically significant.

DISCUSSION

Cirrhosis is the main risk factor for HCC, regardless of the underlying etiology. In our series, all patients were cirrhotic. The most prevalent cause in Europe is HCV infection (25). Over one-half of our patients presented HCV infection, associated or not to alcohol abuse. It is interesting to note that in our setting, the incidence of hepatitis B infection remains low, as has been reported elsewhere (9,18,26). Other data such as the recorded male/female ratio (2.3/1) and mean age at the time of diagnosis of HCC are in line with the findings of other studies carried out in this area (5,9,18,26).

The inclusion of cirrhotic patients in screening programs for HCC has been recommended for years. High alpha-fetoprotein levels are considered to be a risk factor for the development of HCC, and have been related to tumor size. Elevated AFP levels are also regarded as an independent predictor of HCC mortality in patients with cirrhosis due to HCV infection (27), though they are of little use in establishing an early diagnosis of the disease (28). In the present cohort, only 20% showed AFP elevation at the time of diagnosis. It has been questioned whether screening can improve survival. However, such programs have been shown to be able to detect smaller lesions, and this in turn allows the provision of treatment with curative intent (7,10,29). Consequently, screening indirectly contributes to lessen patient mortality. Our findings support this idea, despite the impression that patients with intermediate tumor sizes (3-5 cm) show greater survival. We think that this may be due to the small and less homogeneous nature of this group of individuals, which implies a much larger confidence interval than in the patients with small tumors, where the sample is larger (55 patients) and more homogeneous.

Another well known factor influencing survival is the degree of liver failure. The clinical guides recommend screening in Child-Pugh grade A patients, but not in Child-Pugh grade C cases (19). Uncertainty is greater in the case of patients with moderate liver failure (Child-Pugh grade B), though survival appears to improve when screening is applied in such individuals (30). Our own findings support this assumption. However, since the tumor directly affects liver function, it is difficult to establish whether mortality is attributable to cirrhosis or to tumor growth; these parameters therefore have been jointly analyzed.

The independent predictors of survival in our study were found to be the type of treatment provided (curative intent) and the degree of liver function. Their importance has been recognized by many of the HCC staging classifications, such as the BCLC or the Cancer of the Liver Italian Program (CLIP), and even by systems outside Europe, such as the Japanese Integrated Staging (JIS) classification (31).

Although tumor size was not statistically significant in our study, it was identified as a clinically important factor used to determine staging and treatment for HCC.

In conclusion, in patients with hepatocellular carcinoma, the degree of liver function and the possibility of prescribing treatment with curative intent at the time of diagnosis predict patient survival at the end of follow-up.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55(2):74-108.
2. Colombo M, de FR, Del NE, et al. Hepatocellular carcinoma in Italian patients with cirrhosis. N Engl J Med 1991;325(10):675-80.
3. Ince N, Wands JR. The increasing incidence of hepatocellular carcinoma. N Engl J Med 1999;340(10):798-9.
4. Montalto G, Cervello M, Giannitrapani L, Dantona F, Terranova A, Castagnetta LA. Epidemiology, risk factors, and natural history of hepatocellular carcinoma. Ann N Y Acad Sci 2002;963:13-20.
5. García-Torres ML, Zaragoza A, Giner R, Primo J, del Olmo JA. Incidence and epidemiological factors of hepatocellular carcinoma in Valencia during the year 2000. Rev Esp Enferm Dig 2003;95(6):385-4.
6. Macias Rodriguez MA, Rendon UP, Tejada CM et al. Risk factors for hepatocellular carcinoma in patients with liver cirrhosis. Rev Esp Enferm Dig 2000;92(7):458-69.
7. Pascual S, Irurzun J, Zapater P, et al. Usefulness of surveillance programmes for early diagnosis of hepatocellular carcinoma in clinical practice. Liver Int 2008;28(5):682-9.
8. Velazquez RF, Rodriguez M, Navascues CA, et al. Prospective analysis of risk factors for hepatocellular carcinoma in patients with liver cirrhosis. Hepatology 2003;37(3):520-7.
9. Vergara M, Gil M, Dalmau B, et al. Natural history of hepatocellular carcinoma in a cohort of pacients from a county hospital. Rev Esp Enferm Dig 2008;100(11):682-7.

10. Zapata E, Zubiaurre L, Castiella A, et al. Are hepatocellular carcinoma surveillance programs effective at improving the therapeutic options. Rev Esp Enferm Dig 2010;102(8):484-8.
11. Johnson PJ, Williams R. Cirrhosis and the aetiology of hepatocellular carcinoma. J Hepatol 1987;4(1):140-7.
12. Kew MC, Popper H. Relationship between hepatocellular carcinoma and cirrhosis. Semin Liver Dis 1984;4(2):136-46.
13. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003; 362(9399):1907-17.
14. Llovet JM, Bruix J. Novel advancements in the management of hepatocellular carcinoma 2008. J Hepatol 2008;48(Supl. 1):S20-S37.
15. 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.
16. 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.
17. Bosetti C, Levi F, Boffeta P, Lucchini F, Negri E, La V. Trends in mortality from hepatocellular carcinoma in Europe, 1980-2004. Hepatology 2008;48:137-45.
18. Sort P, Alvarez MA, Bargallo A, et al. Cost of screening for hepatocarcinoma in patients with cirrhosis: a prospective study. Gastroenterol Hepatol 2011;34(8):519-23.
19. Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology 2005;42(5):1208-36.
20. Bruix J, Llovet JM. Prognostic prediction and treatment strategy in hepatocellular carcinoma. Hepatology 2002;35(3):519-24.
21. Llovet JM, Schwartz M, Mazzaferro V. Resection and liver trasplantation for hepatocellular carcinoma. Semin Liver Dis 2005;25:181-200.
22. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60(8):646-9.
23. Wiesner R, Edwards E, Freeman R, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology 2003; 124(1):91-6.
24. Bruix J, Sherman M, Llovet JM, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 2001;35(3):421-30.
25. Trinchet JC, Ganne-Carrie N, Nahon P, N'kontchou G, Beaugrand M. Hepatocellular carcinoma in patients with hepatitis C virus-related chronic liver disease. World J Gastroenterol 2007;13:2455-60.
26. Calvet X, Bruix J, Bru C, et al. Natural history of hepatocellular carcinoma in Spain. Five year's experience in 249 cases. J Hepatol 1990; 10:311-7.
27. Tyson GL, Duan Z, Kramer JR, Davila JA, Richardson PA, El-Serag HB. Level of alpha-fetoprotein predicts mortality among patients with hepatitis C-related hepatocellular carcinoma. Clin Gastroenterol Hepatol 2011;9(11):989-94.
28. Forner A, Vilana R, Ayuso C, et al. Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: Prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. Hepatology 2008; 47:97-104.
29. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol 2004; 130:417-22.
30. Trevisani F, Santi V, Gramenzi A, et al. Surveillance for early diagnosis of hepatocellular carcinoma: is it effective in intermediate/advanced cirrhosis? Am J Gastroenterol 2007;102:2448-57.
31. Marrero JA, Kudo M, Bronowicki JP. The challenge of prognosis and staging for hepatocellular carcinoma. Oncologist 2010;15 (Supl. 4):23-33.