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Rates of Surveillance and Management of Hepatocellular Carcinoma in Patients Evaluated at a Liver Transplant Center

Janice H. Jou, Po-Hung Chen, Alison Jazwinski, Iliana Bouneva, Alastair D. Smith, and Andrew J. Muir

Duke University Medical Center, Box 3913, Durham, NC 27710, USA

Janice H. Jou: janice.jou@duke.edu

Abstract

Objectives—The treatment of choice for HCC with cirrhosis is liver transplantation (LT). We assessed if patients evaluated for hepatocellular carcinoma are being diagnosed by surveillance, the proportion of patients meeting Milan criteria at diagnosis, and rates of liver transplantation.

Methods—All HCC cases in cirrhotic patients at Duke University Medical Center in the MELD era (Feb 2002–Oct 2008) were identified. Surveillance was defined as an imaging exam for detection of HCC in the 12 months prior to diagnosis of HCC. Logistic regression was used to examine predictors of LT.

Results—There were 319 cases meeting diagnostic criteria for HCC. Only 30.7% were diagnosed by surveillance and 43.7% met Milan criteria at diagnosis. Patients diagnosed by surveillance were more likely to meet Milan criteria and to receive LT ($p < 0.0001$ for both outcomes). Surveillance was associated with higher rates of LT with an OR 2.6 (95% CI 1.2–5.7, $p = 0.02$).

Patients managed by a hepatologist were more likely to be diagnosed by surveillance (65.9 vs. 19.0%, $p < 0.0001$). Patients meeting Milan criteria managed by a hepatologist were more likely to receive LT than those referred from other providers (26.4 vs. 8%, $p = 0.009$).

Conclusions—A minority of HCC cases in cirrhotic patients were diagnosed by surveillance, and only 12.5% underwent LT. Patients diagnosed by surveillance were more likely to meet Milan criteria and to undergo LT. These findings highlight the need for increased identification of patients with chronic liver disease and for subsequent referral to hepatologists for enrollment in HCC surveillance programs.

Keywords

Hepatocellular carcinoma; Liver cirrhosis; Liver transplantation; Quality of health care

Introduction

Hepatocellular carcinoma (HCC) is the fifth most commonly diagnosed cancer worldwide [1]. In the United States, the Surveillance, Epidemiology, and End Results (SEER) Program

database of the National Cancer Institute has indicated that the incidence increased from 1.4 per 100,000 from 1976 to 1980 to 6.6 per 100,000 from 2002 to 2006 [2]. Furthermore, the mortality attributed to HCC has increased significantly, paralleling the increase in incidence [3, 4]. Primary liver cancer is now the only cancer in the United States in which death rates in both men and women are increasing [2].

Although the recommendation to perform surveillance for HCC is widely accepted [5] and has been shown to be beneficial [6, 7], it has been reported that surveillance for HCC is underutilized [8]. One important goal of surveillance is to identify patients at an early stage of disease to allow for the most aggressive and effective therapeutic options, which include resection and liver transplantation. The Milan criteria establishes tumor burden limits within which outcomes for liver transplantation in the setting of HCC are more favorable [9]. These criteria state that the tumor must either be <5 cm or that multifocal HCC be confined to three lesions less than 3 cm in size each. For those whose tumor burden falls within the Milan criteria, the treatment of choice in patients with cirrhosis and HCC remains liver transplantation [5]. If a failure to identify chronic liver disease and to subsequently enroll these patients into surveillance programs continues, it is likely that patients referred for further management of HCC to tertiary referral centers offering liver transplantation will not meet Milan criteria at the time of referral.

Given the rising incidence and mortality with HCC and the likely benefit of surveillance, it is important to understand the manner in which patients with HCC present. The aims of this study were to describe the diagnostic approach, management, and outcomes of HCC at a tertiary referral center offering liver transplantation.

Methods

After obtaining permission from the Duke University Medical Center Institutional Review Board, electronic medical records were retrospectively reviewed at Duke University Medical Center for persons greater than 18 years of age from February 1, 2002, to October 20, 2008. Duke University Medical Center is a teaching hospital and tertiary care referral center that offers liver transplantation. Cases of hepatocellular carcinoma were identified by International Classification of Diseases 9 (ICD-9) codes 155.0 (Carcinoma: liver, specified as primary) and 155.2 (Liver, not specified as primary or secondary).

The American Association for the Study of Liver Diseases guideline diagnostic algorithm was then applied individually to each case to identify subjects with HCC [5]. For the diagnosis of HCC, the patient should have a liver lesion ≥ 2 cm with a vascular blush corresponding to the area of suspicion seen on dynamic imaging (computed tomography, magnetic resonance imaging, angiogram) or an alpha fetoprotein (AFP) >200 ng/ml, or a biopsy confirming HCC. For lesions 1–2 cm, two imaging studies confirming a hypervascular lesion must be performed to presume the diagnosis of HCC. Lesions smaller than 1 cm with biopsy-proven HCC were included. Once cases of HCC were identified, only patients with confirmed cirrhosis (by history of portal hypertension and/or imaging) and HCC were included in the analysis. Non-cirrhotic cases were excluded as these patients in

the absence of hepatitis B are not considered surveillance candidates and thus would not address the question of receipt of HCC surveillance in this study.

Surveillance was defined as an imaging exam for the detection of HCC in the year before diagnosis. Suboptimal surveillance was defined as an imaging exam performed for detection of HCC greater than a year prior to diagnosis. Diagnosis by symptoms was defined as a patient without prior diagnosis of HCC who presented with symptoms that led to the diagnosis of HCC. Incidental diagnosis was defined as any patient who was found to have a liver mass after evaluation for reasons unrelated to liver disease or symptoms. HCC cases found on index imaging at the time of cirrhosis diagnosis were also distinguished from those patients receiving surveillance for HCC.

Data Collection

Demographic, clinical, laboratory, radiologic, and pathologic data were collected in an electronic database. Laboratory data were taken from the time of diagnosis HCC or within 3 months of the date of diagnosis. Staging of HCC was determined by the Barcelona Clinic Liver Cancer Staging paradigm [10].

The continuous variables abstracted into the database included age, body mass index, total bilirubin, creatinine, international normalized ratio, sodium, and albumin. Categorical variables abstracted into the database were gender, race/ethnicity, etiology of liver disease, diabetes mellitus, hypertension, hyperlipidemia, injection drug or intranasal cocaine use, family history of liver disease, family history of HCC, and Child-Pugh-Turcotte score. A modified Charlson comorbidity index was used to assess each patient's comorbidity status [11]. Tobacco and alcohol use were categorized as active use and past use. Tobacco was quantified by pack years of use while alcohol was quantified by drinks per week for both active and past use.

In regard to each case of HCC, the number and size of the tumors were recorded as well as date of diagnosis, Barcelona Clinic Liver Cancer Staging, imaging performed for diagnosis (including contrasted CT, MRI, or angiogram), tumor burden within Milan criteria, and treatment for HCC. Patient follow-up parameters abstracted included recurrence or progression of HCC, receipt of liver transplantation and death. Patients were followed until death or October 20, 2008.

Statistical Analysis

Chi-square analysis was used to compare categorical variables. Receipt of curative therapies for HCC including liver transplantation was compared in patients diagnosed by surveillance with those who were not diagnosed by surveillance. Those patients diagnosed by means other than adequate surveillance were analyzed in the non-surveillance group. There were 28 cases of HCC for which the surveillance status was unknown that were included in the analysis in the non-surveillance group. Missing data in the remainder of the statistical analyses were excluded. Logistic regression was used to examine the effects of potential predictor variables on the receipt of liver transplantation while adjusting for confounders. A *p* value of <0.05 was considered statistically significant.

Results

The electronic medical charts of 1,531 patients identified by ICD-9 codes were reviewed. After application of the AASLD guidelines, 456 patients were found to have HCC. The 319 patients with HCC in the setting of cirrhosis were included in the analysis. The sample was then divided into a surveillance group and a non-surveillance group. The demographics of these patients are detailed in Table 1. There were no significant differences between patients receiving surveillance and those not receiving surveillance except that the non-surveillance group had significantly more patients with alcoholic cirrhosis. The median follow-up for this sample was 8.2 months, with 59% having at least 6 months of follow-up. At last follow-up, 63% were known to have died. Of this group of cirrhotic subjects, 30.7% of HCC was diagnosed by surveillance; and 30.4% were diagnosed after presenting with symptoms. Additionally, to examine the possible influence of the AASLD guideline recommendations for surveillance of HCC published in 2005, we examined rates of surveillance from 2002 to 2005 and from 2006 to 2008, and there was no statistically significant difference in surveillance, 27% versus 34% respectively, $p = 0.14$. The mode of diagnosis of HCC for these cirrhotic patients is depicted in Fig. 1. Of the cirrhotic patients with HCC, 43.8% (137/313) met the Milan criteria at the time of diagnosis.

The overall rate of liver transplantation at Duke University Medical Center for this group of patients was 12.5%. The proportion of patients meeting the Milan criteria and subsequent management of HCC in patients diagnosed by surveillance versus those diagnosed without surveillance are represented in Table 2. The receipt of liver transplant was more likely if a patient had been diagnosed by surveillance for HCC (22.5 vs. 7.7%, $p < 0.0001$). Using multivariable logistic regression adjusting for age, gender, Milan criteria, and surveillance for HCC, the odds ratio for the receipt of liver transplantation was 2.6 (95% CI 1.2–5.7, $p = 0.02$) among patients undergoing surveillance compared to those who did not receive surveillance.

There were 200 patients referred from outside providers and 91 patients who were followed by a hepatologist at Duke University Medical Center at the time of diagnosis of HCC. The remainder of the cases of HCC ($n = 28$) were diagnosed in the inpatient setting. Of the patients who were referred from outside providers, 38.5% (77/200) were sent to a hepatologist and 61.5% (123/200) were sent to either an oncologist or surgeon. Only 17 (14%) of the 123 cirrhotic patients with HCC referred to surgery and oncology clinics saw a hepatologist at the tertiary referral center at the time of diagnosis of HCC.

Among patients followed by a hepatologist at our transplant center at the time of diagnosis, 65.9% of HCC cases were diagnosed with serial surveillance exams compared to 19.0% of patients not followed by a hepatologist ($p < 0.0001$). In patients followed by a hepatologist in our transplant center, 61.5% met the Milan criteria at the time of diagnosis and 29.3% of patients referred to Surgery and Oncology met the Milan criteria. When only considering patients meeting the Milan criteria, those managed by a hepatologist at our center were more likely to receive liver transplantation than those meeting the Milan criteria who were referred from other providers (26.4 vs. 8.0%, $p = 0.009$).

Discussion

In this sample of patients with HCC, most patients evaluated for HCC were not diagnosed by surveillance. Rather, the majority of patients were presenting with symptoms as a consequence of HCC, diagnosed with HCC at the time of the diagnosis of cirrhosis, or found incidentally. In current practice, surveillance for HCC is widely accepted for high-risk populations including those patients with cirrhosis from viral hepatitis. Society guidelines from AASLD [5] and EASL [12] both support surveillance for HCC with imaging (ultrasound) every 6–12 months. Our finding that rates of liver transplantation and liver resection for treatment of HCC were higher in patients receiving surveillance is consistent with prior studies [6, 13, 14].

The proportion of liver transplantation for HCC has increased by sixfold since the implementation of the model for end-stage liver disease (MELD) allocation system. Previously, 4.6% of transplantation recipients had HCC compared to 26% since implementation of the MELD system [15]. Fortunately, if the tumor burden exceeds the Milan criteria, there are increasing options for the treatment of HCC including direct therapy to the tumor and chemotherapeutic agents. As with most malignancies, the burden of disease in HCC correlates with outcome [10]. Thus, early identification of HCC may improve the outcomes for patients with cirrhosis and HCC who could potentially be candidates for receipt of liver transplantation.

The factors contributing to low rates of HCC detected with surveillance remain unclear. First, there must be an awareness of the need to perform surveillance. Then, surveillance must be repeated at regular intervals. Diagnosis of chronic liver disease, surveillance, and treatment for HCC are often related to access to health care [16–18]. In this study, we reviewed all cases of HCC evaluated at our medical center by all providers, not limited to hepatology clinics. Those patients meeting the Milan criteria who were followed by a hepatologist in our transplant center were more likely to be diagnosed with surveillance and were also more likely to receive liver transplantation. The reasons for this correlation are unclear. Perhaps those patients who are followed by a hepatologist are aware of their liver disease sooner, enabling surveillance when presenting or progressing to chronic liver disease. Thus, these patients may be enrolled more effectively into surveillance programs for HCC. These patients also may have the insurance and financial means to be seen by a specialist earlier in their course of disease. Future studies are needed to examine this association and to determine the contributing factors leading to these results.

This study is a retrospective, single-center study, which limits its generalizability. Additionally, data for this study was limited to the information contained in the electronic medical record or to those data dictated into clinical encounters and thus missing or omitted data could have affected the results. Variables that may have been important but were not captured in the electronic medical record include: insurance status, patients being seen by a hepatologist elsewhere, and possibly receiving liver transplantation at another center. The quality of data abstraction is also an important contributor to the integrity of a database. Follow-up for some patients was limited as patients were included up until the study end date. There were more patients in the non-surveillance group that had alcoholic cirrhosis as

the underlying liver disease and thus active or recent alcohol use could have affected surveillance rates for HCC and liver transplantation rates in the non-surveillance group.

We also found that few patients seen in oncology or surgery clinics with HCC and cirrhosis were seen in hepatology clinics at the time of diagnosis of HCC. These findings also highlight the need for hepatology clinics to serve as the entry point for HCC patients to facilitate their care and to fully address the complex nature of treatment decisions for each patient. This study demonstrates the importance of surveillance for HCC in cirrhotic patients and highlights the need for increased identification of patients with chronic liver disease and for subsequent referral to hepatologists and enrollment in HCC surveillance programs. Future studies are needed to assess barriers to early detection of HCC and to implement the systematic modifications needed to improve the care of patients with HCC.

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Fig. 1.
Mode of diagnosis of HCC (in %)

Table 1

Patient demographics

	Surveillance (<i>n</i> = 98)		No surveillance (<i>n</i> = 221)		<i>p</i> value
	<i>n</i>	%	<i>n</i>	%	
Age					0.32
65	74	75.5	155	70.1	
>65	24	24.5	66	29.9	
Gender					0.99
Male	78	79.6	176	79.6	
Female	20	20.4	45	20.3	
Race					0.48
White	70	71.4	146	66.1	
Black	18	18.4	45	20.4	
Hispanic	1	1	4	1.8	
Asian	6	6.1	6	2.7	
Other	1	1	6	2.7	
Unknown	0		14	6.3	
Child-Pugh-Turcotte score					0.65
A	52	53.1	102	46.2	
B	33	33.7	83	37.5	
C	10	10.2	22	10	
Unknown	3	3.1	14	6.3	
BCLC staging					0.08
Early stage (A)	57	58.2	94	42.5	
Intermediate stage (B)	19	19.4	56	25.3	
Advanced stage (C)	9	9.2	35	15.8	
Terminal stage (D)	10	10.2	22	10	
Unknown	3	3.1	14	6.3	
MELD score, median (range)	11.0 (6–22)		11.0 (6–29)		0.13
Etiology of liver disease					0.03
Chronic HCV cirrhosis	51	52	91	41.1	

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	Surveillance (<i>n</i> = 98)		No surveillance (<i>n</i> = 221)		<i>p</i> value
	<i>n</i>	%	<i>n</i>	%	
Chronic HCV and alcoholic cirrhosis	12	12.2	36	16.3	
Alcoholic cirrhosis	4	4.1	35	15.8	
Chronic HBV Cirrhosis	8	8.2	19	8.6	
NASH cirrhosis	6	6.1	13	5.9	
Cryptogenic cirrhosis	8	8.2	8	3.6	
Autoimmune hepatitis and cirrhosis	2	2.0	4	1.8	
Other (PBC, PSC, Alpha 1-antitrypsin, hemochromatosis)	7	7.1	6	6.1	

Table 2

Surveillance in cirrhotic patients

	Surveillance (<i>n</i> = 98)	No surveillance (<i>n</i> = 221)	<i>p</i> value
Milan criteria	62/96 (64.6%)	75/217 (34.6%)	<0.0001
Liver transplantation	23 (22.5%)	17 (7.7%)	<0.0001
Resection	15 (15.3%)	17 (7.7%)	0.04
Ablation	17 (17.3%)	24 (10.9%)	0.15
Embolization	21 (21.4%)	36 (16.2%)	0.27
Internal radiation	2 (2%)	1 (0.5%)	0.22
Chemotherapy	5 (5.1%)	29 (13.1%)	0.03
Hospice/No Rx	15 (15.3%)	97 (43.9%)	<0.0001