Hepatocellular Carcinoma:

retrospective cohort study of clinical characteristics, treatment and outcome

Dissertation for application to the Master's degree in Medicine, submitted to the Institute of Biomedical Sciences Abel Salazar of University of Porto.

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Abstract

Aim: The aims of this cohort study are, first, to describe the clinical and etiological profile and, second, to report treatment outcomes of patients with hepatocellular carcinoma presenting to a tertiary care hospital in the North of Portugal.

Methods: Retrospective analysis of the electronic charts of 139 patients admitted in our institution between July 2008 and September 2012.

Results: The final cohort sample included 116 cases. Alcoholic liver disease was identified in 77%, hepatits C infection was seen in 38% and hepatitis B infection in 18% of patients. Cirrhosis was present in 94% of patients. According to Barcelona Clinic Liver Cancer classification, cancer stage at diagnosis was found as follows: 2% very early, 34% early, 40% intermediate, 7.4% advanced and 15.6% at terminal stage. Treatment allocation was decided in a multidisciplinary team and intention-to-cure treatments included 4 hepatic resections, 22 liver transplantations and 18 ablations. Chemoembolization was primarily allocated as palliative treatment in 46 patients and 6 patients were treated exclusively with sorafenib. Fourteen patients received supportive care only. The Kaplan-Meier estimate for median survival for the entire cohort was 36 months. Treatment was associated with prolonged survival and the best outcomes were seen in transplant patients (median not reached, 1 and 3-year survival rate of 85%). Median survival estimates and survival rates at 1- and 3-year for radiofrequency ablation patients and chemoembolized patients were 13 months, 62% and 15% and 26 months, 75%, and 43%, respectively.

Conclusion: Chronic harmful alcohol consumption was found to be uncommonly high in this cohort. The majority of patients were diagnosed at late stages of disease which carries a poor prognosis. Comparing with currently available literature, patients undergoing chemoembolization presented with higher long-term survival rates whereas, surprisingly, ablation patients had poorer outcomes. Further studies are recommended to identify additional prognostic factors.

Key-words: hepatocellular, Barcelona Clinic Liver Cancer staging, alcoholic liver disease, hepatitis C, hepatitis B, liver transplantation, radiofrequency ablation, chemoembolization, northern Portugal.

Resumo

Objectivo: O presente estudo coorte tem como objetivos a caracterização clínica, descrição do perfil etiológico e resultados de sobrevivência de doentes com carcinoma hepatocelular que foram referidos a um hospital central no Norte de Portugal.

Métodos: Análise retrospetiva dos processos eletrónicos de 139 doentes que foram referenciados a esta instituição durante o período de Julho 2008 até Setembro 2012.

Resultados: A amostra final incluiu 116 casos. Hepatopatia alcoólica foi identificada em 77%, infeção pelo vírus da hepatite C em 38% e infeção pelo vírus da hepatite B em 18%. Presença de cirrose verificou-se em 94% dos casos. De acordo com a classificação Barcelona Clinic Liver Cancer, doentes foram diagnosticados no seguinte estádio: 2% estádio 0, 34% estádio A, 40% estádio B, 7.4% estádio C e 15.6% em estádio D. Após decisão em equipa multidisciplinar, foram alocados 4 resseções hepáticas, 22 transplantes de fígado e 18 ablações por radiofrequência. Quimioembolização foi realizada com intenção paliativa em 46 casos, 6 doentes foram tratados exclusivamente com Sorafenib e 14 receberam apenas tratamento sintomático. Utilizando curvas de Kaplan-Meier, a sobrevivência dos doentes neste coorte foi estimada em 36 meses. A realização de tratamento foi associada a sobrevida prolongada, sendo superior nos doentes transplantados (mediana não atingida, taxa de sobrevivência aos 12 e 36 meses de 85%. Estimativas da mediana e taxas de sobrevivência aos 12 e 36 meses em doentes tratados com radiofrequência ou com quimioembolização foram, respectivamente, 13 meses, 62%, 15% e 26 meses, 75%, 43%.

Conclusões: O consumo crónico e excessivo de álcool apresentou uma prevalência invulgarmente alta neste coorte. A maioria dos doentes foi diagnosticada em estádios avançados de doença, associado a um pior prognóstico. Comparando com a literatura atualmente disponível, os doentes tratados com quimioembolização apresentaram uma sobrevida superior num longo termo enquanto doentes tratados por radiofrequência apresentaram resultados inferiores aos expectáveis.

Palavras-chave: hepatocelular, classificação Barcelona Clinic Liver Cancer, hepatopatia alcóolica, hepatite C, hepatite B, transplant hepático, ablação por radiofrequência, quimioembolização, norte de Portugal.

Introduction

Liver cancer ranks as the sixth most common cancer worldwide and is considered a global health problem [1]. Hepatocellular carcinoma (HCC), which represents more than 90% of primary liver cancers [2], has a strong male preponderance with a male-to-female ratio estimated at 2.4 [1].

Chronic viral hepatitis, caused by hepatitis B virus (HBV) and hepatitis C virus (HCV) are the most important risk factors being responsible for up to 54% and 31%, respectively, of global HCC cases [2]. The occurrence of HCC shows a clear geographic distribution, as high incidence and prevalence rates occur in Africa and East Asia, which concentrate 85% of HCC cases in the world, and where the endemic nature of HBV infection accounts for the important burden of this risk factor in HCC epidemiology. In Western countries, lower rates of HCC are found and HBV infection accounts for only 10-15% of the attributable risk factor for HCC [2] [3], whereas chronic HCV infection and harmful alcohol consumption are the more frequent etiological causes [4]. For the past two decades, growing information on patients with nonalcoholic steatohepatitis (NASH) has established this hepatic inflammatory process as important cause of liver cirrhosis and HCC [5]. Incidence of HCC associated with NASH is expected to rise due to better recognition of such etiology in HCC cases previously considered cryptogenic [6], and more importantly, due to the growing epidemics of metabolic syndromes related to obesity and diabetes mellitus [7] [8] [9].

Cirrhosis represents an end stage of liver disease and itself carries a high oncogenic risk [10]. All etiologic forms of cirrhosis may be complicated by tumor formation, but the risk is higher in patients with chronic viral infection [2]. Although HCC can occur in the non-cirrhotic liver [11] [12], presence of a cirrhotic background accounts for up to 90% of HCC cases in the Western countries [13] and the resulting degree of liver dysfunction may hinder cancer treatment [4]. Hence, prognostic prediction and treatment recommendation needs a multidimensional evaluation, considering tumor burden and its invasive pattern, liver function and cancer related symptoms [14] [15]. Although several multidimensional staging systems for HCC are available (Okuda [16], Barcelona Clinic Liver Cancer (BCLC) [17], Cancer of the Liver Italian Program (CLIP) [18] and Japan Integrated Staging (JPS) [19]), the only system currently linking staging with treatment decision is the BCLC system [20]. The BCLC classification is currently endorsed in the European Association for the Study of Liver diseases (EASL [2]) and the American Association for the Study of Liver Diseases (AASLD) [21] most recent reviews of guidelines for management of HCC. Both guidelines currently advocate a less invasive diagnostic approach, as advances in imaging techniques have enabled diagnosis based on

identification of radiological hallmarks of HCC (contrast uptake in arterial phase and washout in the venous/late phase) [22].

Alfa-fetoprotein, a known tumor biomarker widely used in the HCC subset, is no longer recommended for diagnosis or screening [2]. Screening for HCC should be performed in populations at high risk every 6 months using ultrasound, targeting patients with cirrhosis, HBV carriers with active hepatitis or family history of HCC and chronic HCV-infected patients that present with advanced liver fibrosis F3 [2].

Surveillance aims for cancer diagnosis at earlier stages, where treatments such as liver transplantation, resection and local ablation are performed with intention to cure, and can achieve an excellent outcome of 5-year survival rates reaching 70-90% in optimally selected patients [23] [24] [25] [26] [27].

Despite more widespread surveillance and advances in diagnosis and treatment availability, HCC is still more frequently diagnosed at non-early stages of disease even in Western countries [15]. Even though palliative treatments such as chemoembolization and oral chemotherapy (sorafenib) are proven to improve survival [28] [29], patients with advanced disease have a poor prognosis. Moreover, terminal stages bear a very poor prognosis with less than a 6-month life expectancy and no survival benefit from treatment [17]. Overall, liver cancer is one of the most fatal cancers and ranks worldwide as third cause of cancer-related death [1].

Methods

Study design and Selection of Participants

Between July 2008 and September 2012, all patients referred to a multidisciplinary consultation in our institution in the North of Portugal with a presumptive diagnosis of HCC were eligible for the present study. Patients were identified as having code 155.0 from the International Classification of Diseases, 9th revision (ICD-9). Being an academic tertiary care hospital and a center for liver transplantation, the majority of patients were referrals from other health care institutions for either confirmation of diagnosis and/or treatment with posterior follow-up.

A retrospective analysis was performed by review of electronic medical records, which included admission and discharge notes and medical reports from auxiliary imaging techniques and treatments. Exclusion criteria included: very significant unavailability of information in the electronic charts; lack of reference to HCC etiology and absence of clinical and laboratory information in medical charts that would allow exclusion of chronic viral hepatitis and alcoholic liver disease; patients referred from external institutions exclusively for treatment and patients lost to follow-up. Study methodology was approved by institutional board review.

HCC Diagnosis

The diagnosis of HCC was histologically proven with biopsy or established according to non-invasive criteria as defined by EASL and AASL guidelines [2] [21], using imaging techniques of computerized tomography (CT) and magnetic resonance imaging (MRI). Non-invasive diagnosis of HCC was assumed in cirrhotic patients with nodules of more than 2 cm and upon identification of HCC radiological hallmarks on at least one imaging technique. Patients with nodules of 1-2 cm had diagnosis preferably supported by two positive image findings. Biopsy was performed in cases of uncertain or atypical radiological findings and in non-cirrhotic patients. Additionally, diagnosis of HCC during specific screening was noted. Date of diagnosis was assumed when a nodule with high suspicion of HCC was first identified with posterior confirmation of diagnosis. Such methods aimed to prevent confounding date of HCC diagnosis with the identification of regenerative hepatic nodules. Since this study also analyzed patients referred from other health care services, in some cases this time may possibly have been underestimated.

Clinical characterization

HCC patient profiles were characterized with laboratory data, identification of etiology of liver disease, assessment of liver status and tumor characterization.

Laboratory data

Laboratory data included full blood count and liver function tests including aspartate transaminase (AST), alanine transaminase (ALT), bilirubin, gamma glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), albumin, international normalized ratio (INR) and prolonged prothrombin time (pPT). HCV infection was screened with anti-HCV (COBAS EleCsys, Roche, Switzerland) and confirmatory test of HCV infection was performed using western blotting. HBV infection was identified by the presence of HBsAg and infection status was characterized with anti-HBs, anti-HBc, anti-HBe, HBeAg using ECLIA (COBAS, Roche, Switzerland). Serum alfa-fetoprotein (aFP) was measured using ECLIA (COBAS, Roche, Switzerland).

Etiology

Chronic viral hepatitis was considered in patients seropositive for HCV (antibody) and/or HBV (detectable HBsAg). Alcoholic liver disease had been considered by physicians when excessive and chronic consumption of alcohol was identified during patient anamnesis and additional information from laboratory data commonly used in clinical practice when such pattern of consumption is suspected (increased GGT, MCV, AST/ALT ratio). If information in medical cases was not clear about previous exclusion of chronic viral hepatitis or alcoholic liver disease, then HCC was classified as cryptogenic. NASH was suspected in patients presenting with previous diagnosis of non-alcoholic fatty liver disease (NAFLD) on ultrasound and/or its risk factors (obesity, diabetes or insulin resistance, hyperlipidemia). Biopsy was necessary for confirmation of HCC-related NASH. Expected less commonly seen etiologies such as exposure to aflatoxin, inherited metabolic diseases and autoimmune hepatitis were grouped in one category (“other etiologies”). Presence of other less established risk factors for HCC and co-morbidities such as smoking, obesity (Body Mass Index ≥30kg/m^2), diabetes and hyperlipidemia was retrieved from medical records. The latter two were identified as having been previously diagnosed elsewhere or by identification of specific chronic medication (oral anti-diabetics/insulin therapy or hypolipidemic agents, respectively).

Assessment of liver status

Cirrhosis was assumed upon ultrasonographic findings and CT imaging and clinical signs that are known to correlate with advanced hepatic fibrosis and portal hypertension such as presence of thrombocytopenia (<100.000), splenomegaly, esophageal varices and ascites [30], [31]. Biopsy was performed on patients with atypical presentation or absence of such findings. Child-Pugh score [32] was used for indirect evaluation of liver function [2].

Tumor characterization

Data necessary for tumor characterization were retrieved from image reports of abdominal ultrasound, CT or MRI studies. In similar fashion to the BCLC classification, the number of lesions were grouped into three categories: 1 lesion, 2 to 3 lesions and 4 or more lesions. The size of the biggest lesion was categorized as follows: up to 2 cm, between 2 and 3 cm and more than 3 cm. Invasive pattern was evaluated as presence of portal venous invasion of the main trunk or a first-order branch (right or left main trunk) and presence of extrahepatic spread.

Staging and Treatment

The BCLC staging system [17] was used for classification of HCC stage and orientation for treatment allocation, consisting of the following stages: very early (0), early (A), intermediate (B), advanced (C) and terminal (D). When appropriate for statistical analysis, BCLC stages were grouped into 2 categories: early HCC stage, comprising stages 0 and A and non-early HCC (stages B, C and D). Final treatment decision for all patients was made by a multidisciplinary team comprising internists, gastroenterologists or hepatologists, liver transplant and hepatobiliary-pancreatic surgeons, medical oncologists and radiologists.

All treatment options were equally available from the beginning of the study. Potentially curative treatments included orthotopic liver transplantation, hepatic resection (including lobectomy and segmental resection) and ablation with radiofrequency. Palliative treatments included transarterial therapies and systemic oral therapy with sorafenib. Two types of transarterial therapies were offered at our institution: bland catheter embolization (TAE) using Lipiodol was performed until 2010; thereafter, chemoembolization (TACE) using drug-eluting beads containing a solution of doxorubicin was the standard transarterial therapy. Some patients performed multiple sessions of the same treatment (multiple sessions of TACE or ablation with radiofrequency) or combined different treatment modalities. Multiple therapies were offered to selected patients in one of the following scenarios: those who presented with

tumor *de novo* or tumor recurrence with or without evolution to subsequent BCLC stage; as palliative treatment for control of symptoms and increase of survival; as downstaging intervention for tumors without Milan criteria for liver transplantation; or as neoadjuvant therapy to locoregional therapies or those on the waiting list for transplant. Symptomatic and supportive care was offered to patients in terminal stages or with contraindications or refusal of any other therapy.

Follow up and evaluation of outcomes

Follow-up consultation included complete clinical examination, full blood count, liver function tests, serum alpha-protein and CT image. All patients were offered follow-up in an outpatient regimen and frequency of consultation was dependent on type of treatment. For patients performing invasive treatments, follow-up was performed one month after procedure and 3 months thereafter during the first year. If there were signs of residual tumor or tumor recurrence, patients were re-evaluated for additional treatment sessions; if not, control image, was made every 3 to 6 months. Patients starting oral chemotherapy (sorafenib) were followed for management of side-effects every 1 to 3 months, according to treatment tolerability and evolution of liver function.

Death was the only primary end-point analyzed and was classified as either HCC-related (when due to tumor progression or liver failure) or HCC-unrelated. Overall survival estimates were calculated from date of diagnosis until death occurred. When analyzing treatment outcomes, time 0 was assumed as the day when treatment was performed, or day of first prescription for patients taking sorafenib. Specifically, for patients undergoing adjuvant therapies or downstaging for potentially curative treatment, time 0 was assumed when the latter was performed.

Statistical Analysis

The results are expressed as mean and standard deviation values or median and range for interval variables and as proportions for categorical and ordinal variables. Correlation of interval variables was analyzed using Pearson’s correlation test. If normal distribution could be assumed, comparison of interval variables between two or more independent samples was analyzed using the independent t-test or one-way ANOVA, respectively. Interval variables without normal distribution, ordinal and categorical variables were analyzed using the Wilcoxon-Mann-Whitney or Kruskall-Wallis tests when appropriate. Proportions were analyzed using Pearson's chi-square test; Fischer’s exact test was used as

an alternative in contingency tables of 2x2 variables. Survival rates were analyzed using the Kaplan-Meier method and differences between groups were evaluated using the log-rank test. When complete follow-up data was not available, data on survival was censored at the time of the last documented contact with the patient. A p-value of <0.05 was considered significant; when using sequential Mann-Whitney tests, p-value significance was calculated using the Bonferroni correction. Statistical analyses were performed with SPSS for Windows, version 21.0 (IBM, Chicago, IL, USA).

Results

A total of 139 patients had their medical cases reviewed for the present study. Twenty three patients were excluded from further analysis: 15 patients had significant lack of clinical data in their electronic records; 4 patients had other primary liver tumors (cholangiocarcinoma) and 1 had secondary liver tumor, but had been incorrectly coded with ICD 155.0; one patient with haemochromatosis and two with NASH etiologies were excluded due lack of representativity. The final cohort sample included 116 patients. For 93 patients it was possible to record previous attendance in a HCC screening program, of whom 42 (45%) had HCC diagnosed during surveillance consultation. A single lesion measuring 1 to 2 cm was diagnosed in 10 cases, of which 75% had been diagnosed during screening. In the majority of patients, HCC was confirmed with lesions of >2 cm, of which 50% had been diagnosed during screening surveillance.

Clinical characterization

The mean age at presentation was 61.2 ± 10.5 years (range 28–89 years) and 102 subjects (88%) were male (male-to-female ratio 7.3:1). Tables I and II summarize clinical characterization for this cohort.

HCC etiology

The etiologies of HCC were alcoholic liver disease (44%), combined etiology (32.7%), HCV infection (13.8%) and HBV infection (9.5%). Combined etiology was seen only as alcoholic liver disease (ALD) alongside only one type of viral infection. No co-infection of HCV and HBV was found in this cohort. Mean age at time of HCC diagnosis of patients with combined etiology was lower than those seen in any single etiology. Patients with alcohol as single risk factor presented with the highest mean age (65.6 ± 9.8 years) in this cohort. However, statistical significance was only seen between this group and those with combined HCV infection and ALD (55.4 ± 5.5 years; p<0,001).

As only half of medical records included the necessary information for BMI calculation, analysis of obesity as co-morbidity was not performed. Concerning the remaining risk factors and co-morbidities, shown in table I, diabetes was more consistently seen in patients with ALD (p<0.008) and smoking habits were significantly higher in patients with combined etiologies (p<0.002).

Table I. Clinical characterization of patients according to etiology

	Diagnosis						
	All etiologies n (%)	**Alcohol n (%)**	**HCV n (%)**	**HBV n (%)**	**Alcohol + HCV n (%)**	**Alcohol + HBV n (%)**	**p-value**
	116	51 (44%)	16 (13.8%)	11 (9.5%)	28 (24.1%)	10 (8.6%)	
Gender							
Male	102	47	14	7	24	10	>0.05
Female	14	4	2	4	4	0	
Age mean ± SD	61.9 ± 10.5	65.6 ± 9.8	60.3 ± 11.5	60.1 ± 14.8	55.36 ± 5.5	58.25±8.7	**0.001**
range	28-89	46-89	39-77	28-74	44-67	46-72	
Liver analytics mean ± SD (range)							
AST	87.25 ± 68.48 (22 - 412)	57.61 ± 30.97 (22 - 182)	108.29 ± 59.55 (26 - 234)	143.36 ± 121.13 (25 - 412)	101.32 ± 62.48 (30 - 270)	93.22 ± 87.49 (29 - 256)	>0.05
ALT	67.93 ± 56.84 (11 - 407)	43.26 ± 30.44 (11 - 193)	108.71 ± 94.16 (27 - 407)	94.45 ± 73.42 (17 - 237)	74.73 ± 43.39 (19 - 158)	73.44 ± 36.17 (20 - 154)	>0.05
GGT	213.52 ± 238.44 (20 - 1542)	243.79 ± 293.36 (29 - 1542)	142.07 ± 115.72 (24 - 491)	179.27 ± 151.76 (25 - 480)	201.05 ± 211.41 (20 - 925)	252.44 ± 243.26 (52 - 776)	>0.05
ALP	159.94 ± 169.45 (52 - 1561)	170.77 ± 121.29 (65 - 666)	124.29 ± 53.77 (56 - 237)	155.36 ± 67.96 (90 - 274)	176.09 ± 310.88 (52 - 1561)	129.78 ± 75.7 (81 - 323)	>0.05
Bilirubin	1.59 ± 1.63 (0.33 - 11.31)	1.75 ± 2.1 (0.33 - 11.31)	1.47 ± 1.1 (0.47 - 4.56)	1.19 ± 0.76 (0.47 - 3.02)	1.68 ± 1.35 (0.52 - 7.03)	1.27 ± 1.13 (0.37 - 3.40)	>0.05
Albumin	3.65 ±0.71 (1.93 - 4.78)	3.70 ± 0.66 (1.93 - 4.72)	3.77 ± 0.60 (2.77 - 4.73)	3.71 ± 0.62 (2.59 - 4.59)	3.36 ± 0.85 (2.05 - 4.59)	3.78 ± 0.81 (2.44 - 4.78)	>0.05
INR	1.24 ± 0.38 (0.85 - 4.40)	1.17 ± 0.20 (0.85 - 1.85)	1.29 ± 0.30 (1 - 1.95)	1.48 ± 0.98 (0.97 - 4.40)	1.25 ± 0.23 (0.87 - 1.60)	1.20 ± 0.15 (0.99 - 1.42)	>0.05
pPT	2.84 ± 2.32 (0 - 11.40)	2.60 ± 2.29 (0 - 11.40)	2.88 ± 2.67 (0 - 9.00)	2.28 ± 1.67 (0.5 - 4.90)	3.69 ± 2.58 (0 - 8.40)	2.29 ± 1.77 (0.2 - 5.9)	>0.05
Platelet count ($x10^9$/L	124.29 ± 74.91 (31 - 409)	135.16 ± 87.72 (31 - 409)	104.5 ± 67.66 (31 - 269)	160.36 ± 57.93 (67 - 251)	96.78 ± 51.29 (31 - 249)	129.33 ± 69.67 (45 - 215)	>0.05
aFP (ng/ml)							
<20	48 (51.6%)	28 (65%)	5 (38.5%)	3 (27.25%)	10 (47.6%)	3 (33.3%)	>0.05
20-200	19 (20%)	4 (11%)	5 (38.5%)	3 (27.25%)	4 (19.1%)	3 (33.3%)	>0.05
>200	28 (28.4%)	9 (24%)	3 (23%)	5 (45.5%)	7 (33.3%)	3 (33.3%)	>0.05
Co-morbidities							
Smoking	47 (45.2%)	17 (33.3%)	4 (26.7%)	1 (10%)	18 (66.7%)	7 (70%)	**0.002**
Diabetes	43 (38.1%)	28 (54.9%)	2 (13.3%)	1 (10%)	9 (33.3%)	3 (30%)	**0.008**
Hyperlipidemia	14 (12.7%)	9 (17.6%)	2 (13.3%)	1 (10%)	2 (7.4%)	0 (0%)	>0.05

Cirrhosis, portal hypertension and assessment of liver function

HCC with underlying cirrhosis was present in 94% of the cases (table II). All patients with chronic HCV infection, either as single or as combined etiology, developed HCC in a cirrhotic liver, whereas almost half of patients with HBV alone presented with no underlying cirrhosis. Patients with history of heavy alcohol consumption were significantly more likely to develop HCC in cirrhotic liver than those with HBV infection alone ($p<0.0001$).

Clinical signs of portal hypertension and parameters for assessment of liver function are described in detail for each etiology in table II. Presence of ascites was significantly more common in patients with both VHC infection and ALD. Although not achieving statistical significance, the same sub-group of patients presented with the highest Child-Pugh scores and with the highest frequencies in other surrogates of portal hypertension such as presence of esophageal varices and thrombocytopenia.

Table II. Characterization of cirrhosis, liver function and tumor burden stratified by underlying liver disease.

	Diagnosis						
	All etiologies n (%)	**Alcohol n (%)**	**HCV n (%)**	**HBV n (%)**	**Alcohol + HCV n (%)**	**Alcohol + HBV n (%)**	**p-value**
Cirrhosis							
present	102 (94.4%)	45 (97.8%)	15 (100%)	5 (55.6%)	28 (100%)	9 (90%)	<0.000
absent	6 (5.6%)	1 (2.2%)	0 (0%)	4 (44.4%)	0 (0%)	1 (10%)	
Child-Pugh							>0.05
A	42 (43%)	19 (45.5%)	7 (53.8%)	6 (54.5%)	6 (27.3%)	4 (44.4%)	
B	40 (41%)	17 (40.5%)	5 (38.5%)	4 (36.4%)	10 (45.4%)	4 (44.4%)	
C	15 (16%)	6 (14.3%)	1 (7.7%)	1 (9.1%)	6 (27.3%)	1 (11.2%)	
Platelet count ($x10^6$/L)							>0.05
<100.000	48 (48%)	20 (46.5%)	8 (57.1%)	2 (18.2%)	14 (60.9%)	4 (44.4%)	
>100.000	52 (52%)	23 (53.5%)	6 (42.9%)	9 (81.8%)	9 (39.1%)	5 (55.6%)	
Esophageal varices							>0.05
present	46 (52.3%)	21(56.8%)	5(45.5%)	2 (22.2%)	15 (68.2%)	3 (33.4%)	
absent	42 (47.7%)	16 (43.2%)	6 (54.5%)	7 (77.8%)	7 (31.8%)	6 (66.7%)	
Ascites							0.017
present	28 (26.2%)	12 (26.1%)	0 (0%)	1 (9.1%)	12 (46.2%)	3 (30%)	
absent	79 (73.8%)	34 (73.9%)	14 (100%)	10 (90.9%)	14 (53.8%)	7 (70%)	
Number of lesions							>0.05
1	59 (55%)	27 (57.4%)	9 (60%)	4 (40%)	13 (52%)	6 (60%)	
2-3	15 (14%)	8 (17%)	3 (20%)	0 (0%)	3 (12%)	1 (10%)	
>3	33 (31%)	12 (25.5%)	3 (20.%)	6 (60%)	9 (36%)	3 (30%)	
Size of solitary lesions							>0.05
<2 cm	5 (9.6%)	1 (4.1%)	2 (28.6%)	1 (33.3%)	1 (8.3%)	0 (0%)	
2 - 5 cm	31 (59.6%)	13 (54.2%)	4 (57.1%)	1 (33.3%)	8 (66.7%)	5 (83.3%)	
>5 cm	16 (30.8%)	10 (41.7%)	1 (14.3%)	1 (33.3%)	3 (25%)	1 (16.7%)	
Size of multinodular lesions							
n	32	13	6	2	7	4	
mean size (mm) ± SD	57.47 ± 40.6	65.54 ± 49.9	76.67 ± 43.9	42 ± 11.3	38 ± 17.9	50.75 ± 34.0	
range	(20 - 198)	(21 - 198)	(25 - 132)	(34 – 50)	(20 - 70)	(23 - 100)	
Portal vein invasion							>0.05
present	13 (11.7%)	4 (8.2%)	1 (6.7%)	2 (18.2%)	5 (19.2%)	1 (10.0%)	
absent	98 (88.3%)	45 (91.8%)	14 (93.3%)	9 (81.8%)	21 (80.8%)	9 (90%)	

Tumor characterization

Tumor burden and vascular invasion are described in table II. No association was seen between higher tumor burden or presence of portal vein invasion and underlying etiology. Multinodular tumors were more likely to present with portal vein thrombosis than solitary tumors (20.8% versus 3.4%, respectively; $p<0.004$). Tumor pattern (solitary or multinodular lesions) was not associated with the serum level of alpha-fetoprotein (using both cut-offs of 20 and 200ng/ml). No dependent correlation was found between this tumor marker and nodule size. Patients diagnosed during screening were more likely to be seen with solitary tumor than unscreened patients (70% versus 49%; $p<0.05$) and with smaller mean size of solitary tumors (33.9 mm versus 59.8 mm; $p<0.003$). However, such patients were not more commonly diagnosed with tumors smaller than 2 cm.

Staging

BCLC stage could be determined for 96 patients (table III). Patients at stage A had mainly solitary tumors ≤5cm (91%) and where seen with approximately equal proportion of Child A (45.5%) and Child B (54.5%). Child-Pugh score distribution was not significantly different in patients diagnosed at intermediate stage (59% in Child-Pugh A and 41% in Child-Pugh B). Only three (20%) patients at terminal stage had portal invasion at time of diagnosis. Patients diagnosed during HCC screening were more likely to be found at earlier HCC stages (BCLC classification 0 or A) (p<0.003).

Table III. Clinical characterization according to BCLC classification.

	Early HCC stage n (%)		**Not Early HCC stage** n (%)			**p-value**
Diagnosis						
Screened	20 (52.6%)		18 (47.4%)			**<0.003**
Not Screened	11(22.4%)		38 (77.6%)			
Etiology						>0.05
Alcohol	33.3%		66.7%			
HCV	42.9%		57.1%			
HBV	30%		70%			
HCV + Alcohol	25%		75%			
HBV + Alcohol	44.4%		55.6%			
	BCLC 0 n (%)	**BCLC A** n (%)	**BCLC B** n (%)	**BCLC C** n (%)	**BCLC D** n (%)	
All patients	2 (2%)	33 (34%)	39 (40%)	7 (7.4%)	15 (15.6%)	
Child-Pugh						>0.05*
A	2 (100%)	15 (45.5%)	23 (59%)	1 (14.3%)	0 (0%)	
B	0 (0%)	18 (54.5%)	16 (41%)	6 (85.7%)	0 (0%)	
C	0 (0%)	0 (0%)	0 (0%)	0 (0%)	15 (100%)	-
Tumor burden						>0.05†
Solitary	2 (100%)	30 (91%)	11 (28%)	1 (14.3%)	8 (53.3%)	
Multinodular (>2 lesions)	0	3 (9%)	28 (72%)	6 (85.7%)	7 (46.7%)	

* Comparison between patients classified with stage A versus patients at stage B
† Comparison between patients classified with stage B versus patients at stage C

Treatment

Information on treatment performed (table IV) was available in 110 patients and three groups were defined: those treated with a potentially curative treatment; those who only had palliative treatment; and those who only received supportive treatment. Potential curative treatment was undertaken by 44 (40%) patients as follows: 4 resections, 22 liver transplants and 18 ablations by radiofrequency. Neo-adjuvant treatments were performed in 12 patients (10 of the liver transplanted, one of resection and one of RFA) and 5 of the transplanted patients underwent downstaging using TACE/TAE. The second group of patients consisted of 52 (47%) patients performing exclusively palliative treatments, of which 46 had multiple sessions of TACE/TAE (a total of 127 sessions, with a range of 1 to 6 consecutive sessions

per patient) and 6 patients received only sorafenib. For 14 (13%) patients only supportive care was offered. Comparing patients from the two groups of treatment, potentially curative treatment and palliative treatment, the former ones were more likely to have been classified with earlier stages of HCC ($p<0.001$) and to be seen within Milan criteria ($p<0.000$). No differences were seen for Child score or for frequency of portal vein invasion. All patients receiving only symptomatic care had been classified as non-early HCC. Comparing these with treated patients, such patients were more likely to exceed Milan criteria ($p<0.05$), to present with portal vein invasion ($p<0.000$) and with higher Child-Pugh scores ($p<0.000$).

Table IV. Staging, liver function and tumor burden according to intention of treatment.

	Intention-to-cure	Palliative	p-value	Treated patients	Supportive	p-value
BCLC			**<0.001**			-
Early HCC	23 (60.5%)	12 (24%)		35 (39.8%)	0 (0%)	
Non-Early HCC	15 (39.5%)	38 (76%)		53 (60.2%)	14 (100%)	
Child-Pugh			>0.05			**<0.000**
A	20 (57.1%)	20 (43.3%)		40 (49.4%)	2 (14.3%)	
B	11 (31.4%)	22 (47.8%)		33 (40.7%)	5 (35.7%)	
C	4 (11.4%)	4 (8.7%)		8 (9.9%)	7 (50%)	
Milan Criteria			**<0.000**			**<0.05**
within	30 (76.9%)	14 (28%)		44 (49.4%)	3 (21.4%)	
without	9 (23.1%)	36 (72%)		45 (50.6%)	11 (78.6%)	
Portal vein invasion			>0.05			**<0.000**
Present	2 (4.8%)	3 (5.8%)		5 (5.3%)	6 (42.9%)	
Absent	40 (95.2%)	49 (94.2%)		89 (94.7%	8 (57.1%)	

Outcome and survival analysis

Forty-three patients died during follow-up, of which 39 had death caused by hepatic failure or HCC progression and for the remaining 4 information on death cause was unavailable. Required information for survival analysis was available in a total of 105 patients, of which 39 (37%) died, 41 (39%) were confirmed to be alive at the end of follow-up and 25 (24%) were lost to follow-up. The median follow-up period was 15 months (range: 0–67). Median overall survival (OS) estimates using Kaplan-Meier method for the entire cohort was 35 months and the 1- and 3-year survival rate was 80% and 48%, respectively (fig. 1). The median, 1-year and 3-years OS estimates for treated patients were 46 months, 90% and 55%, respectively (fig. 2). Median and 1-year OS for patients that just received supportive care were 5 months and 25% (fig. 2); patient survival in this group did not exceed 15 months. Treated patients had significantly higher OS than those in the later group ($p<0.0001$).

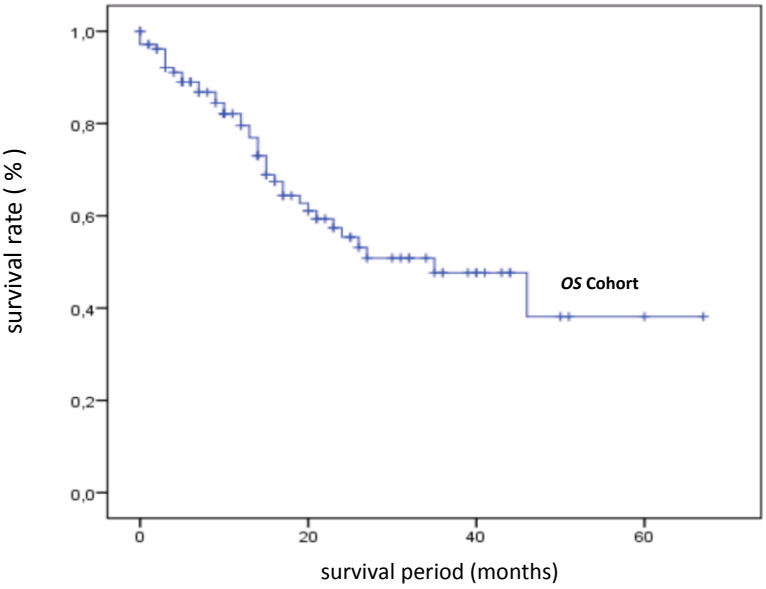

Fig. 1. Kaplan-Meier overall survival (OS) estimation for the entire cohort (*n*=105 patients).

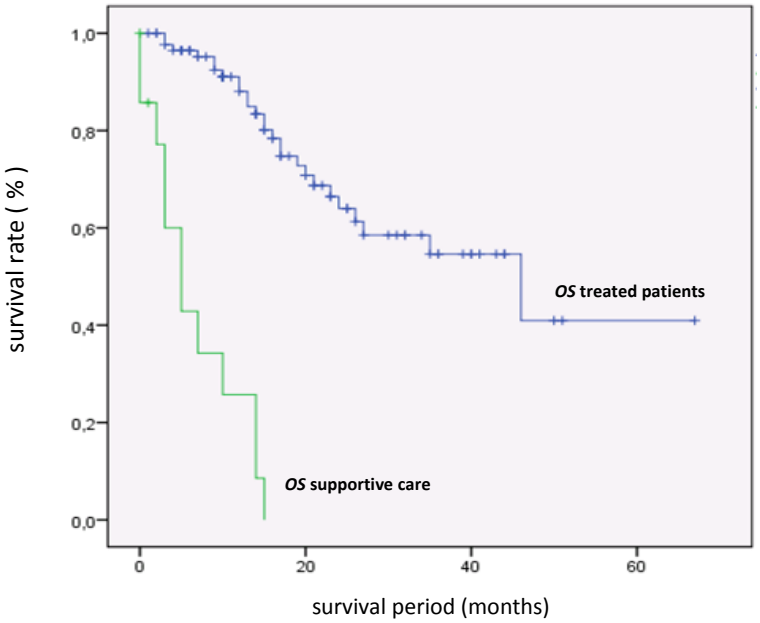

Fig. 2. Kaplan-Meier overall survival (OS) estimation stratified by patients receiving any treatment (*n*=88 patients) and patients receiving only supportive care (*n*=14 patients). Log-rank test of survival rate: treated versus supportive care, p<0.0001).

Sub-group analysis

Major HCC prognostic factors for HCC survival are described according to treatment received in table V. Since only a small number of patients underwent resection or had had exclusively received sorafenib, survival analyses could not be computed. Transplant patients showed a simultaneous 1- and 3-year survival of 85% (median not reached; fig. 3). Only one patient had in-hospital death (third postoperative day due to hepatic artery thrombosis). The remaining two deaths were also due to surgical complications (one hepatic artery thrombosis and one portal vein thrombosis), occurring on the fifth and sixth postoperative month, respectively. Ablation patients had median OS of 13 months and 1- and 3 year survival of 62% and 15% and those performing TACE/TAE treatments had median survival of 26 months and 1- and 3 year survival of 75% and 43% (both in fig. 3). No complications or in-hospital mortality were seen in any patient undergoing resection, ablation or TACE/TAE.

Differences in outcomes were only compared between treatments that included patients with similar prognostic profile (table V). Comparing patients from the three treatments, whose outcomes had been computed in this cohort, a similar prognostic profile was only seen between patients performing transplantation or radiofrequency ablation. The former showed significantly higher survival rates than ablation patients (p<0.003, fig 3).

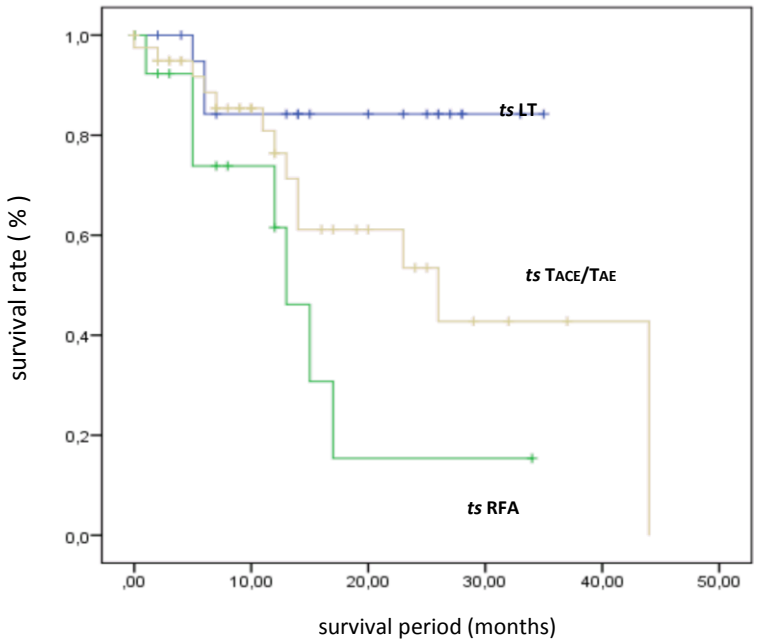

Fig. 3. Kaplan-Meier treatment survival (*ts*) estimation for 22 patients receiving liver transplantation (LT), 16 patients treated with radiofrequency ablation (RFA) and 40 patients undergoing chemoembolization (TACE) or bland embolization (TAE). Log-rank test of survival rate: liver transplantation versus radiofrequency ablation, p<0.003).

Table V. Major prognostic factors for survival of patients with hepatocellular carcinoma, stratified by treatment received.

	Resection	Transplant	RFA	TACE/TAE	Sorafenib	p-value 1*	p-value 2 †	p-value 3 ‡
Age (mean ± SD)	73.67 ± 6.66	55.76 ± 5.16	62.18 ± 11.56	65.12±8.99	55.0± 8.75	>0.05	**<0.0001**	>0.05
Child-Pugh						>0.05	>0.05	>0.05
A	3 (100%)	8 (47.1%)	9 (60%)	19 (47.5%)	1 (16.7%)			
B	0	7 (41.2%)	4 (26.7%)	18 (45%)	4 (66.7%)			
C	0	2 (11.8%)	2 (13.3%)	3 (7.5%)	1 (16.7%)			
Number of lesions						>0.05	>0.05	**<0.003**
1	3 (75%)	13 (68.4%)	15 (88.2%)	21 (47.7%)	1 (16.7%)			
2-3	0 (0%)	2 (10.5%)	2 (11.8%)	10 (22.7%)	0 (0%)			
> 3	1 (25%)	4 (21.1%)	0 (0%)	13 (29.5%)	5 (83.3%)			
Size of solitary lesion						>0.05	**<0.002**	**<0.0001**
< 2 cm	0	1 (7.7%)	2 (13.3%)	1 (4.8%)	0 (0%)			
2-5 cm	0	11 (84.6%)	13 (86.7%)	10 (47.6%)	1 (100%)			
> 5cm	3 (100%)	1 (7.7%)	0	10 (47.8%)	0 (0%)			
Milan criteria						>0.05	**<0.002**	**<0.0001**
Within	0	13 (72.2%)	17 (100%)	13 (29.5%)	1 (16.7%)			
without	4 (100%)	5 (27.8%)	0	31 (70.5%)	5 (83.3%)			
Portal Vein						>0.05	>0.05	>0.05
Present	0	1 (4.8%)	1 (5.9%)	1 (2.2%)	2 (33.3%)			
Absent	4 (100%)	20 (95.2%)	16 (94.1%)	45 (97.8%)	4 (66.7%)			
Ascites						>0.05	>0.05	>0.05
present	0	3 (14.3%)	5 (31.3%)	8 (18.6%)	3 (50%)			
Absent	4 (100%)	18 (85.7%)	11 (68.8%)	35 (81.4%)	3 (50%)			
Bilirubin						>0.05	>0.05	>0.05
≤2.0	3 (100%)	14 (87.5%)	12 (85.7%)	34 (81%)	3 (60%)			
>2.0	0 (0%)	2 (12.5%)	2 (14.3%)	8 (19%)	2 (14.3%)			
aFP (ng/ml)						>0.05	**<0.005**	**<0.05**
<200	3 (100%)	16 (100%)	14 (93.3)	25 (62.5%)	3 (50%)			
≥200	0 (0%)	0 (0%)	1 (6.7%)	15 (37.5%)	3 (50%)			

* Comparison of prognostic factors between patients receiving liver transplantation with patients undergoing radiofrequency ablation

† Comparison of prognostic factors between patients receiving liver transplantation and those performing palliative chemoembolization

‡ Comparison of prognostic factors between patients undergoing radiofrequency ablation and those performing palliative chemoembolization

Discussion

The aim of this retrospective cohort study is to increase the availability of epidemiological data concerning HCC patients in Portugal, in particular clinicopathological characterization, etiological profile and survival outcomes in patients treated at a tertiary care center in the North of Portugal.

The majority of patients were male (88%) and the mean age at presentation of all patients was 61.3 ± 10.5 years. These findings are in line with several European studies that also reported HCV infection and harmful alcohol consumption as leading etiologic causes for HCC [33] [34], [35] [36] [20] [10]. In our cohort study alcohol consumption was the most frequent risk factor, presenting either as a single etiology (44%) or in combination with HCV or HBV infection (32.7%). The total proportion of patients HCV infected (35%) or HBV infected (17%) was similar to the range of reported infection rates reported in some European HCC series [37] [38] [39] [33]. However, presence of important alcoholic consumption history in 72% of our patients with confirmed HCC represents an unusually high proportion compared to those described in current literature. Assessing alcohol consumption poses several difficulties that may lead to overdiagnosis [40]. However the probability of such hypothesis may be hinder by three facts. Firstly, a local study addressing the clinical characterization of HCC patients (*n*=84) at a different institution also reported a considerably high prevalence (63.2%) of alcohol as risk factor for HCC [41]. Secondly, according to the OECD – Health Data (2008) report Portugal has the 8th higher mean of annual alcohol consumption per capita in the world (11.4l) [42]. Thirdly, our institution is located in the North of Portugal, a region with higher prevalence of alcohol consumption than in other regions in mainland [43]. Additionally, results from a Portuguese national study evaluating the burden of disease attributable to alcohol drinking [44] reported significant male gender predominance in those with excessive drinking (>60g ethanol/d). Considering these facts and adding together the high proportion of reported alcohol history in our patients may explain the very high male-to-female ratio in our study (7.3:1).

HCC predominantly arose in clinically evident or histologically proven liver cirrhosis (94%), which has been also seen in large cohort European studies [34] [39] [20] [14]. Irrespective of the underlying liver disease, cirrhosis is a major factor able to modulate HCC risk and the annual risk of developing HCC in cirrhotic liver is estimated between 1% to 6% [11]. Although the risk of cirrhosis is higher for those with hepatitis infection [2], alcoholic cirrhosis is probably the most important risk factor for HCC in populations with low prevalence of HBV and HCV infection and low exposure to aflatoxins [45], such as developed Western countries [9]. Once

cirrhosis is established, a higher risk of HCC correlates with the severity of portal hypertension [46] and liver stiffness as measured by transient elastography [47] [48]. In the present study, chronic HCV infection and alcohol abuse were etiologic factors very likely to develop HCC in a cirrhotic liver, whereas the occurrence of HCC in non-cirrhotic liver was more likely to happen in HBV-infected patients. Of note, patients with comorbid HCV infection and alcoholic liver disease were seen with more severe portal hypertension. These associations are in agreement with those described in the literature that we briefly review below.

Alcohol drinking is associated with an increased risk of developing cirrhosis and liver cancer [49]. Although HCC can develop in patients with alcohol-induced liver disease who do not have cirrhosis [40], it occurs remarkably more frequently in a cirrhotic liver [45]. This finding is consistent with the concept that the hepatocarcinogenicity of alcohol abuse is most likely due to the development of cirrhosis [12]. Recently, a meta-analysis estimated the relative risk (RR), according to specific doses of alcohol, for developing cirrhosis and liver cancer with adjustment for gender, age and hepatitis viral infection [50]. Estimated RR of developing liver cirrhosis for doses of 50g/day and for 100g/day were 7.13 (95%CI 6.36–8.00) and 26.52 (95%CI 22.26–31.59), respectively; the RR of liver cancer in absence of cirrhosis for an alcohol intake of 50g/day and for 100g/day were 1.40 (95%CI 1.25–1.56) and 1.81 (95% CI 1.50–2.81), respectively. In a large Swedish cohort (51), the relative risk for HCC in patients having cirrhosis due to alcoholic liver disease was 22.4 (95% CI 16.8–29.2) times higher than the risk in the general population.

In HCV-infected patients alone, HCC occurs predominately in those with cirrhosis [52], [53], [54], [55], [56], although it can occur, less commonly, in its absence [37], [57], [3]. The risk for developing cirrhosis 20 years after initial HCV infection among those chronically infected varies between studies, but is estimated at around 10-15% for mean and 1-5% for women [58]. The annual incidence of HCC in subjects with established HCV-related cirrhosis is estimated to be 0.5%-5% in Western countries [46] [59] [60]. Recently, the HALT-C trial (Hepatitis C Long-Term Treatment against Cirrhosis) [46] proposed a score [61] for risk stratification of HCC in patients with chronic HCV infection, comprising older age, black race, lower platelet count, higher alkaline phosphatase, esophageal varices and smoking as predictors of higher risk. Such risk stratification is important to optimize and improve the cost-effectiveness of surveillance programs.

Cirrhosis occurs in 20 to 30% of HBV-infected patients [62], [63]. In contrast with HCV infection and heavy alcohol consumption, around 40% of chronic HBV infected patients develop HCC in non-cirrhotic liver [64]. In this cohort, a similar proportion of non-cirrhotic patients were found in those solely infected with HBV. Long-term follow-up studies have

demonstrated that approximately 2% per year of patients with cirrhosis due to HBV infection develop HCC [65].

Additionally, a considerable amount of patients had combined etiologies (32%), in whom the mean age at diagnosis of HCC was lower than those with a single etiology. In patients with chronic viral hepatitis induced either by HCV infection or HBV infection, the effect of alcohol abuse has been well described in other studies as having a synergic effect [66] [67] and that progression of liver disease severity is very rapid and aggressive [68]. The co-existence of these etiological HCC causes (alcohol and HBV or alcohol and HCV infection) are associated with increased risk of developing both cirrhosis and HCC and with HCC occurring at an earlier age [69] [70] [71]. Some studies advocate some explanations such as alcohol's ability to enhance both HBV and HCV replication and also through its oxidative stress mechanisms, among others more thoroughly described elsewhere [72] [40], [73], [52] [74].

Diagnosis of HCC

Regarding diagnosis, only 11% of patients had HCC confirmed on a nodule less than 2 cm, of which half had to perform biopsy for histological confirmation. The majority of patients were diagnosed with tumor size bigger than 2 cm. The risk of satellites and microscopic vascular invasion greatly increases beyond this size cut-off and levels of tumor recurrence and treatment failure rise exponentially as the tumor burden increases [75] [76]. HCC diagnosis in small tumors represents a major clinical challenge. Firstly, the radiological hallmark in such tumors only occurs in a small proportion of patients [77] and secondly, even with dynamic contrast-enhanced MRI and 4-phase multidetector CT, up to 25-30% of small tumors are expected to be undernoted [78]. Biopsy is still required in most instances [2], but nonetheless, sensitivity of liver biopsy depends itself upon nodule size and pathological diagnosis is particularly complex for nodules between 1 and 2 cm [79]. Currently, up to 30% of new HCC diagnoses in Japan correspond to small tumors of less than 2 cm, due to widespread surveillance programs [80]. Although only 5-10% of patients in the West are presently diagnosed with very-early HCC, but this is expected to rise in parallel with the wider implementation of surveillance policies [23]. Surveillance for HCC aims to reduce disease-related mortality by increasing the number of patients diagnosed within early stages of disease and therefore enhancing the applicability and cost–effectiveness of curative therapies [2]. Although HCC surveillance is generally accepted, its implementation is suboptimal in real-life practice [81]. Early cirrhosis is usually clinically unapparent, and a substantial proportion of patients develop hepatocellular carcinoma before cirrhosis is recognized [82] [83].

In this cohort only 45% of the patients had been diagnosed during surveillance programs, which is a suboptimal adherence (<60%) [84]. Though diagnosis of tumors smaller

than 2 cm was not significantly more common in screened patients, it is noteworthy that such patients were more frequently diagnosed with tumors within Milan criteria and inferior mean size of solitary tumor, therefore achieving significant migration of HCC diagnosis to earlier stages (BCLC stage 0 and A). As result of implementation of surveillance in Western countries among cirrhotic patients, the trend of diagnosing patients in earlier HCC stages is expected to rise from 5-10% (until 1990) to up to 40-60% in 2010-2020 [(23)]. According to BCLC classification, 36% of patients in this cohort were classified as early HCC stages, 47% were found in intermediate or advanced stage and 16% were in terminal stage. Such distribution between early and non-early stages was similar to those reported in other studies using BCLC classification [(85) (86) (87) (88)].

Treatment outcomes

Consistent with current HCC-treatment state-of-art, treatment decision had impact on patient prognosis. The twenty-two patients receiving liver transplantation showed the best prognosis among all patients: a 1 and 3-year survival rate up to 85%, which was similar to that reported in recent HCC surgical series [(89) (90) (91) (92) (93)]. However, outcome evaluation in liver transplantation should also include the 5-year survival rate and recurrence-free rate which could not be computed due to short cohort period and because information relating to recurrence was not systematically retrieved from medical records. Recurrence of tumor is a major factor in evaluation of long-term outcomes of liver transplantation in HCC patients. Optimal selection of patients according to Milan criteria has significantly improved rates in terms of 5-year survival (from less than 40% up to 70%) and recurrence (from 32-54% [(94)] to below 15% [(95)]). Tumor recurrence might result from previously undetected extrahepatic metastasis or from release of tumor cells during surgical manipulation, which includes transplantation itself and also previous interventional therapy such as ablation or chemoembolization [(96)].

Compared with other studies with patients performing radiofrequency ablation with tumor within Milan criteria [(97) (98) (99) (100) (101) (102)], survival in this cohort was found to be inferior for both time cut-offs (reported 1-year survival rate ranged from 87% to 98% and 3-year survival from 57% to 82%). Known independent predictors of survival in radiofrequency ablation are initial complete response, Child-Pugh score, number or size of nodules and baseline alpha-fetoprotein levels [(2)]. Except for tumor response, which was not assessed, patients in this cohort were seen with similar clinicopathological characteristics as for Child-Pugh score, serum bilirubin level, tumor number and size, baseline alpha-fetoprotein and additionally age. Approximately 60% of our ablation patients had tumor <3 cm, which is an important size cut-off for the expected rate of complete tumor necrosis [(103)]. When reviewing

individually ablation patients, a significant number of patients presented with clinical signs of portal hypertension such as platelet count <100.000 (47%), ascites (31%) and esophageal varices (56%). In the above studies, presence of esophageal varices was not systematically described. For the remaining two, only presence of ascites (range: 0 to 9%) was considerably lower than the proportion found in ablation patients in this cohort. Additionally, with exception of one cohort study [(102)], etiology distribution was also a obvious difference: where most of these studies had mainly patients with viral etiology (range from 82% to 92% whereas in this study only 68%), alcoholic liver disease alone was considerably more frequent (range from 8% to 14% compared to 34% in this sub-group of patients). However, in this study alcoholic etiology did not seem to be associated with worst liver function or severity of portal hypertension.

Overall, the median survival for intermediate HCC cases is expected to be about 20 months after chemoembolization [(2)]. In this study, no distinction was made between TACE and TAE. Although bland embolization is no longer recommended by the EASL guidelines [(2)], a meta-analysis of randomized controlled trials found no differences in survival outcomes between these two sub-types of treatment [(104)]. Considering the two randomized trials [(105)] [(106)] where survival benefit from chemoembolization was first identified as reference for comparison, patients in this cohort have shown similar median overall survival estimates (range: 17 – 28.7 months) and 1-year survival rate (range: 57 – 82%). However, estimate for 3-year survival was considerably higher in this cohort (43% versus a range from 26 up to 29%). Comparing with the study were best outcomes were achieved [(105)], patients had matching Child-Pugh score, tumor size, absence of portal vein invasion, serum bilirubin level and proportion of patients with ascites. In this study, a slightly higher preponderance of solitary tumor (47.7% versus 32%) and fewer patients with <100 ng/ml of alpha-fetoprotein (55% versus 82.5%) were seen. As in the sub-group of patients treated with radiofrequency ablation, alcoholic liver disease as the sole etiology was much more frequent (56.5% versus 11%).

Limitations of this study

The quality of data reported was to some extent impaired due unavailability of complete clinical, analytical and radiological information in the electronic charts. Additionally, as this cohort analyzed data in a referral hospital and because both digital and physical records exist, a considerable amount of patients had essential information for optimal HCC characterization only attached in the latter. A more thorough sub-group data analysis in this cohort was also limited to small sample size of some sub-groups of patients, precluding outcome analysis in resection patients and those treated exclusively with sorafenib. Also,

treatment outcome analysis might be biased due to necessary grouping to overcome statistical limitations of small sized samples. In this cohort, a significant proportion of patients underwent multiple therapies such as neo-adjuvant treatments and downstaging in patients receiving potentially curative treatments. Nevertheless, current state-of-art is controversial about the benefit or disadvantage in such cases as robust data from randomized controlled trials are lacking at the time of writing of this report.

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