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Should LI-RADS or Liver Biopsy be used to Diagnose Suspected Hepatocellular Carcinoma? Assessment of Current Practice Patterns and Perspective from a Metropolitan Cancer Center

Commentary Article

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Author Details

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Background

Worldwide, liver cancer is the fifth most common malignancy and the fourth leading cause of malignancy-related deaths [1]. Hepatocellular carcinoma (HCC) makes up >80% of new cases of liver cancer, with >80% of those cases occurring in sub-Saharan Africa or in East Asia. In fact, China alone holds >50% of new cases of HCC [2,3]. In the United States, HCC is the fastest growing cause of cancer-related death in men, although notably, the largest proportional increases occurred among whites (Hispanics and Non-Hispanics) [4].

American Association for the Study of Liver Diseases guidelines recommend MRI of the liver or multiphase CT for diagnostic evaluation of HCC [5]. In 2011, the Liver Imaging Reporting and Data System (LI-RADS) introduced a standardized method based on expert reviews, experiences, and consensus to radiologically categorize HCC diagnoses. It was created to limit inter-reader differences in assessment of HCC by radiologists, both regionally and internationally. If a patient has an LI-RADS score of 4 or especially 5, imaging alone can be sufficient for diagnosis. Biopsy is only recommended when radiology results are not definitive [6]. Additionally, the European Association for the study of the Liver (EASL) recommends liver biopsy to confirm HCC in non-cirrhotic livers. This recommendation recognizes the limitations of non-invasive HCC imaging criteria in non-cirrhotic livers, which have not been validated, and that misdiagnosis can occur between intrahepatic cholangiocarcinoma and HCC [7].

Challenges of LI-RADS in Diagnosing HCC

The hallmark imaging features for HCC diagnosis are only identified in about 60% of cases, and multiple studies have shown the sensitivity and positive predictive value of radiologic diagnosis to be <90% [8,9]. Both CT and MRI are reported to have specificity around 90%; however, both imaging modalities consistently have lower sensitivity and positive predicative tests around 80%. Misdiagnosis of intrahepatic cholangiocarcinoma occurred in 4% of patients who were thought to have typical HCC [7]. Other challenges include disease with atypical features that are difficult to distinguish from other malignancies, such as intrahepatic cholangiocarcinoma, combined HCC-cholangiocarcinoma, arterioportal shunt, and hemangioma. These imaging features become especially challenging in patients with liver cirrhosis or chronic liver disease, which accounts for many patients undergoing evaluation for HCC [8,9]. Thus, accuracy of diagnosis of HCC is imperative for timeliness to treatment.

Liver Biopsy

Compared with imaging, tissue biopsy carries a reduced risk of misdiagnosis and provides more information. In non-cirrhotic patients, liver biopsy is necessary for an accurate diagnosis of HCC, as imaging provides even lower specificity in this setting [10]. In fact, the EASL strongly recommends that liver biopsy be performed in non-cirrhotic patients to diagnose HCC and in patients with discordant radiologic findings [11].

In recent years, percutaneous liver biopsies have become safer and more efficient via improvements in imaging technology and innovative needle designs [12]. Additionally, endoscopic ultrasound-guided liver biopsy has evolved as a safer, more efficient alternative to traditional percutaneous, transjugular, or surgical liver biopsy [13]. These concurrent advancements in biopsy techniques and safer tool-guided practices have been reported to result in lower risks of adverse events, and lower overall liver biopsy–related risks. Multiple studies have shown the number of serious adverse events associated with liver biopsy to be very low [14]. The HALT-C trial evaluated liver biopsies in patients with either fibrosis or cirrhosis from hepatitis C and its associated complications, revealing an adverse event rate of only 1.1%. The most common adverse event was bleeding (16 cases, 0.6%), and no biopsy-related deaths were reported [15].

Unlike other solid tumors, for which the genetic mutational landscape have been identified to make associated targeted therapy possible, understanding and development of targeted treatment modalities for HCC remain in early stages of development. This disparity can be attributed to reliance on radiographical diagnosis for HCC, rather than pathology. Recent clinical trials have sought to bridge this knowledge gap by incorporating liver biopsy [7].

The lack of knowledge about the molecular drivers of HCC is compounded by conflicting beliefs about whether a liver biopsy is ethical when performed for research purposes [16]. In the era of personalized medicine, molecular characterization of biopsy samples is a critical tool for accurate diagnosis and prognosis. To allow a more accurate diagnosis for patients suspected of having HCC and to allow for subtyping and molecular analysis of HCC, the potential of liver biopsy's safety and diagnostic utility needs to be reassessed. For this study, we assessed the safety of liver biopsy in patients suspected of having HCC and the accuracy of imaging techniques and scoring systems in predicting the presence of HCC over time in a single specialty center.

Practice Norms at a Metropolitan Cancer Hospital

We performed a retrospective review of patients who underwent liver biopsy for suspected HCC between January 1, 2010, and January 1, 2020, at the Memorial Hermann Hospital Texas Medical Center (MH-TMC) and Memorial Hermann Northeast Cancer Center (MH-NE). We gathered data and analyzed records for 408 adults who were referred to these two centers and underwent biopsy for suspected HCC at these two sites. The histology results of the biopsy for patients with suspected HCC are summarized in Figure 1. The most common result was HCC (82.2%); the remaining patients (17.8%) had diagnoses other than HCC. The most common non-HCC diagnosis was adenocarcinoma not otherwise specified (NOS; 3.7%), followed by lymphoma (3.4%) and cholangiocarcinoma (2.8%).

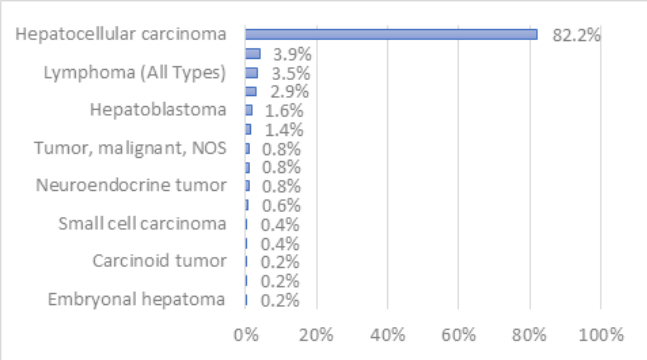

Figure 1: Tumor Histology Results from Liver Biopsy for Patients with Suspected HCC.

In terms of imaging, the patients had prior imaging done at different imaging centers throughout the greater Houston region and were subsequently referred to MH-TMC and MH-NE for liver biopsy. Of these patients, 330 (81%) had pre-biopsy imaging with MRI, CT, or ultrasound. Eighty-eight percent (88%) of the studies were done with contrast, but only 19% of the studies were multi-phasic dedicated liver studies. Only 10 (17%) of patients who underwent dedicated liver imaging had LI-RADS reported. In place of LI-RADS, descriptive comments were used in most radiologic reports. One-hundred and fourteen (38%) of the imaging reports were written as suspicious or not able to exclude HCC. Of the 78 patients with a final histologic diagnosis of disease other than HCC, 8 patients (10%) had imaging reported as "concerning or could not exclude HCC." The pathologic diagnosis for these 8 patients included 2 with adenocarcinoma, 2 with carcinoma NOS, 1 with cholangiocarcinoma, 1 with neuroendocrine tumor, and 1 with sarcomatoid carcinoma.

The median age at biopsy was 66 years; 69% of patients were male, 65% were White, and 20% were Black/African American. Some 259(79%) of patients with HCC had evidence of cirrhosis. The most common causes of cirrhosis were hepatitis C (43%), non-alcoholic fatty liver disease (17%), and alcoholic liver disease (16%). We collected data on six comorbidities that were determined to be most relevant for HCC. The most common of these was hypertension, which occurred in 263 patients (64.5%), followed by diabetes (39.2%), hyperlipidemia (24%), coronary artery disease (14.7%), bleeding diathesis (2.69%), and HIV infection (1.47%).

The overall biopsy complication rate was low at 1.23% (n=5). Most of the patients (97%) underwent core needle biopsy; the rest underwent fine-needle aspiration. More than half of biopsies were done in the outpatient setting and 45.83% were done as inpatient. Complications included bleeding (80%, n=4), hospitalization (60%, n=3), infection (20%, n=1), and death (20%, n=1). In the 5 patients with complications, increased creatinine was associated with bleeding complications; however, one patient was receiving dialysis (Cr = 11.20), so this result should be interpreted with caution. In the univariate analysis of existing comorbidities, concurrent medication use (including anticoagulant), CP and MELD-NA score, and other laboratory findings were not associated with any biopsy complications. The one death in our population occurred 15 days after biopsy, when the patient presented with hypovolemic and hemorrhagic shock secondary to hemoperitoneum. The patient had advanced disease; unfortunately, this was followed by subsequent multiorgan failure, and the family withdrew care.

Bridging the Gap

Few studies in the literature have commented on overall adherence to LI-RADS and inter-person reliability. A study of 143 observations demonstrated overall good adherence with LI-RADS reporting, with an exception rate of 8% of images reported as LIRADS-5 but meeting LIRADS-4 criteria [17]. Yakoo et al. [18] reported in a cross-sectional study with 93 patients with cirrhosis that discordant MRI LI-RADS observations are common and would have impacted clinical management in 43.5% of the study subjects18.

Our study reveals potential gaps that exist in the workup of suspected HCC in many areas. Despite introduction of the LI-RADS system in 2011, the low adherence to LI-RADS reporting among the radiologists was consistent throughout our study, showing a need to educate radiologists on the standardization of LI-RADs reporting. The imaging studies were done throughout the greater Houston area, which included radiologists in community practice. Additionally, this study highlights an educational gap among physicians in understanding which radiology studies (I.e. multiphasic CT or MRI) are needed to diagnosis liver cancer. We recommend that dedicated liver imaging be the first

part of the workup for patients with suspected hepatic malignancy. In our study, we noted that 10% of the patients who had imaging "concerning or could not exclude HCC" were found to have a different diagnosis based on pathology from the liver biopsy; this included 2 patients with LI-RADS-5 lesions. This is unsurprising, given that the majority of our patients had evidence of cirrhosis, which can influence the radiographic hallmarks of HCC, as mentioned.

Notably in our study, of the 408 patients who underwent biopsy for suspected HCC, only 82.2% of the liver biopsies yielded HCC. The remaining 17.8% biopsies revealed other cancers, including adenocarcinoma NOS and cholangiocarcinoma, which are treated differently than HCC, despite radiologic studies having reported findings consistent with HCC, including 2 patients with LIRADS-5 lesions. This underlines the importance of obtaining a correct pathologic diagnosis in a patient who would have been treated for HCC based on radiologic studies alone. Furthermore, we found 2 cases for whom, despite a LI-RADS-5 score, indicating very high likelihood of HCC, the final histologic analysis resulted in a different diagnosis. This highlights an area of needed improvement in LI-RADS reporting.

Our data review's low complication rate of 1.23% in suspected HCC patients who underwent liver biopsy is consistent with historical data in patients with liver disease [15]. Neither comorbidities nor being on antiplatelet medications or anticoagulants predicted biopsy complications in our review. Also, although this patient population had more advanced disease, as shown by higher CP scores, this was not associated with biopsy complications [19]. The 5-year survival rate for liver cancer in 2020 remains poor at 18%, although this has increased from only 3% approximately four decades ago [20]. To combat this dismal prognosis, more therapies are currently under investigation, including the molecular targeted therapies in HCC. Schulze et al. identified putative driver genes associated with recurrently altered pathways, defining the genomic landscape of HCC and potentially allowing for new therapeutic targets or clinical trials [21]. In the future of HCC therapy, we expect an increasing need to use liver biopsy as a reliable tool to obtain histopathologic information, as well as to prognosticate and guide therapeutic options.

Conclusion

A brief review of the current practice standards at our metropolitan cancer center shows the need for updated standards in the workup and diagnosis of HCC, especially in community practice. Dedicated imaging and LI-RADS reporting should be standardized as the initial part of workup for HCC. Furthermore, owing to the limitations of imaging techniques, liver biopsy should become part of the standard of care for diagnosis of HCC and to understand the molecular profiles of HCC to increase our understanding of the tumor biology of HCC, leading to better treatment options based on personalized medicine.

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