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Utilization and Accuracy of Biopsy in Patients with Hepatocellular Carcinoma in a Community based Setting

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Abstract

Background and aim: Liver biopsy is not routinely recommended for the diagnosis of hepatocellular carcinoma (HCC). Identification of characteristic imaging findings is usually sufficient for diagnosis and biopsy is recommended for a subset of patients with indeterminate lesions based on imaging or clinical characteristics. The study aim was to determine real-world utilization and accuracy of liver biopsy in patients ultimately diagnosed with HCC in a community setting during an era when liver biopsy was commonly utilized.

Methods: In this retrospective study, 388 consecutive patients diagnosed with HCC between 1/2005 and 12/2006 in a northern California managed care population were evaluated to determine if they underwent liver biopsy during diagnostic workup for HCC. We evaluated predictors of biopsy and performed descriptive statistics, univariate and multivariate logistic regression.

Results: Liver biopsy was performed in 244 patients (62.9%). Inconclusive or false negative biopsies occurred in 47 patients (19.3%). Of those biopsied, 206 (84.4%) underwent single biopsy, 33 (13.5%) underwent 2 biopsies, and 5 (2.1%) underwent > 2 biopsies. Tumors < 2 cm accounted for 8.2% of biopsies. Absence of cirrhosis increased odds of biopsy (Odds ratio [OR] 3.9, 95% confidence interval [CI] 1.7-8.6) whereas alpha-fetoprotein > 500 ng/mL decreased odds of biopsy (OR 0.18, 95% CI 0.09-0.35). Cancer stage, number of lesions, lesion size, and Model for End-Stage Liver Disease score were not statistically significant predictors of undergoing biopsy.

Conclusions: False negative and inconclusive liver biopsies occur in one-fifth of patients who undergo diagnostic biopsy for liver cancer in a community based setting.

Keywords

Hepatocellular carcinoma, Biopsy, Cancer, Diagnosis

Introduction

Liver cancer is the second most common cause of cancer-related death worldwide. It is the fifth most common cancer in men and the ninth among women [1]. Accounting for 70-85% of primary liver cancers, hepatocellular carcinoma (HCC) is the major histologic subtype [2]. The incidence of HCC in the United States continues to increase. According to Surveillance Epidemiology and End Results (SEER) registries, overall annual age-adjusted incidence rates of HCC have increased from 1.4 per 100,000 in 1975-1977 to 4.8 per 100,000 in 2005-2007 [3]. In the United States, prognosis for HCC has improved in recent years as more cases are treated at early stages. SEER registry data have demonstrated that between 1975-1977 and 1998-2007, the 5-year cause-specific HCC survival increased from 3% to 18% [4]. For patients with limited stage disease, the survival rate is over 60% at 5 years for those treated with curative therapies, including liver transplantation, resection and ablation [5-8]. In order to facilitate timely initiation of effective therapies, early and accurate diagnosis is paramount.

HCC diagnosis is often made by characteristic radiographic findings of intense arterial enhancement followed by washout during the portal venous or delayed phase of dynamic contrast-enhanced imaging, which are highly sensitive, specific and repeatedly validated [9,10]. The American Association for the Study of Liver Disease (AASLD) 2010 Updated Practice Guidelines describe a diagnostic algorithm for liver lesions that hinges on nodule size, specifically greater or less than 1 cm [9]. These guidelines were developed for use in patients with cirrhosis but can also be applied to patients with chronic hepatitis B without known cirrhosis. According to these guidelines, the role of liver biopsy is limited and should be reserved for nodules greater than 1 cm with an indeterminate or atypical appearance on one or sequential dynamic imaging techniques [9]. This was an update to the 2005 AASLD Practice Guidelines, which recommended the presence of characteristic imaging findings on two dynamic contrast-enhanced imaging studies in order to establish an HCC diagnosis for nodules 1-2 cm in size [11]. According to the 2005 guidelines, biopsy was recommended for nodules greater than 2 cm with an atypical vascular pattern on one dynamic imaging technique. For nodules 1-2 cm in size, if the vascular pattern was typical on only one dynamic imaging study or atypical on two dynamic imaging techniques, then biopsy was recommended [11]. Studies have since demonstrated that typical appearances of arterial hypervascularity and venous or delayed phase washout are so highly specific that only a single imaging technique with these findings is sufficient for diagnosis, reducing the need for biopsy [12,13].

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Table 1: Demographic and baseline clinical characteristics (n = 388).

Variable	N	%
Age (years)		
Median (range)	64 (20 - 97)	N/A
Gender		
Male	273	70.4
Female	115	29.6
Ethnicity		
White	181	46.7
Black	44	11.3
Asian	87	22.4
Hispanic	75	19.3
Other	1	0.3
Known cirrhosis		
Yes	295	76
No	93	24
Etiology of liver disease		
Hepatitis C	100	25.8
Hepatitis C + Alcohol	86	22.2
Hepatitis B	57	14.7
Alcohol	56	14.4
Other	89	22.9
Alpha-fetoprotein (ng/mL)		
Median (range)	76 (1 - 35350)	N/A
Model for End-Stage Liver Disease (MELD) score		
Median (range)	10 (6 - 40)	N/A

The use of liver biopsy, therefore, should be limited to a subset of patients in whom the diagnosis of HCC cannot be established via dynamic contrast-enhanced imaging. Despite these recommendations, various analyses of SEER registry data suggest that 30 to 70% of HCC cases are histologically confirmed [4]. Liver biopsy for diagnostic confirmation has several limitations, including bleeding, needle tract seeding, and inability to sample the lesion due to ascites, coagulopathy or tumor location. Another major limitation is obtaining a false-negative result, which may be due to sampling error or inability to distinguish between well-differentiated HCC and dysplastic nodules. The false negative rate for nodules less than 2 cm may be as high as 30% when studied in the context of a clinical research study performed at an expert center [10]. Little data exist, however, regarding test performance and results in community settings where a large majority of cancers are diagnosed. The aim of this study is to characterize the real world utilization of liver biopsy, predictors of biopsy use, and biopsy performance among patients ultimately diagnosed with HCC in a community based setting.

Methods

Study population

During the period from January 2005 to December 2006, 388 consecutive adult patients over 18 years of age diagnosed with HCC in a large Northern California managed care population were retrospectively identified in our database. Standard demographic, clinical and pathologic data were collected. These included age, sex, ethnicity, presence or absence of known cirrhosis (defined by presence of ICD-9 code for cirrhosis and/or ascites, hepatic encephalopathy or varices), etiology of liver disease, alpha-fetoprotein (AFP), Model for End-Stage Liver Disease (MELD) score, and tumor size, number and stage. All patients were ultimately diagnosed with HCC via serum tumor markers, diagnostic radiographic study, histology, cytology, or direct visualization.

Statistical evaluation

The patient's baseline characteristics are expressed as medians (ranges) for continuous data and frequencies (percentages) for categorical data. Univariate and multivariate logistic regression analyses were performed with a priori variables including presence of cirrhosis, etiology of liver disease, MELD score, AFP, and number and size of tumors in order to evaluate predictors of undergoing liver biopsy. Statistical significance was set at $P < 0.05$. The data were evaluated by using STATA 10.0 (College Station, TX).

Table 2: Biopsy use

Variable	N	%
Liver biopsy		
Yes	244	62.9
No	144	37.1
Size of tumor biopsied		
< 2 cm	20	8.2
≥ 2 cm	224	91.8
Number of biopsies per patient		
1	206	84.4
2	33	13.5
≥ 3	5	2.1
Inconclusive biopsy		
Yes	47	19.3
No	197	80.1

Results

Patient characteristics

Patient demographic and baseline clinical characteristics are summarized in table 1. Of the 388 patients in this cohort, 70.4% were men. The median age was 64 years (range 60-97). The median MELD score was 10 (range 6-40) and the median AFP was 76 ng/mL (range 1-35350). Cirrhosis was identified in 76% of patients. Etiologies of liver disease included hepatitis C (25.8%), hepatitis C in addition to alcohol (22.2%), hepatitis B (14.7%) and alcohol use alone (14.4%). Other etiologies, including fatty liver disease, primary biliary cirrhosis, and hemochromatosis, accounted for 22.9% of cases. The median nodule size was 6 cm (range 1-10 cm). 56% of patients had 1 nodule, 14% had 2-3 nodules and 30% had greater than 3 nodules. 9.3% had tumors less than 2 cm. Overall, 32% of patients were within Milan criteria, defined as the presence of a single lesion less than 5 cm or a maximum of three lesions, none of which are greater than 3 cm [14].

Liver biopsy use

The utilization of liver biopsy in this study cohort is summarized in table 2. Liver biopsy was performed in 244 out of 388 patients (62.9%). The indication for biopsy was diagnosis of HCC. Biopsies were not performed at the time of treatment nor were they utilized for treatment stratification. Tumors less than 2 cm in size accounted for 8.2% of biopsies. 20 of 36 (55.6%) patients with lesions under 2 cm underwent biopsy as compared to 224 of 352 (63.6%) patients with lesions over 2 cm ($p = 0.17$). Inconclusive or false negative biopsies occurred in 47 patients (19.3%). Of the patients who underwent biopsy, 206 (84.4%) underwent a single biopsy, 33 (13.5%) underwent 2 biopsies, and 5 (2.1%) underwent 3 or more biopsies. In five patients, a false negative biopsy result led to delays in ultimate histologic diagnosis of HCC of over one year.

Predictors of liver biopsy

Utilizing multivariate logistic regression, several factors influenced the likelihood of undergoing biopsy. The absence of clinical cirrhosis increased the odds of undergoing biopsy (Odds Ratio [OR] 3.9, 95% confidence interval [CI] 1.7-8.6). An AFP level greater than 500 ng/mL decreased the odds of undergoing biopsy (OR 0.18, 95% CI 0.09-0.35). Cancer stage, number of lesions, size of lesions, and MELD score were not statistically significant predictors of undergoing biopsy in multivariate modeling.

Discussion

Liver biopsy is not routinely recommended in practice guidelines for HCC diagnosis in the presence of highly specific and sensitive radiographic features on dynamic contrast enhanced imaging. We found that false negative results and inconclusive biopsies occurred in 19.3% of biopsies performed in a community based setting where liver biopsy was utilized in 62.9% of patients diagnosed with HCC.

Liver biopsy use has decreased over time, as demonstrated by recent analysis of SEER data from 1992 to 2008. Among 21,390 cases of HCC during 1998 to 2008, 70% were histologically confirmed. However, from 1992 to 2008, the incidence rate of histologically unconfirmed HCC increased 2.5 times more quickly than the incidence rate of HCC that was histologically confirmed [4]. Another analysis of SEER data from the second half of this period, between 2002 and 2005, demonstrated that among 3693 patients with HCC, only 32.4% underwent one or more biopsies [15]. Thus, in order to optimize the yield of our study to evaluate the performance of liver biopsy in HCC diagnosis in a community based setting, we elected to study the time period from 2005 to 2006 when liver biopsy was more frequently used than it is currently. This time period also correlated with publication of the 2005 AASLD practice guidelines in which biopsy was recommended more often, specifically for 1) nodules greater than 2 cm with an atypical vascular pattern on one dynamic imaging technique and 2) nodules 1-2 cm in size if the vascular pattern was typical on only one dynamic imaging study or atypical on two dynamic imaging techniques [11].

The use of liver biopsy for HCC diagnosis has limitations, including a high rate of false negative results in prior reports at referral centers. This may result from sampling error or challenges in confidently distinguishing between dysplastic nodules and well-differentiated HCC [10], but might also result from diagnostic bias due to the types of patients seen at referral centers, including patients with earlier stages of disease (i.e., more likely to receive resection or transplant) or those with diagnostic uncertainty. While the overall sensitivity, specificity and positive predictive value of biopsy for HCC diagnosis are reported to be over 89%, the negative predictive value has been reported to be as low as 14% [16-18]. However, these data regarding test characteristics of biopsy are derived from older studies performed in university referral centers. For example, Durand *et al.* reported a 10% false negative rate in 137 biopsies performed for HCC diagnosis between 1986 and 1996 in an academic setting [16]. Similarly, Huang *et al.* reviewed 455 biopsies performed in an academic setting between 1981 and 1990 and showed a false negative rate of 14% [19]. In a more recent study performed between 2003 and 2006 in a select group of prospectively enrolled patients from the Barcelona Clinic Liver Cancer group, the false negative rate of biopsy was 30% in 60 patients with hepatic nodules less than 2 cm in size [10].

The performance of liver biopsy in community-based settings has not been well described. In our cohort of 388 patients with HCC, 62.9% underwent liver biopsy for diagnosis, yielding a large sample size for evaluation of biopsy performance characteristics. 19.3% of these patients had a false negative or inconclusive biopsy. 15.6% of patients required more than one biopsy. In a contemporary community based setting, these data underscore that a negative biopsy of a liver lesion does not rule out HCC. For lesions that have a negative biopsy for HCC, clinical guidelines recommend ongoing radiographic monitoring or repeat biopsy [9].

Our study evaluated tumor and patient characteristics to determine potential reasons for obtaining liver biopsy. Data suggest that properly performed dynamic contrast-enhanced imaging can confirm the diagnosis without biopsy in the majority of lesions greater than 2 cm [20]; however, in our study, 91.8% of nodules biopsied were greater than 2 cm. Clinical factors that affected the use of biopsy were evaluated in our study. Appropriate clinical factors did affect the likelihood that patients underwent biopsy. Those with an AFP greater than 500 ng/mL were less likely to undergo biopsy, whereas the absence of cirrhosis increased the likelihood of undergoing biopsy in our study. The use of diagnostic sequences in accordance with guidelines has been suggested to result in lower rates of liver biopsy [15].

Given the retrospective nature of this study, the complete rationale regarding why providers requested liver biopsy and the medical specialties involved in each step of decision making were not readily available. Review of biopsy specimens by a pathologist was not feasible given the large number of biopsies. Radiology reports were reviewed however central review of imaging for characteristic enhancement and washout patterns was not performed. As a result, adequate triage to biopsy based on radiographic findings cannot be commented upon within the current study. Additionally, radiologist level of training and expertise in liver imaging was unknown. While this is a limitation to our study, real world experience suggests that biopsies are frequently performed despite radiology findings, particularly if not reviewed in an expert center. We have not calculated the positive or negative predictive values of liver biopsy nor provided biopsy complication rates as this would require biopsy of all patients with potentially suspicious liver nodules, a practice which is not consistent with current clinical guidelines or practice.

During our study period, liver biopsy was frequently utilized in the diagnosis of HCC. One notable limitation in the use of liver biopsy for this purpose is the moderate rate of false negative and inconclusive biopsies, which occurred in one fifth of patients undergoing biopsy in our cohort. There is ongoing debate in the literature regarding the role of biopsy for histologic diagnosis of HCC citing the potential benefits of morphologic and molecular subtyping of HCC to develop diagnostics, enhance prognostication, and improve targeted therapies [21,22]. Our data underscores important considerations regarding use of liver biopsy in clinical settings and highlights the need for careful assessment of the benefits and risks to patients.

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