



Improved Outcomes Following Hepatocellular Carcinoma (HCC) Diagnosis in Patients Screened for HCC in a Large Academic Liver Center versus Patients Identified in the Community

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Abstract

Background and Aims: Hepatocellular carcinoma (HCC) is the sixth most commonly occurring cancer worldwide. Knowledge and adherence to HCC surveillance guidelines has been associated with earlier detection. We sought to evaluate characteristics and outcomes following HCC diagnosis in patients screened for HCC in a large academic liver center versus patients diagnosed and referred from the community. **Methods:** We reviewed the records of patients diagnosed with HCC in the liver center of an academic institution from January 1999 till December 2013. Patients were classified into two groups: patients followed in our hepatology clinic and patients with HCC recently referred to our center. Univariate analysis was performed using chi-squared test and multivariate analysis was performed using SPSS 22.0. **Results:** The records of 410 patients were reviewed, and included 77.3% of patients referred from the community and 22.7% of patients followed in our clinic. In the clinic group, 75.6% were identified with one nodule at initial diagnosis, compared to 65.6% in the referral group. Patients in the referral group were more likely to present with tumors ≥ 5 cm at diagnosis, with 28.7% compared to 5.4% in the clinic group ($p < 0.0001$). Patients referred from the community were also less likely to undergo transplant, with 32.2% as compared to 48.4% of the clinic group ($p < 0.004$). **Conclusion:** Patients with chronic liver disease managed in an academic liver center present in the early stage of HCC diagnosis and are more likely to meet the Milan criteria and undergo transplant. Early referral to a specialized transplant center, if feasible, where a multidisciplinary approach is utilized might be essential in the management of chronic liver disease.

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide, the third leading cause of cancer-related mortality and the fastest rising cause of cancer death in the United States.^{1,2} There are global variations in the incidence of HCC, with the highest incidence rates in South East Asia and Sub-Saharan Africa.^{2,3} As the overall incidence rate for HCC has increased over the last two decades, the distribution has shifted towards white Hispanic and non-Hispanic individuals, aged 45–60 years. This increase is at least partially attributable to the rise in hepatitis C virus (HCV)-related HCC.^{3,4} Worldwide, hepatitis B virus (HBV) is responsible for 50–80% of HCC cases, whereas 10–25% of cases are thought to be a result of HCV infection.²

Although recent advances in management have contributed to improved survival, the overall 5-year survival rate is still $< 25\%$.^{1,5} Several observational cohort and case control studies, as well as one randomized trial, have shown that patients who undergo HCC surveillance have an earlier stage of HCC at diagnosis, potentially receive curative therapy and have an increased rate of 5-year survival (between 40–70%).^{3,6} These findings support the notion that screening is effective in detecting smaller sized tumors in at-risk patients. Based on such findings and taking into consideration the biological characteristics of tumor (doubling time), surveillance is recommended every 6 months for at-risk patients in the United States, according to the American Association for the Study of Liver Diseases (AASLD) guidelines.⁷

HCC surveillance is underutilized in many at-risk patients, as reported in a recent meta-analysis that demonstrated that only $< 20\%$ of patients with cirrhosis undergo surveillance.⁸ Specialized hepatology or gastroenterology care results in a significantly higher likelihood of receiving regular surveillance, compared to patients seen by primary care physicians.^{6,9} However, only 20–40% of patients with cirrhosis are followed by gastroenterologists or hepatologists

Keywords: Hepatocellular carcinoma; Liver transplant; Tumor.

Abbreviations: AASLD, American Association for the Study of Liver Disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MELD, model for end-stage liver disease; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; UNOS, United Network for Organ Sharing.

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nationally.⁸ The most common reason cited for lack of surveillance was failure by physicians to order surveillance tests in patients with cirrhosis. Additional reasons for non-adherence to surveillance include unrecognized liver disease prior to HCC presentation, patient concordance, and limited access to infrastructure and appropriate testing in rural areas.^{5,8,9}

Tumor size is a known risk factor for poor survival following resection in HCC, and many HCC prognostic systems include tumor size as an important variable.¹⁰ An essential part of the Milan criteria currently used by the United Network for Organ Sharing (commonly referred to as UNOS) and Medicare to guide patient selection for cadaveric liver transplant evaluates tumor size. In this study, we sought to evaluate characteristics and outcomes following HCC diagnosis in patients receiving specialized hepatology or gastroenterology care prior to the diagnosis of HCC versus patients followed in the community and referred to us upon diagnosis of HCC.

Methods

The study protocol was approved by the Institutional Review Board of Rutgers Health Sciences (Newark, NJ, USA). In this retrospective analysis, we reviewed the records of patients with diagnosis of HCC in the liver center of a large academic institution from January 1999 till December 2013. HCC was diagnosed by contrast-enhanced computed tomography, magnetic resonance imaging or histologically in some cases when diagnosis was uncertain with imaging studies. Patients were classified into two groups: clinic patients and patients referred from the community. Clinic patients were defined as those who received continued care, comprising at least two visits in our gastroenterology and/or hepatology clinics prior to the diagnosis of HCC. Referral patients were defined as those who did not receive medical care from our clinics and were referred upon diagnosis of HCC.

The records of a total of 410 patients were reviewed in this study, among which 317 (77.3%) were patients referred from the community (referral group) and 93 (22.7%) were patients primarily followed in our clinic (clinic group). Statistical analysis was performed with the Statistical Package for the Social Sciences, version 22. Univariate analyses were performed using Pearson's chi-squared statistics. A *p* value of <0.05 was considered statistically significant.

Results

The median age in the referral group was 64 years (range: 25–90 years) and the median age in the clinic group was also 64 years (range: 36–89 years). In the referral group, 253 (79.8%) were men and 64 (20.2%) were women; in the clinic group, 72 (77.4%) patients were men and 21 (22.6%) were women. Among the patients referred from the community, 122 (38.4%) were Caucasians, 45 (14.2%) were Hispanics, 33 (10.4%) were African Americans/Africans, 19 (6.0%) were Asians/Pacific Islander and 12 (3.8%) were Middle Easterners; the ethnicity was unknown for 86 (27.1%) patients in this group. Among the clinic patients, 35 (37.6%) were Caucasians, 17 (18.3%) were Hispanics, 13 (14%) were African Americans, 9 (9.7%) were Asians/Pacific Islanders and 4 (4.3%) were Middle Easterners; the ethnicity was unknown for 15 (16.1%) patients in this group. There was no statistical difference in demographics between the two groups (Table 1).

Table 1. Comparison of demographics of patients in the referral group and the clinic group

	Referral group (%)	Clinic group (%)	<i>p</i> value
Sex			0.617
Male	253 (79.8)	72 (77.4)	
Female	64 (20.2)	21 (22.6)	
Age			0.716
≤64	167 (52.7)	47 (50.5)	
≥65	150 (47.3)	46 (49.5)	
Marital status			0.668
Single	69 (21.8)	20 (21.5)	
Married	197 (62.1)	53 (57.0)	
Divorced	27 (8.5)	11 (11.8)	
Widowed	24 (7.6)	9 (9.7)	
Ethnicity			0.771
Caucasian	122 (38.4)	35 (37.6)	
African American/ African	33 (10.4)	13 (14.0)	
Hispanic	45 (14.2)	17 (18.3)	
Middle Eastern	12 (3.8)	4 (4.3)	
Asian/Pacific Islander	19 (6.0)	9 (9.7)	
Unknown	86 (27.1)	15 (16.1)	
Born in US			0.688
Yes	98 (30.9)	44 (47.3)	
No	70 (22.1)	28 (30.1)	
Unknown	149 (47.0)	21 (22.6)	

There were no significant statistical differences in age, sex, marital status, ethnicity, immigrant status, etiology of HCC and model for end-stage liver disease (MELD) score at diagnosis between the two groups (Table 1 and Table 2). However, 75.6% of patients were identified with one nodule at initial diagnosis in the clinic group versus 65.6% in the referral group, and patients in the referral group were more likely to present with tumors ≥5 cm at time of diagnosis, representing 28.7% compared to 5.4% in the clinic group (*p* < 0.0001) (Table 2). Referral patients were also less likely to undergo transplant, representing 32.2% compared to 48.4% of clinic patients (*p* < 0.004) (Table 3).

In our study, HCV was identified as the most common etiology of HCC, with 61.2% of cases in the referral group and 71% of cases in the clinic group, which is consistent with prior studies that have attributed HCV to be responsible for the rising incidence of HCC in the United States. Patients with HBV infection were more likely to present with tumors >3 cm as compared with patients with HCV infection, according to univariate analysis in both the clinic and referral patient groups. Also, with regards to other treatment modalities of HCC, patients referred from the community were more likely to receive surgical resection, representing 12.3% as compared to 4.3% in the clinic group (*p* = 0.027). There was no difference in radiofrequency ablation (RFA) or transarterial chemoembolization (TACE) utilization between the two groups.

Table 2. Comparison of HCC characteristics in the referral group and the clinic group

	Referral group (%)	Clinic group (%)	<i>p</i> value
MELD score at diagnosis			0.446
≤9	129 (40.7)	30 (32.3)	
10–19	159 (50.2)	56 (60.2)	
20–29	20 (6.3)	6 (6.5)	
30–39	3 (0.9)	1 (1.1)	
Unknown	6 (1.9)	0 (0.0)	
Number of nodules at diagnosis			0.334
1	208 (65.6)	70 (75.3)	
2	58 (18.3)	11 (11.8)	
3	18 (5.7)	5 (5.4)	
>3	33 (10.4)	7 (7.5)	
Tumor size at diagnosis in cm			<0.0001
<1	1 (0.3)	6 (6.5)	
1–1.9	55 (17.4)	30 (32.3)	
2–2.9	66 (20.8)	34 (36.6)	
3–3.9	60 (18.9)	14 (15.1)	
4–4.9	31 (9.8)	4 (4.3)	
≥5	89 (28.7)	5 (5.4)	
Unknown	14 (4.4)	0 (0.0)	

Table 3. Comparison of HCC management in the referral group and the clinic group

	Referral group (%)	Clinic group (%)	<i>p</i> value
RFA			0.845
Yes	82 (25.9)	25 (26.9)	
No	235 (74.1)	68 (73.1)	
TACE			0.840
Yes	181 (57.1)	52 (55.9)	
No	136 (42.9)	41 (44.1)	
Transplant			0.004
Yes	102 (32.2)	45 (48.4)	
No	215 (67.8)	48 (51.6)	
Surgical resection			0.027
Yes	39 (12.3)	4 (4.3)	
No	278 (87.7)	89 (95.7)	

In our study, we did not find any statistically significant association between age, sex, etiology of HCC, presence of renal failure, presence of hypertension and the likelihood of clinic or referral patients to undergo transplant, on univariate analysis (logistic regression). In regards to tumor size, our study showed no significant association between age, sex, presence of renal failure, presence of diabetes, and the likelihood to present with tumor sizes >3 cm. We did find that patients with HBV infection were more likely to present

with tumors >3 cm as compared with patients with HBC infection, on univariate analysis in both the clinic and referral patient groups.

Discussion

It has been reported that the incidence of patients with advanced liver disease, and with cirrhosis in particular, will substantially increase in the next few decades.¹ Cirrhotic patients, and potentially patients with advanced fibrosis at the stage of bridging, among others according to the AASLD guidelines, should benefit from a thorough HCC screening and surveillance.⁷ Early identification has been associated with better survival rates or even cure.

Liver transplantation has been proven to be a lifesaving procedure for individuals with early stage HCC, having 4-year survival rates of >70%, comparable to individuals without HCC.¹¹ In individuals who do not meet the Milan criteria for transplant, other management options, such as surgical resection, TACE and percutaneous local RFA, have been utilized, but they have been shown to result in a higher rate of tumor recurrence than liver transplantation.¹²

In our study, we found that patients who received care in our academic liver center were likely to present with smaller tumor sizes at diagnosis of HCC, compared with patients referred from the community ($p < 0.0001$). Referral patients were also less likely to undergo transplant, at 32.2% and compared to 48.4% of clinic patients ($p = 0.004$). The possible rationale for these findings is likely multi-factorial. A principal contributing factor could be lack of adherence to surveillance guidelines. Patients receiving adequate surveillance for HCC are more likely to present with small tumor sizes at diagnosis. Among the patients who did not receive transplant and followed in our clinic, 55.6% of them did not meet criteria for liver transplant due to reasons such as active alcohol abuse, lack of social support, extensive tumor spread or the presence of multiple medical co-morbidities. A number of patients (20%) were either lost to follow-up and could not be reached despite multiple attempts or travelled to another state to seek care. At our institution, 15.6% of patients declined transplant and 8.9% of patients were listed but died due to septic shock or complications of cerebrovascular accidents or were still on the list as of the time this study was conducted.

A substantial amount of prior studies have analyzed in-depth the differences between medical care by specialists versus care by general practitioners. In their area of expertise, specialists were found to be more knowledgeable about management options, more likely to use more resources and more likely to adhere to routine screening guidelines.¹² In the management of chronic liver diseases, gastroenterologists and hepatologists have similarly been shown to be more adherent to surveillance guidelines for HCC than general practitioners or physicians of other specialties.^{6,9} In our study, the largest number of referrals to our liver center were from community gastroenterologists and hepatologists (64.4%). The second largest number of referrals was from primary care physicians (14.2%). Other referrals were mainly from infectious disease specialists, oncologists, surgical oncology and general surgery. In the current literature, the two main factors associated with non-adherence to HCC surveillance include physicians failing to order the appropriate surveillance tests and the under-diagnosis of liver disease.⁹ Others suggested possibilities include patient's health care literacy, low socio-economic status, poor overall access to

health care, systemic failures in following up on missed appointments and limited access to referral for potential curative therapy.¹³

A proposed additional rationale for our findings could be related to the multidisciplinary approach utilized in our liver center. The optimal management of patients with chronic liver diseases and HCC requires a multidisciplinary approach, involving skilled hepatologists, interventional radiologists, transplant surgeons and support staff. In a study performed at San Francisco Veterans Affairs Medical Center, there was a significant increase in patients presenting with early stage HCC and an improvement in overall survival after a multidisciplinary team was implemented.¹⁴ When a multidisciplinary approach is employed in the management of chronic disease, location of the treatment team in a single clinic facility has also been associated with improvements in quality of care, preventive care and adherence to guidelines.¹⁵

Our liver center utilizes a similar multidisciplinary approach that involves management of patients with chronic liver disease, as well as the management of HCC. The utilization of multidisciplinary clinics in patients with chronic liver diseases may be essential in improving clinical outcomes, such as presentation at early stages of HCC, likelihood to receive a transplant and overall survival. The multidisciplinary approach allows for seamless transition of care from the outpatient to the inpatient setting when their patients are admitted to the hospital.

We found in our study that patients referred from the community were more likely to receive surgical resection than patients in the clinic group. This finding could possibly be attributed to a higher prevalence of HCC caused by chronic hepatitis B in our referral group (12.6%) as compared to our clinic group (4.3%), as patients with cirrhosis or alcoholic disease would be suboptimal candidates for surgical resection.

The strengths of our study include its diverse cohort as well as the specialized liver facility at which it was carried out. The main limitation of our study was the lack of survival data for comparison, as some referred patients who were deemed not eligible for liver transplantation after being evaluated at our center opted to return to their referring physicians for further management. However, various studies have consistently shown that smaller tumor sizes and liver transplantation are independently associated with increased survival in patients with HCC. Another limitation of this study is the substantial difference between the number of patients in each arm, specifically 317 in our community group and 93 in our clinic group. Also worth mentioning is the fact that accurate data for HCC surveillance utilization in patients referred from the community was not available upon referral, so direct comparison of adherence to HCC surveillance in the two groups were not performed. However, presentation with advanced tumor on diagnosis of HCC was used to infer surveillance patterns.

In conclusion, HCC is currently the fastest rising cause of cancer death in the United States. Biannual surveillance in at-risk individuals will result in earlier diagnosis, and the utilization of more curative treatment modalities, such as liver transplant and surgical resection, will thus prolonging survival. Surveillance is underutilized; only about 20% of eligible patients undergo surveillance. Specialized gastroenterology and hepatology care is associated with higher utilization of adequate surveillance. Patients seen in our specialized liver transplant center were more likely to present with a smaller tumor size at diagnosis of HCC and more likely to undergo transplant, compared to patients referred from the community.

A multidisciplinary approach, when feasible, may be essential for optimal clinical outcomes in the management of chronic liver diseases. More studies are needed, however, to identify and target factors associated with suboptimal surveillance of HCC and delayed referrals to a liver transplant center when such options are available.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study design, analysis and interpretation of data, manuscript writing, critical revision, statistical analysis, administration (NO), analysis and interpretation of data, statistical analysis (YW), manuscript writing, critical revision (CP, BK), study design, analysis and interpretation of data, manuscript writing, critical revision, statistical analysis, administration (NP).

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