Scandinavian Journal of Gastroenterology

ISSN: 0036-5521 (Print) 1502-7708 (Online) Journal homepage: http://www.tandfonline.com/loi/igas20

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To cite this article: Jenna Stefansdottir, Erik Christensen & Frank Vinholt Schiødt (2017) Hepatocellular carcinoma in Danish patients: a single Copenhagen center experience, Scandinavian Journal of Gastroenterology, 52:6-7, 768-772, DOI: 10.1080/00365521.2017.1304985

To link to this article: http://dx.doi.org/10.1080/00365521.2017.1304985

SCANDINAVIAN JOURNAL OF GASTROENTEROLOGY, 2017
VOL. 52, NO. 6-7, 768–772
http://dx.doi.org/10.1080/00365521.2017.1304985

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ORIGINAL ARTICLE

Hepatocellular carcinoma in Danish patients: a single Copenhagen center experience

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ABSTRACT

Objective: Hepatocellular carcinoma (HCC) is a common cause of cancer, and most HCC patients have underlying cirrhosis. Retrospectively, we aimed to characterize patients with newly diagnosed HCC at a Danish hospital and to investigate survival and identify predictive factors for survival.

Methods: All patients diagnosed with HCC from January 2008 to December 2014 were retrospectively enrolled in this study. Overall survival was estimated by using the Kaplan–Meier method. A multivariate Cox regression analysis was performed to identify predictive factors for survival.

Results: Sixty-seven patients were diagnosed with HCC (incidence rate 3.55/100,000 people/year). Ninety-three percent had underlying cirrhosis. Alcohol-related liver disease and chronic viral hepatitis B or C were responsible for 55 and 31% of cases, respectively. Median survival was 81 days and 1-month, 3-months and 1-year cumulative survival rates were 74, 40 and 17%, respectively. We identified the presence of portal vein thrombosis, high Child–Pugh score, high MELD score and high AST as independent negative prognostic factors for survival. Survival was poorer in patients seen for the first time when the diagnosis of HCC was made than in patients followed in the outpatient clinic ($p = .06$) indicating a substantial delay in diagnosis.

Conclusions: Survival was poor in this cohort of patients, almost exclusively caused by delay in diagnosis and admittance to hospital. An increased general information about HCC and the possibilities of therapy seems warranted.

ARTICLE HISTORY
Received 1 December 2016
Revised 4 March 2017
Accepted 7 March 2017

KEYWORDS
Cirrhosis; hepatocellular carcinoma; outcome; prognosis

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer in men and the seventh in women. Most cases are seen in developing countries (~85% of all HCC cases). HCC is the third most frequent cause of cancer death [1]. This aggressive cancer is often diagnosed in an advanced stage and in patients with a compromised liver function and has been characterized by a poor prognosis [2]. With the last decades' progress in imaging and therapy, there are now therapies that can improve survival in patients diagnosed with HCC at an early and intermediate stage [2]. The majority of patients with HCC has underlying cirrhosis, often on the basis of chronic alcohol consumption or chronic viral hepatitis B or C. In countries with a high incidence of HCC, the underlying chronic liver disease is mostly caused by persistent infection with hepatitis B or C viruses, whereas alcohol-related liver diseases are more common in Denmark and the other Nordic countries that are considered areas with low incidence of chronic viral hepatitis [3]. HCC can appear in the absence of cirrhosis in some cases of chronic hepatitis B infection [4]. HCC can be associated with nonalcoholic fatty liver disease (NAFLD) and a recent study suggested that NAFLD could become a significant cause of HCC in USA in the future [5].

Prediction of survival in HCC is generally difficult since the TNM system cannot be applied directly to prognosis, as the liver function must also be taken into account [6]. Over the years many attempts to identify prognostic factors have been made [7–9]. The most commonly used prognostic model that at the same time is a clinical staging and treatment system is the Barcelona clinic liver cancer (BCLC) staging system. The BCLC model divides patients into early, intermediate, advanced and terminal stage based upon a combination of tumor size, liver function and physical condition and offers different treatment options for each stage [10].

The incidence rate of HCC in Denmark is 2/100,000 persons per year and seems to be slowly increasing [11,12]. Although survival is improving in recent years, a study from central and northern Denmark showed that the 1-year survival for patients with HCC was still only 37% in 2007–2009 [13].

In this study, we aim to characterize patients with newly diagnosed HCC at a Danish hospital and to identify predictive factors for survival.

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Patients and methods

Methods

The diagnosis of HCC was in most cases made according to standard methods involving histology and/or the typical radiologic vascular pattern of hypervascularity of a hepatic lesion in the arterial phase and 'washout' in the venous/portal venous phase in a three-phase CT scan of the upper abdomen [14]. In other cases, the diagnosis was made by magnetic resonance imaging (MRI) or positron emission tomography–computed tomography (PET-CT) or histology.

Patients

Patients that were diagnosed with HCC (ICD-10 C22.0) at our Department, from January 2008 to December 2014 were retrospectively enrolled in the study. The recruitment population was 270,000 people. After diagnosis, the patients were referred to a multidisciplinary conference at a tertiary HCC center for evaluation with regard to a possible curative or palliative treatment. All patients were treated according to standard regimens [10].

The following data were collected from medical records: age, gender, etiology, presence and degree of ascites, hepatic encephalopathy, esophageal varices, biochemistry (liver tests, platelets, hemoglobin, sodium, creatinine and α-fetoprotein), radiological data and treatment. Variables were summarized as the median (and range) or percentage. Baseline liver function at the time of diagnosis was assessed according to the Child–Pugh classification and the model for end-stage liver disease (MELD).

Statistical analysis

Survival was calculated from the date of diagnosis to the date of death or the end of the study (censored cases). In cases where the diagnosis was made by autopsy, the date of diagnosis was the same as the date of death. Overall survival, 1-month, 3-months and 1-year survival rates were estimated using the Kaplan–Meier method. Prognostic factors were identified using the Cox proportional hazard regression model [15]. For variables having a markedly skew distribution, their logarithmic value was used in the Cox regression analyzes in order to fulfill the assumption of proportional hazards [15]. Variables significant in univariate analysis were then further analyzed in a multivariate Cox model where insignificant variables were eliminated using the backward elimination technique. A p value of $<.05$ was considered statistically significant.

Results

Baseline characteristics

Sixty-seven patients were diagnosed with HCC in the study period. Thus, the incidence rate was 3.55/100,000/year. Baseline characteristics are summarized in Table 1.

Table 1. Baseline characteristics of patients with HCC ($N = 67$).

Age (years)	66 (55–91)
Gender (male/female)	60/7 (89.5%/10.5%)
Alcohol	37 (55.2%)
Alcohol and HBV/HCV	6 (9%)
HBV	5 (7.5%)[a]
HCV	10 (15%)[a]
Unknown	10 (15%)
Cirrhosis	62 (92.5%)
Complications of cirrhosis	
Ascites	
Mild	11 (16.4%)
Moderate	12 (17.9%)
Severe	18 (26.9%)
Esophageal varices	26 (38.8%)
Hepatic encephalopathy	11 (16.4%)
MELD score	10 (6-29)
Child–Pugh class	
A	25 (37.3%)
B	25 (37.3%)
C	17 (25.4%)
BCLC	
A	9 (13.4%)
B	14 (20.9%)
C	21 (31.3%)
D	23 (34.3%)
Number of lesions (single/multiple)	9/58 (13.4%/86.6%)
Portal vein thrombosis	35 (52.2%)
Milan criteria met	3 (4.5%)
α-Fetoprotein	
<20 ng/ml	15 (22.4%)
20–399 ng/ml	22 (32.8%)
>400 ng/ml	29 (43.3%)

Results are presented as number (%) or median (range).
HBV: hepatitis B virus; HCV: hepatitis C virus;
[a]One patient had both chronic HBV and HCV infection.

Diagnosis was based on the typical radiologic pattern in 48 patients and histology was available in 10 patients.

A majority of the patients had an advanced disease at the time of the diagnosis, with one-third of the patients classified as BCLC D. Eight patients died within 10 days from the diagnosis.

Survival

Sixty-one (91%) patients died during the follow-up period. The cumulative survival probability is shown in Figure 1. The median survival was 81 days the range being 0–1507 days and the 1-month, 3-months and 1-year survival rates were 74.6, 40.3 and 17.1%, respectively.

As seen in Figure 2, the survival was poorer in patients seen for the first time in the hospital when the diagnosis of HCC was made (Group 1) than in patients having been followed in the outpatient service prior to HCC being diagnosed (Group 2) (Log-rank test: $p = .06$). For Group 1, the median survival was 72 days and the 1-month, 3-months and 1-year cumulative survival rates were 72.3, 34.0 and 12.4%, respectively. For Group 2, the median survival was 100 days and the 1-month, 3-months and 1-year cumulative survival rates were 80.0, 55.0 and 28.9%, respectively.

Treatment

Five patients with BCLC A at the time of diagnosis had a singular lesion.

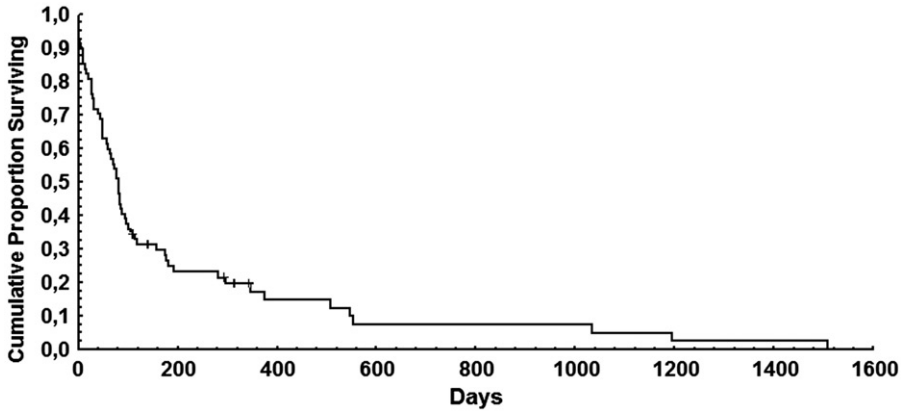

Figure 1. Cumulative survival probability estimated using the Kaplan–Meier method.

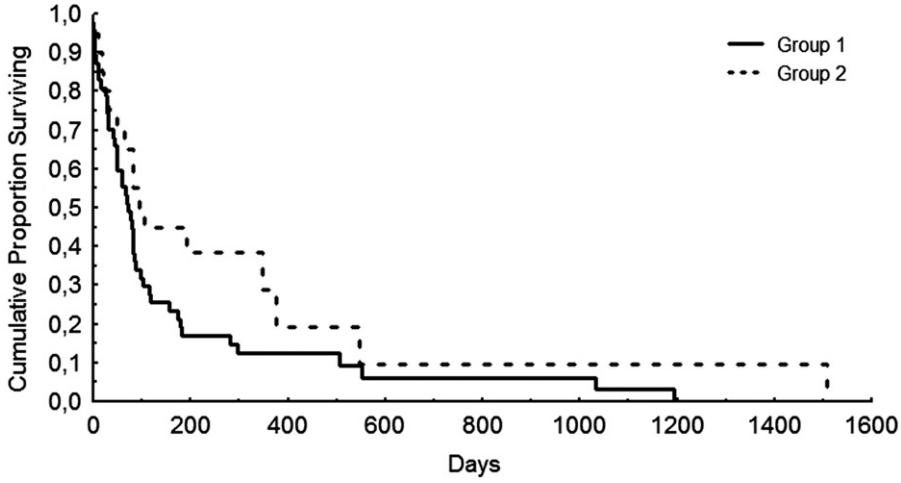

Figure 2. Cumulative survival probability estimated using the Kaplan–Meier method in patients diagnosed with HCC at their first hospital admission (Group 1, $N = 47$) and in patients previously seen in the outpatient service (Group 2, $N = 20$).

Three were offered resection. One of them—the only patient meeting the Milan criteria—was not considered a candidate for liver transplant because of a psychiatric disorder.

Two patients with singular lesions could not be offered resection because they had significant medical conditions. Three patients were treated with radiofrequency ablation (RFA) (one as a second-line treatment) and one with transarterial chemoembolization (TACE). In the group of patients with BCLC B, one who had a singular lesion and a portal vein thrombosis was treated with resection, three patients were treated with TACE and four patients were treated with chemotherapy with the oral multikinase inhibitor sorafenib, due to portal vein thrombosis or performance status 1–2. Six patients got no treatment, either because of a compromised liver function or because of active drinking or lack of compliance.

Ten patients started treatment with sorafenib. No patients were referred for liver transplantation. There was no correlation between treatment and survival.

Prognostic factors

In univariate Cox regression analysis, the variables shown in Table 2 were significant.

Table 2. Results of univariate Cox regression analyzes.

Variable	Scoring	Beta	Standard error	*p* value
Albumin	g/L	−0.0913	0.0235	.0001
Sodium	mmol/L	−0.0733	0.0286	.0104
α-Fetoprotein	ln(U/L)	0.192	0.0648	.0031
Bilirubin	ln(μmol/L)	1.039	0.195	<.0001
AST	ln(U/L)	0.800	0.176	<.0001
Alkaline phosphatase	ln(U/L)	0.558	0.167	.0009
Creatinine	ln(μmol/L)	1.691	0.398	<.0001
Ascites	0–3	0.485	0.115	<.0001
Hepatic encephalopathy	0;1	1.223	0.354	.0005
Portal vein thrombosis	0;1	1.288	0.317	<.0001
Child–Pugh score	5–15	0.421	0.0667	<.0001
MELD	4–40	0.196	0.0267	<.0001

In the multivariate Cox regression analysis, the presence of portal vein thrombosis, a high Child–Pugh score, a high MELD score and a high level of ASAT were independent negative prognostic factors as shown in Table 3.

Discussion

In this study, we describe patients diagnosed with HCC in our center between 2008 and 2014. More than half of the patients had alcohol-related liver diseases and almost one-third had chronic viral hepatitis (hepatitis B or C), one-third of which concomitantly had chronic alcohol consumption.

Table 3. Multivariate Cox regression model.

Variable	Scoring	Beta	Standard error	*p* value
Portal vein thrombosis	0;1	0.948	0.324	.0034
Child–Pugh score	5–15	0.211	0.0885	.0173
MELD	6–40	0.141	0.0354	<.0001
AST	ln(U/L)	0.403	0.171	.0183

We found a 1-year survival of only 17.1% which is considerably lower than reported by Montomoli et al. [13] from central and northern Denmark. In their study, the underlying disease was not reported. The poor survival of our patients was probably a consequence of several problems. First, the large proportion with alcohol-related cirrhosis and alcoholism often indicates an otherwise unhealthy lifestyle including regular tobacco use in patients where the underlying chronic liver disease causes compromised liver function. The chronic alcohol consumption can be a barrier to realizing being ill [16]. These patients may be less likely to contact the health system and to be admitted to hospital. That may explain the delay in diagnosis, which is the second factor for the poor prognosis. Also, some patients were only diagnosed at autopsy which of course exclude any chance of treatment. Third, social problems are abundant in the recruitment area of our hospital (the Copenhagen North East area) and a large proportion of the patients were in the low income groups, having a poorer education and this may have contributed to a decreased awareness of the illness and the possibilities of having an effective treatment. An increased general information to the public and the general practitioners about the disease and the possibilities of therapy seems warranted. Fourth, many patients had advanced disease with multiple HCC lesions on diagnosis, making curative treatment difficult.

HCC is an aggressive cancer with poor prognosis that often is diagnosed in an advanced stage and in patients with an underlying chronic liver disease with compromised liver function. In our study, we found an incidence of 3.55/100.000/year in the period from 2008 to 2014 which is somewhat higher than reported by Jepsen et al. [11]. This is probably due to an increased attention on the risk of HCC in cirrhosis in the last years.

In the univariate analysis, a large number of variables indicative of a markedly deteriorated liver function were associated with a poor prognosis (Table 1). However, in the Cox regression analysis only high Child–Pugh score, high MELD score, presence of portal vein thrombosis and a high AST (aspartate aminotransferase) level were independently associated with a poor prognosis.

Albumin, bilirubin, ascites and hepatic encephalopathy, which were significant in the univariate analyzes, are all included in the Child–Pugh score. Serum creatinine was also significant in univariate analysis and this variable is included in the MELD score together with bilirubin. The association of a high AST with a poor prognosis is infrequently observed in cirrhosis prognosis models; however, in these patients a high AST level could be indicative of a more aggressive tumor growth, destroying the liver cells with a high intensity. The presence of portal vein thrombosis is known to be a negative prognostic factor and the BCLC staging system regards portal vein invasion as advanced (Stage C) disease, for which systemic therapy in the form of sorafenib is the only recommended treatment. Both Child–Pugh and MELD scores are prognostic scores for patients with cirrhosis of the liver and over nine out of ten of our patients had cirrhosis.

Figure 2 shows a marked difference in survival between patients already known in our outpatient clinic and those coming directly to our Department. Surprisingly, two-thirds of our patients were seen for the first time by us when the diagnosis of HCC was established and these patients had a very poor prognosis with only 12% surviving 1 year. For patients already known to us survival was better as ~30% survived 1 year. The surprisingly high number of previously unknown patients may reflect the very low socioeconomic status of the patient population in our region of Copenhagen with few patients seeing their general practitioner when symptoms of disease occur.

In conclusion, HCC seems to be an increasingly frequent complication in cirrhosis. Survival was very poor in our patient cohort, probably due to factors related to alcoholism, social problems, and a delay in diagnosis; in particular, in patients having the diagnosis of HCC when seen for the first time in the hospital. We suggest that all cirrhotic patients should be admitted to an outpatient cirrhosis clinic in order to detect HCC at an earlier stage.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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