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An Indeterminate Nodule in the Cirrhotic Liver Discovered by Surveillance Imaging is a Prelude to Malignancy

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Abstract

Background—Surveillance imaging often shows indeterminate lesions in the cirrhotic liver, which may represent early hepatocellular carcinoma (HCC), dysplastic or regenerative nodules, or vascular shunts. The risk of HCC after identification of an indeterminate nodule is not well described.

Methods—We identified 252 patients with cirrhosis and at least one indeterminate nodule discovered on surveillance imaging over a 4-year period. The incidence of HCC development within 2 years of nodule identification was measured along with baseline risk factors associated with developing HCC.

Results—The incidence of HCC in this population was 21% (53 of 252), and risk factors associated with HCC included chronic viral hepatitis, male gender, and low platelet count. The median time from identification of an indeterminate nodule to diagnosis of HCC was 2.7 months. Patients with indeterminate nodules who developed HCC were more likely have to have an indeterminate nodule with arterial enhancement.

Conclusions—The 2-year incidence of HCC in the setting of cirrhosis and an indeterminate nodule discovered by surveillance imaging may be as high as one in five persons. Early follow-up imaging, biopsy, or empiric treatment should be considered for those at higher risk. Further, this population is well suited for early detection biomarker and chemoprevention studies.

Keywords

hepatocellular cancer; hepatic cirrhosis; liver neoplasms

INTRODUCTION

The incidence of hepatocellular carcinoma (HCC) continues to rise in the United States and remains the second leading cause of cancer death worldwide [1]. Patients with underlying cirrhosis—no matter the cause—account for 80–90% of HCC cases [2]. When cirrhotic

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patients are followed over a five-year time period, the risk for development of HCC is greater than 10% [3]. Therefore, screening ultrasound (US) exams for HCC in at-risk patients are recommended every 6 months by the American Association for the Study of Liver Diseases [4].

A suspicious mass found on surveillance US may be subsequently diagnosed as HCC using contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) based on characteristic features of early arterial enhancement and venous phase washout. Small liver nodules (<2 cm) without the complement of characteristic imaging findings, termed indeterminate nodules, are commonly seen in cirrhotic patients and pose a diagnostic dilemma for clinicians [5]. While such nodules may be amenable to biopsy, there are many challenges to routine biopsy including the high frequency of benign nodules in the cirrhotic liver, cost, false negative rates, and the increased complications associated with thrombocytopenia or coagulopathy, both common in patients with cirrhosis [6].

The incidence of HCC development in the setting of an indeterminate nodule discovered on surveillance imaging is not well described, and it is uncertain which indeterminate lesions are most likely to progress to HCC. Previous studies have demonstrated that factors such as age, male gender, and hepatitis C are risks for the development of HCC, although these factors have not been specifically identified as risk factors for progression of an indeterminate nodule [3,7]. The purpose of this study was to determine the incidence of HCC development within 2 years of detection of any indeterminate nodule in the cirrhotic liver by imaging with CT or MRI. We looked to identify characteristics of indeterminate nodules on imaging associated with a future diagnosis of HCC. Further, we sought to identify risk factors associated with HCC in this group.

METHODS

This study was approved by the Institutional Review Board at The Ohio State University Wexner Medical Center. Patients with cirrhosis from any cause and any indeterminate nodule reported by MRI or CT between the years 2008 and 2012 were identified using radiology reports from the medical record. An indeterminate nodule was defined as any abnormal mass less than 2 cm in size without the full complement of imaging characteristics of HCC. Patients with any history of HCC or any mass on the index imaging study with all diagnostic features of HCC were excluded. Medical records were reviewed to collect demographic and clinical information, and the incidence of HCC was defined as the number of patients in the cohort who developed any mass in the liver with imaging features consistent with HCC or who had HCC proven by biopsy within 2 years of the index imaging study.

Baseline characteristics and imaging characteristics were compared between the two groups using Fisher's exact test for categorical variables and the Mann-Whitney U test for comparison of median values. Multivariate binary logistic regression analysis was used to determine variables independently associated with risk of HCC. Survival curves were generated using the Kaplan-Meier method and significant differences determined by the log rank test. Statistical results were two sided and $P < 0.05$ was considered statistically

significant. All statistical analyses were done using IBM Statistical Package for Social Sciences 21.0 (Chicago, IL).

RESULTS

Over a four-year period, there were 252 patients with cirrhosis who had at least one indeterminate liver nodule discovered by surveillance imaging. The median number of indeterminate nodules was 1.0 (range 1–5). The incidence of HCC in these patients during the period of study follow-up was 21% (N=53). Risk factors for development of HCC included male gender, any viral hepatitis and lower platelet count (Table I). All three of these factors were independently associated with development of HCC by multivariate analysis (data not shown). Patients who developed HCC within 2 years of discovery of any indeterminate nodule on the index imaging study were more likely to have at least one nodule with arterial enhancement (Table II).

The median number of years from the initial diagnosis of cirrhosis to the development of an indeterminate nodule by CT or MRI was 2.6 years. Median follow-up after identification of any indeterminate nodule was 15.3 months, and the average time to development or confirmation of diagnosis of HCC was 2.7 months (range 0–25.9 months). For patients who developed HCC, the initial imaging study was MRI in 45 (85%) and CT in 8 (15%). Pathologic confirmation of HCC was obtained in 20 patients (38%), and of these 8 (15%) underwent biopsy prior to any therapy and the others (12, 23%) were confirmed by biopsy at the time of surgical resection, ablation, or transplant. Median OS was 41.8 months in those who developed HCC compared to 62.8 months in those who did not (Figure 1) ($P<0.01$).

In the 53 patients who developed HCC, 35 (66%) had a solitary nodule initially and the rest (18, 34%) had two or more nodules. At the time of HCC diagnosis, 33 patients (62%) were within Milan criteria. There were 46 (87%) patients who developed HCC within a previously identified nodule; the remaining patients all developed HCC in an area separate from the nodule on the index imaging study. Patients with HCC were initially treated with surgical resection (8, 15%), ablation (13, 25%), chemoembolization (17, 32%) or transplant (4, 7%). All four patients had HCC within Milan criteria at the time of transplantation, which occurred between 4 and 53 months after the initial concern for an indeterminate nodule. There were 11 patients (21%) with HCC who were not able to undergo therapy or were treated at another hospital.

Causes of cirrhosis included hepatitis B (N=24, 9.5%), hepatitis C (N=107, 42%), alcohol (N=59, 23%), and non-alcoholic steatohepatitis (NASH, N=45, 18%). The proportion of patients with chronic hepatitis viral infection (B or C) was higher in the group that developed HCC (Figure 2). The relative risk of developing HCC was specifically higher in those with hepatitis C cirrhosis and an indeterminate nodule (2.1 vs. other causes of cirrhosis, $P=0.01$) whereas the relative risk was equivalent in patients with hepatitis B (1.0 vs. other causes, $P=0.99$). There were seven patients with hepatitis B and C co-infection in the entire cohort, and two of them developed HCC (29%).

DISCUSSION

The finding of any indeterminate nodule on surveillance imaging in the cirrhotic liver must raise alarm for physicians as at least one in five patients will develop HCC within the next two years. Those at highest risk are men with viral hepatitis and portal hypertension. The results in this study are consistent with similar studies in which the incidence of nodule progression to HCC is 14–23% [5,8]. Not surprisingly, the vast majority of patients developed HCC within a previously identified nodule. At our institution, patients with cirrhosis and imaging studies concerning for possible HCC are routinely reviewed by a weekly multidisciplinary Liver Tumor Board comprised of hepatologists, hepatobiliary surgeons and surgical oncologists, transplant surgeons, diagnostic and interventional radiologists, medical and radiation oncologists. For most indeterminate nodules discovered on surveillance imaging, follow-up imaging in 3 months is recommended by the Tumor Board (the exact number of these cases reviewed is not known by the authors but it is most probable the majority were reviewed). This likely explains the approximately 3-month median interval to “progression” of indeterminate nodules to HCC in our study; many such nodules were already early HCC that had not yet developed all classic imaging features.

We generally favor short-interval repeat liver protocol multiphase MRI for indeterminate nodules less than 2 cm in the cirrhotic liver rather than second study (CT scan). While this differs from NCCN (National Comprehensive Cancer Network) guidelines, the finding of one classic enhancement feature on a CT scan would be followed by another MRI at 3 months for a less than 2 cm lesion according to the guidelines. Given the indolent nature of many small (early) HCCs, we have not found the omission of an immediate second imaging study to result in negative outcomes. Nevertheless, this may limit the external validity of our findings when compared to other institutions. Other limitations include the small number of CT scans and US studies which precluded a subset analysis comparing these common imaging modalities and the loss to follow-up in some less compliant patients with indeterminate nodules.

Chronic viral hepatitis, male gender, and low platelet count were factors that increased the risk of HCC in those with cirrhosis and indeterminate nodules, and these are also risk factors for HCC in general [9]. The combination of alcohol and hepatitis C has a synergistic damaging effect to liver parenchyma [10], and many of our patients had both of these risk factors which may explain the high incidence of HCC in our cohort. Thrombocytopenia is common with cirrhosis complicated by portal hypertension [11]. It is unclear whether portal hypertension itself increases the risk of HCC, but our study suggests there may be a relationship and this deserves further study.

It has been suggested that small HCCs have a relatively long tumor doubling time and an often indolent early course [12]. Despite this, the 21% incidence of HCC in the cirrhotic population with indeterminate nodules suggests early intervention is appropriate for some at higher risk. A randomized trial by Zhang et al. found a 37% reduction in HCC mortality with routine 6 month surveillance exams [13] which allows for earlier intervention. In the least, early follow-up imaging, biopsy, or empiric treatment should be considered for those at highest risk, such as indeterminate nodules in men with hepatitis C.

In summary, the risk of HCC after discovery of any indeterminate nodule in the cirrhotic liver is about one in five. In the least, this study reinforces the need for surveillance imaging programs for higher risk patients. Further, the indeterminate nodule population is well-suited for early detection biomarker studies and for studies examining biologic inhibitor or chemoprevention strategies for HCC.

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Fig. 1.

Kaplan–Meier curves for overall survival in patients with cirrhosis and at least one indeterminate nodule discovered by surveillance imaging, stratified by those who did or did not subsequently develop hepatocellular carcinoma (HCC).

Fig. 2.

Primary causes of cirrhosis in patients with cirrhosis and at least one indeterminate nodule discovered by surveillance imaging, stratified by those who did or did not subsequently develop hepatocellular carcinoma (HCC). NASH—non-alcoholic steatohepatitis; Hep C—hepatitis C; Hep B—hepatitis B; EtOH—alcoholic cirrhosis.

TABLE I

Clinical Factors in Patients With Cirrhosis and Indeterminate Nodule(s)

Factor	All	HCC	No HCC	P
Number of patients	252	53 (21%)	198 (79%)	
Gender (male)	154 (61%)	41 (27%)	113 (73%)	<0.01
Age (median, range)	56 (25–81)	57.1	55.1	0.06
Any viral hepatitis	N=124 (49%)	35 (28%)	89 (72%)	<0.01
AFP (mean, range)	5.5 (1.5–6,048)	7.5	5.2	0.15
Total bilirubin (median, range)	1.6 (0.4–31.2)	1.7	1.5	0.43
INR (median, range)	1.3 (1.0–3.2)	1.3	1.2	0.55
Albumin (median, range)	3.0 (1.5–4.4)	2.8	3.0	0.10
Platelet count (median, range)	77k (12k–366k)	51k	88k	<0.01
Creatinine (median, range)	0.76 (0.33–2.99)	0.75	0.76	0.88
Number of nodules (median)	1.0	1.0	1.0	0.34
MELD	9.98	11.4	9.5	0.09

AFP, alpha fetoprotein; INR, international normalized ratio; k, thousand; MELD, model for end-stage liver disease.

TABLE II**Imaging Characteristics of Indeterminate Nodules in the Cirrhotic Liver**

Imaging characteristic	HCC (N=50^a)	No HCC (N=191^a)	<i>P</i>
Arterial enhancement	33 (66%)	82 (43%)	<0.01
Venous washout	7 (14%)	10 (5%)	0.06
Rim enhancement	1 (2%)	6 (3%)	0.99
	HCC (N=42^{a,b})	No HCC (N=17^{a,b})	<i>P</i>
Restricted diffusion	1 (2%)	2 (0.1%)	0.48

^aExcludes patients with index imaging study lacking both arterial and delayed contrast phases.

^bExcludes patients if index imaging study was CT and not MRI.