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Characteristics and survival of hepatocellular carcinoma in non-cirrhotic liver.

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ABSTRACT

Introduction: the characteristics, screening, and survival of hepatocellular carcinoma (HCC) for patients without cirrhosis have not been fully studied.

Methods: A retrospective cohort study was performed in non-cirrhotic patients with histological HCC, between January 2004 and October 2018. Their characteristics, treatment, follow-up and overall survival were described.

Results: 25 of the 332 patients with HCC met the inclusion criteria (7.5%), 76% were males and the median age was 69.9 years. The main etiology of liver disease was the hepatitis virus B (HBV) (32%), followed by non-alcoholic steatohepatitis (NASH) (20%). Liver fibrosis was mild (0-1) in 44% of cases. The nodule was diagnosed by ultrasonography in 32% of cases, 60% were found incidentally and 8% due to clinical symptoms. The Barcelona Clinic Liver Cancer (BCLC) staging was 0 in 4% of cases, A in 88%, B in 4% and C in 4%. The main initial treatment was surgical resection (76%) and

8% refused to be treated. Percutaneous ethanol injection, chemoembolization, sorafenib and palliative care were each performed in 4% of cases. There were some complications in 21% of patients treated with surgery, half of them were severe. The median follow-up was 22.2 months (2.9-150.6) and 56% were in remission and the median overall survival was 57.4 ± 29.8 months. The overall cumulative survival at 1, 3 and 5 years was 84%, 61.6% and 47.9%, respectively.

Conclusion: 7.5% of HCC presented without cirrhosis and almost half of patients had mild fibrosis. HBV was the main cause of HCC, followed by NASH. The most frequent BCLC stage at diagnosis was early stage and surgery was the most common treatment. Overall cumulative survival at 5 years was almost 50%.

Key words: Hepatocellular carcinoma. Non-cirrhotic liver. Liver cirrhosis. Barcelona Clinic Liver Cancer staging. Liver resection.

INTRODUCTION

Hepatocellular carcinoma (HCC) mainly appears in patients with liver cirrhosis. Screening via ultrasonography every 6 months by experienced personnel improves the diagnosis and the possibility of curative treatment in this group of patients (1-5). Screening is also recommended for patients with hepatitis B virus (HBV) chronic liver disease, without cirrhosis, with an intermediate or high risk of HCC. This was recently defined by the European guidelines according to PAGE-B scoring system (platelet, age, gender, hepatitis B virus). Furthermore, screening is also recommended in patients with chronic liver disease stage 3 fibrosis, regardless of the etiology (4). The possibility of a major risk in patients with non-alcoholic steatohepatitis (NASH) and the need for screening is an emerging trend. However, this has not yet been established and its cost-effectiveness needs to be explored (6-8).

Currently, the development of HCC in non-cirrhotic liver has been poorly studied. Some studies have been reported from other geographical areas. However, the results cannot be extrapolated to our country due to geographical variability (4). Other studies have used some inclusion criteria that are not recommended in the guidelines (1-5), as

half of the patients included do not have cyto-histology (9). On the other hand, some case series only focus on a single therapeutic alternative (10-15). Moreover, the only clinical report published in our country has a shorter follow-up and includes patients treated ten years ago without the benefit of systemic therapy, radioembolization (16,17) and the improvement of surgical techniques. In addition, liver disease etiology is changing due to a reduction of viral causes and an increase in NASH (18).

This study was performed in non-cirrhotic patients diagnosed with HCC by cyto-histology. The aims of the study were to evaluate the proportion of HCC in non-cirrhotic liver and to analyze the epidemiological, clinical, diagnostic and staging characteristics. Furthermore, the results of the therapeutic options in this group of patients in the clinical practice were also assessed.

METHODS

A retrospective cohort study was performed in non-cirrhotic patients diagnosed with HCC by cyto-histology, between January 2004 and October 2018. The diagnosis was according to the recommendations of the European Association for the Study of the Liver (EASL) and the criteria of the American Association for the Study of liver diseases (AASLD). The epidemiological and clinical characteristics, diagnostic methods, staging, treatment, evolution and survival were analyzed.

The exclusion of liver cirrhosis was performed by histological criteria such as a liver biopsy (LB) and/or the surgical piece, transient elastography (FibroScan®) or the absence of any unequivocal criteria of cirrhosis (clinical/analytical/ultrasonography/upper endoscopy). Ultrasonography was performed by trained hepatologist, with more than 25 experience years in our department. The FibroScan® was performed with a medium probe, without ascites or liver congestion data and was considered appropriate when at least ten optimal results with interquartile range (IQR) < 30% were obtained. A cut-off point of < 9 kPa was considered to exclude advanced fibrosis-cirrhosis (19,20). This could not be performed in all patients without histological data as the technique only became available in 2008 and there is no XL probe in our center. Fibrosis stages were identified according to METAVIR score (21,22).

Ultrasonography was performed annually in patients with HBV chronic liver disease and every 1 or 2 years for the remaining chronic liver diseases, according to the criteria of the hepatologist. The nodule was punctured using fine needle puncture aspiration (FNA) and/or microbiopsy. The differentiation degree of HCC was defined as well, moderately or poorly differentiated (23). A thoracic and abdominal contrast-enhanced computed tomography (CT) scan was used to study tumor extension.

Imaging findings were studied in the different dynamic imaging explorations. The typical hallmark for HCC was defined as that used in liver cirrhosis as the combination of hypervascularity in late arterial phase and washout on portal venous and/or delayed phases (1,5), without considering the lack of validity of non-invasive criteria in non-cirrhotic liver (1-5).

Therapeutic strategies were used according to the BCLC system as follows. Liver transplant (LT) in a reference center, liver resection (LR), percutaneous ethanol injection (PEI), radiofrequency (RF) that were available since November 2007. Furthermore, transarterial chemoembolization (TACE) with lipiodol and adriamycin until 2006 and with lipiodol and DC Bead® particles (Biocompatibles, Surrey, UK), sorafenib (since June 2009) and palliative treatment since 2007. Combination therapy was used when appropriate.

Statistical analysis was performed using the SPSS 15 software. Categorical variables are described as percentages and absolute numbers. Quantitative variables are expressed with the median and interquartile range. Survival curves were estimated using the Kaplan-Meier method.

RESULTS

Epidemiological characteristics

Three hundred and thirty-two patients diagnosed with HCC between January 2004 and October 2018 were evaluated, 25 were non-cirrhotic patients (7.5%). The patients were divided into the following three-year time periods: 6.3% in 2004-2006, 5.5% in 2007-2009, 10% in 2010-2012, 7.1% in 2013-2015 and 7.7% in 2016-October 2018 ($p = 0.89$). The absence of liver cirrhosis was found in 19 patients (76%) with LB and/or in the surgical specimen, 1 (4%) with FibroScan® and 5 (20%) due to unequivocal

clinical/analytical/ultrasonography/upper endoscopy criteria.

Fibrosis stage was mild fibrosis (0-1) in 11 patients (44%), 4 were stage 0 and 7 were stage 1. Moderate fibrosis (2-3) was found in 8 patients (32%), 6 were stage 2 and 2 were stage 3. Fibrosis was staged by FibroScan® in 1 patient (8.1 kPa, stage 2). The clinical, analytical, ultrasonography and upper endoscopy findings that were performed by trained hepatologist with structured criteria in a single-center were evaluated in five patients without fibrosis information. None of these explorations showed data compatible with cirrhosis. From these 5 patients, 2 patients refused the recommended treatment and 3 were at an advanced age and were not candidates for surgery. Thus, LB did not change the treatment. One case was 74 years old with comorbidities who was initially treated with PEI, another was 84 years old with tumoral portal invasion treated with sorafenib and the final case was 86 years old with comorbidities who received only symptomatic treatment.

The median age was 69.9 (31-86) years. Nineteen patients (76%) were male and twenty-four patients (96%) were Caucasian and 1 (4%) was black race. With regard to the liver etiological study, 44% had markers of viral infection: 8 (32%) hepatitis B virus (HBV) and 3 (12%) hepatitis C virus (HCV); 5 (20%) had NASH; 1 (4%) alcoholism and NASH; 2 (8%) alcoholism; 1 (4%) hereditary hemochromatosis gene (performed by family screening with normal serum ferritin and transferrin saturation), 1 (4%) acute intermittent porphyria and in 4 (16%) had an unknown etiology. All patients with NASH were diagnosed with HCC during the last 5 years (2013 to 2018). The PAGE-B score was calculated at diagnosis in Caucasian patients with chronic HBV hepatitis, with/without antiviral treatment. 1 low risk (without antiviral treatment) and 6 intermediate risk (3 with treatment and 3 without antiviral treatment) scores were obtained. The test was not applied to the black patient. With regard to HBV infection markers, all patients had an active infection with positive surface antigens, only 1 was positive for the e antigen, 3 patients had < 2000 IU HBV DNA and 5 > 20000 IU/ml. At the time of HCC diagnosis, 3 patients were receiving treatment with HBV nucleoside analogs with a complete virological response during 2, 2.9 and 7 years and 2 were diagnosed simultaneously with HCC and HBV. None of the patients had been treated for HCV. Ten patients (40%) were smokers.

Prior to the HCC diagnosis, 11 patients (44%) were included in the follow-up program in our hepatology department. The diagnosis was made during follow-up by ultrasonography in 8 cases (32%), 15 (60%) were incidental and 2 (8%) were symptomatic. The complete epidemiological characteristics are shown in table 1.

Tumor characteristics

A single nodule was detected in 24 patients (96%). The median size of the single or main nodule was 46 (14-159) mm. Only 1 (4%) case had vascular invasion and none had extrahepatic spread. All patients were ECOG 0 (Eastern Cooperative Oncology Group). The median alpha-fetoprotein (AFP) was 31.9 (1-1521) ng/ml. With regard to the differentiation degree, 16 (64%) were well differentiated and 9 (36%) were moderately differentiated. The tumor characteristics are shown in table 2.

Staging and treatment

According to the BCLC (Barcelona Clinic Liver Cancer) staging system, 92% were early stage (1 stage 0, 22 stage A), 1 (4%) was stage B and 1 (4%) was stage C.

The initial treatment used was LR, which was performed in 19 cases (76%). Postoperative complications included 1 case of early postoperative death (5.2%) due to respiratory distress syndrome and multi-organ failure 10 days after surgery. One major complication occurred (5.2%) of ischemic stenosis of the bile duct that was initially resolved with surgical reoperation. However, the patient subsequently died due to a hepatic drained collection, pulmonary empyema with a torpid evolution and renal and cardiac complications. There were also 2 minor complications (10.4%) that were resolved with medical treatment.

Other treatments included 1 (4%) case with PEI, 1 (4%) TACE, 1 (4%) sorafenib, 1 (4%) symptomatic treatment and 2 (8%) rejected treatments. The patient treated with PEI presented a persistence of viable tissue treated with TACE and sorafenib. The patient treated with TACE suffered a progression with pulmonary metastases and received sorafenib. One patient was treated directly with sorafenib due to presenting vascular tumor invasion and 1 with an advanced age and comorbidities was only a candidate for symptomatic treatment.

Survival

The median follow-up was 22.2 (2.9-150.6) months, with 14 patients (56%) in remission. The median overall survival was 57.4 ± 29.8 months, with a 44% death rate. This included 2 deaths due to postsurgical complications, 5 due to tumor progression and 4 due to non-HCC causes. The 1, 3 and 5 year survival rates were 84%, 61.6% and 47.9%, respectively (Fig. 1).

DISCUSSION

HCC in non-cirrhotic liver is an infrequent disease. In our series, 7.5% of HCC developed in non-cirrhotic livers, without a statistically significant increase during the follow up period. The rate was 6.2% in a previous single-center study (16) and 13% in a multicenter study (18). Patients with fibrosis stage information (80%) were considered as inclusion criteria and also patients without cirrhosis information but with a combination of clinical/analytical/ultrasonography/upper endoscopy tests (20%). Including these patients allowed us to cover the entire spectrum of patients with non-cirrhotic HCC and not only those treated surgically. In this way, the study represents the real clinical practice.

The median age was 69.9 (31-86) years and 75% were males. A higher mean age and lower prevalence of males have been reported in non-cirrhotic patients compared to cirrhotic patients (7,8). The etiology of liver disease was found in 84% of cases, with a predominance of viral etiology (32% HBV, 12% HCV). The second most common etiology was NASH (20% and 4% associated with alcohol). All these cases were identified during the last 5 years (2013-2018). NASH has been described as a cause of HCC with an increasing incidence in developing countries (8,24-26). In fact, whether screening for HCC in a non-cirrhotic stage is cost-effective is being considered (6-8).

The recent European guideline (4) defined by PAGE-B scoring system recommend that non-cirrhotic Caucasian patients on antiviral therapy of HBV should undergo biannual ultrasonography screening. All of our patients with these characteristics would have been identified by PAGE-B as an intermediate risk. In fact, if we extend this method to patients without antiviral treatment, only 1 case would have been identified as low

risk. The guidelines also recommend assessing the individual risk of patients with stage 3 fibrosis. However, only 10% of our patients had stage 3 disease, 50% had mild fibrosis (0-1), which similar to previous studies (16,19,31).

None of the HCV patients had been treated with antivirals prior to the HCC diagnosis. Currently, there are several studies to determine whether the new direct-acting antivirals lead to an increase in HCC incidence (32). There is also some controversy with regard to HCV treatment in HCC patients. Nowadays, there is no clear evidence in favor of this association (33).

Other etiological factors that have been related to HCC in non-cirrhotic patients such as increasing alcohol intake and liver metabolic diseases (8% of each in our series). Furthermore, congenital and liver vascular diseases and toxic substances such as aflatoxin B1, iron overload, anabolic androgenic steroids, estrogens, and certain germline mutations have also been studied (27). A study in non-cirrhotic patients with HCC and with no increasing alcohol intake or the presence of HBV or HCV found that 43% of patients had microsatellite instability. Thus, this factor was related with the HCC pathogenesis (34).

In our series, most of patients had a single lesion with a median size of 46 mm (14-159). In published studies, patients at diagnosis had larger liver lesions (7-12,16,27-30) compared to cirrhotic patients. This was due to the absence of ultrasonography screening. Tumor portal invasion and extrahepatic metastases is more variable (from 6.9% to 25%) (7,8,16,31), as well as the degree of tumor differentiation. Some authors have stated that these HCC are more aggressive tumors than in cirrhotic patients (10,28). This is in contrast with our series, in which 64% HCC had a well differentiated disease and there was a single case of tumor portal invasion and no cases had metastasis at diagnosis. The main BCLC stage was 0-A (92%), despite the fact that only 32% patients were diagnosed during follow-up by ultrasonography.

According to current recommendations, non-invasive criteria are exclusive to cirrhotic patients due to the high pre-test probability in this group. Thus, pathology is necessary in non-cirrhotic patients (1-5). In our series, 64% had typical hallmarks for HCC, at least in some of the dynamic imaging explorations performed. Previous studies showed similar results on contrast-enhanced CT scan and contrast-enhanced magnetic

resonance (MR) imaging (35).

Most of the patients were treated by LR (76%), as in previous studies. The best functional liver reserve and the absence of portal hypertension in non-cirrhotic patients allow more aggressive surgeries. Therefore it is recommended as a first-line therapy (10-12,28,36-38). Age older than 70 years, large LR (more than 2 segments) (13), a greater tumor size, satellitosis and macrovascular invasion are related to a poorer survival due to increased recurrence (8,30). The post-surgical mortality described is 2.7-13.3% (15,16,27,37), without a clear and homogeneous defined period. Recurrence appeared in 39.7% of cases during the first 2 years (12), 69% at 5 years and there were no differences between cirrhotic and non-cirrhotic patients in most studies (11,27,30, 36.38). Nineteen patients were treated with LR, 14 (73.7%) remained in remission, 3 (15.8%) relapsed and 2 (10.4%) died after surgery. 1 (5.2%) case died due to complications within the first 30 days after surgery and 1 (5.2%) required a second surgery and was readmitted with infectious, cardiological and renal complications and subsequently died 5 months after surgery.

None patients were transplanted, as in most studies (8,9,16,40). In another study, the LT was an exceptional treatment (1.08%) (7). LT is infrequent in non-cirrhotic patients with HCC, as LR is the treatment of choice and had similar survival rates to LT in cirrhotic patients (11,27,41). The international consensus in 2012 recommended LT as a rescue therapy for intrahepatic recurrence after 12 months of LR. In addition, they also recommended that it be used as a first-line therapy in unresectable tumors that do not meet the Milan criteria (42) but have vascular invasion or metastasis (43). Good prognostic factors are AFP < 100 ng/ml, less than 4 nodules and a length less than 5cm (36,37). Non-surgical therapy efficacy data in non-cirrhotic patients are very scarce, as they are used in a lower proportion than in cirrhotic patients (8,31). Our patient treated with PEI and the one treated with TACE suffered a tumor progression and required systemic therapy.

The 1, 3 and 5 year survival rate was 84%, 61.6% and 47.9%, respectively. This is very similar to the study by Nuñez et al. in Spain (16) and in the range of other studies, which describe very variable intervals (66-86.9% after 1 year and 29-64% after 5 years) (10,14,28,31,39,40,44). The most favorable data are from studies with LR as a single

therapy. In our study, 36.4% patients died due to causes that were not related to HCC. These were related to age and comorbidity, for instance 16% had other cancers. With regard to survival, previous studies showed an absence of statistically significant differences between cirrhotic and non- cirrhotic patients (28), including one adjusted by age and LT (8).

The strength of our study in HCC non-cirrhotic patients is that it has the longest follow-up in our country, it reveals the current incidence and it does not focus on a single therapy.

Furthermore, we evaluated patients until October 2018 and the study therefore includes new changes in HCC etiology and therapeutics. The limitations are the sample size, the fact that it is a single-center study and the absence of LB in non-tumoral liver in all cases. However, it allowed us to demonstrate the real clinical practice. Future prospective multicenter studies are necessary to expand the knowledge of this disease and to identify risk factors that allow the definition of a high-risk group of non-cirrhotic HCC patients that may require screening.

In conclusion, 7.5% of HCC developed in a non-cirrhotic liver. Almost half of patients had mild fibrosis. This occurred predominantly in patients with chronic liver disease, main viral etiology and NASH during the last years. The PAGE-B scoring system identified all Caucasian HBV patients on antiviral therapy as within the intermediate risk group. The most frequent BCLC stage at diagnosis was early stage and surgery was the most common treatment. Overall cumulative survival at 5 years was almost 50%.

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Table 1. Clinical and epidemiological characteristics of HCC in non-cirrhotic patients (n: 25)

Age (median and range) years	69.9 (31-86)
Sex (male), n (%)	19 (76%)
Race, n (%) • Caucasian • Black	 24 (96%) 1 (4%)
DM, n (%)	7 (28%)
AH, n (%)	13 (52%)
Metabolic syndrome, n (%)	5 (20%)
Hypothyroidism, n (%)	2 (8%)
HIV (19 patients), n (%)	0
BMI (15 patients) (median ± SD)	27.2 ± 3.6
Previous follow-up for liver disease, n (%)	11 (44%)
Etiology for liver disease, n (%): • Virus HBV HCV	21 (84%) 11 (44%) 8 (32%) 3 (12%)

• NASH	5 (20%)
• Alcohol	2 (8%)
• NASH + alcohol	1 (4%)
• Hereditary hemochromatosis*	1 (4%)
• Acute intermittent porphyria	1 (4%)
HCC diagnosis, n (%):	
• Follow-up ultrasonography	8 (32%)
• Casual diagnosis	15 (60%)
• Symptoms	2 (8%)
*Fibrosis stage**:*	
• Mild (0-1)	11 (44%)
• Moderate (2-3)	9 (36%)
• Unknown	5 (20%)
Other cancer, n (%):	4 (16%)
• Lung	2 (8%)
• Gastric	1 (4%)
• Urothelial	1 (4%)
Bilirubin (median ± SD) mg/dl	0.6 ± 0.4
Albumin (median ± SD) g/dl	4.1 ± 0.6
AST (median ± SD) U/L	34.6 ± 18
ALT (median ± SD) U/L	37.2 ± 18.6
GGT (median ± SD) U/L	67.7 ± 51.4
AP (median ± SD) U/L	96.8 ± 49.8
Creatinine (median ± SD) mg/dl	0.9 ± 0.2
Sodium (median ± SD) mEq/L	140.2 ± 2.2
INR (median ± SD)	1 ± 0.6
Platelets (median ± SD) x 103 µ3	224.1 ± 66.6

*A patient with the hereditary hemochromatosis C282Y/H63D gene, performed by family screening, but with normal serum ferritin and transferrin saturation. **19 patients by histology and 1 by transient elastography (8.1 kPa). DM: diabetes mellitus;

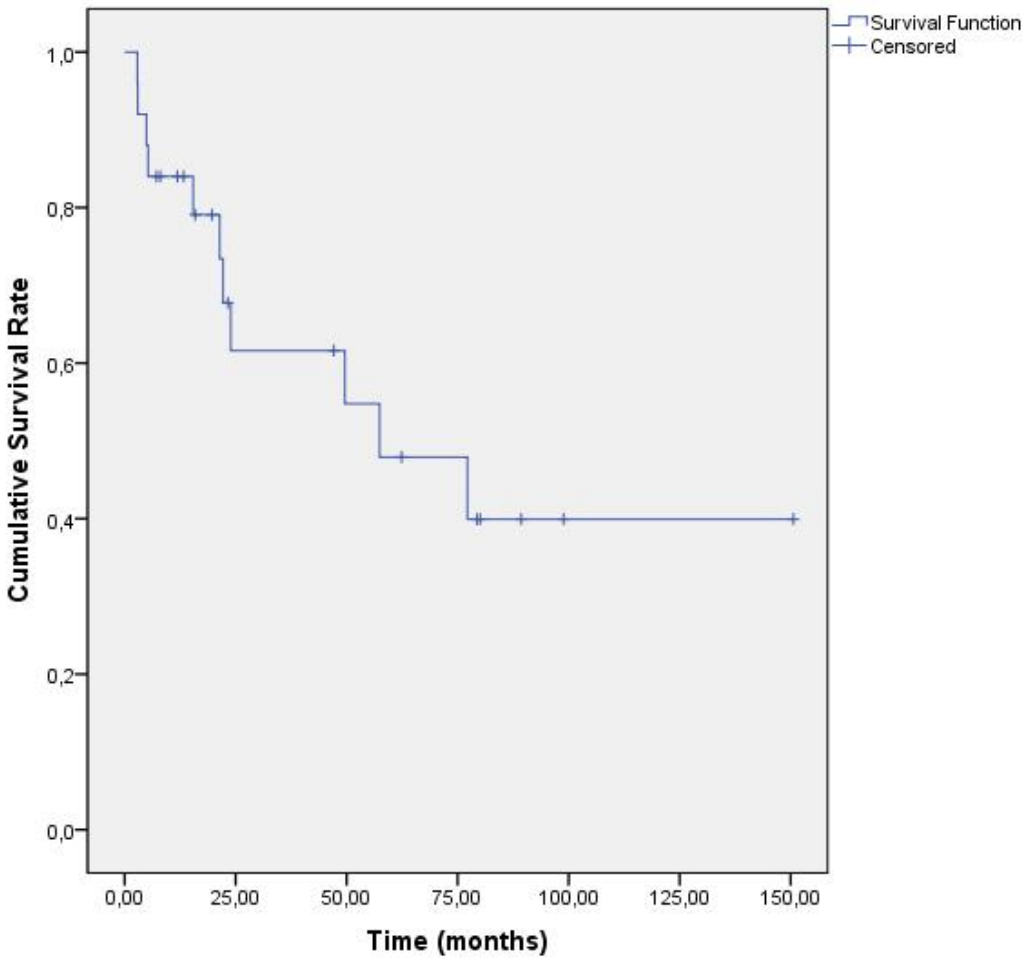
AH: arterial hypertension; HIV: human immunodeficiency virus; BMI: body mass index; HBV: hepatitis B virus; HCV: hepatitis C virus; NASH: non-alcoholic steatohepatitis; HCC: hepatocellular carcinoma; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma glutamyl transpeptidase; AP: alkaline phosphatase; INR: international random proportion.

Table 2. Tumor characteristics of HCC in non-cirrhotic patients (n: 25)

Number of nodules: Single, n (%) Two, n (%)	 24 (96%) 1 (4%)
Size (median and range) mm	46 (14-159) mm
Typical hallmark:* • Any dynamic imaging exploration (25 patients) • Contrast-enhanced ultrasonography (SonoVue®) (14 patients) • Contrast-enhanced CT scan (25 patients) • Contrast-enhanced MR imaging (11 patients)	 16 (64%) 7 (50%) 12 (48%) 7 (63.6%)
Vascular invasion, n (%)	1 (4%)
Extrahepatic spread, n (%)	0
ECOG 0, n (%)	25 (100%)
AFP (median and range) ng/ml	31.9 (1-1521)
Differentiation degree, n (%) • Well differentiation • Moderate differentiation	 16 (64%) 9 (36%)
BCLC staging, n (%): • Stage 0 • Stage A • Stage B • Stage C • Stage D	 1 (4%) 22 (88%) 1 (4%) 1 (4%) 0

*The combination of hypervascularity in the late arterial phase and washout on portal venous and/or delayed phases. CT: computed tomography; MR: magnetic resonance; ECOG: Eastern Cooperative Oncology Group; AFP: alpha-fetoprotein; HCC:

hepatocellular carcinoma; BCLC: Barcelona Clinic Liver Cancer.



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The Spanish Journal of Gastroenterology

Figure 1. Overall survival. Median follow-up: 22.2 (2.9-150.6) months. Median overall survival: 57.4 ± 29.8 months. The 1, 3 and 5 year survival rate was 84%, 61.6% and 47.9%, respectively.