Tissue Diagnosis of Hepatocellular Carcinoma

Deepali Jain

Department of Pathology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India

The current American Association for the Study of Liver Diseases (AASLD) guideline provides strategies for achieving the diagnosis of hepatocellular carcinoma (HCC) based on the size of liver nodules seen on surveillance imaging. For lesions less than 1 cm in size, follow-up surveillance imaging is recommended. Lesions larger than 2 cm require typical radiological hallmark on dynamic imaging. Lesions of 1–2 cm in size require typical imaging features including intense uptake of contrast during arterial phases followed by decreased enhancement during portal venous phases on at least 2 imaging modalities. In cases of atypical radiological features of the suspected lesion, tissue diagnosis either by fine needle aspiration or biopsy should be obtained. Although fine needle aspiration could give a smaller risk of seeding than biopsy, biopsy has been preferred over cytology. Percutaneous biopsy of HCC carries a potential risk of tumor seeding along the needle tract. However the risk is low and there is no clear evidence of post transplant recurrence due to needle tract seeding. Histopathologic assessment can differentiate between premalignant lesions such as dysplastic nodules and early HCC. Atypical variants of HCC can be recognized morphologically which may have associated prognostic value. (J Clin Exp Hepatol 2014;4:S67–S73)

Hepatocellular carcinoma (HCC) is the sixth most common cancer in the world.[1] Its incidence is expected to rise in the future due to anticipated increase in cirrhosis secondary to viral hepatitis. Over the past 2 decades, the incidence of HCC has tripled, and hepatitis C virus (HCV) related HCC is the fastest-rising cause of cancer-related death in the United States.[2–4]

Hepatocellular carcinoma develops within an established background of chronic liver disease in 70–90% of all patients.[5] The most frequent risk factor for HCC is chronic hepatitis B virus (HBV) infection in Asia and Africa. However HCV predominates as a risk factor in Europe and Japan.[2] Other well established risk factors are alcoholism, non-alcoholic fatty liver disease and diabetes.[6–8]

Treatment depends on early diagnosis by screening high-risk patients when HCC is small and remains localized to the liver. Various studies suggest surveillance of HCC in cirrhotic patients irrespective of its etiology. Surveillance of non-cirrhotic patients is also advocated, especially in HBV carriers with serum viral load >10,000 copies/ml[9] or HCV infected patients with bridging fibrosis. Patients with HCV infection and advanced fibrosis remain at risk for HCC even after achieving sustained virological response following antiviral treatment.

The preferred imaging method for screening is ultrasonography (USG) which is well tolerated and widely available. However, the sensitivity of USG for HCC detection is low because small nodules can be missed in a cirrhotic liver.[10] Use of contrast-enhanced USG improves the diagnostic performance of USG for HCC.

The most used serological test in clinical setting for screening is alpha-fetoprotein (AFP) but it is no longer considered as a surveillance test by most recent guidelines of American Association for the Study of Liver Diseases (AASLD) due to the same reason of low sensitivity.[11] Computed tomography (CT) and magnetic resonance imaging (MRI) have a high sensitivity (55%–91%) and specificity (77%–96%) in diagnosing HCC.[10]

According to the guidelines established by European Association for the Study of the Liver (EASL) and the AASLD, a nodule larger than 2 cm that displays a typical vascular pattern on contrast-enhanced CT or contrast-enhanced MRI can be considered HCC without biopsy.[12,13]

For lesions measuring between 1 and 2 cm, the diagnosis of HCC is confirmed when typical vascular pattern is seen on both the imaging modalities. Otherwise, these lesions should not be treated as HCC without histological

Keywords: HCC, pathology, tissue diagnosis
Received: 24.6.2013; *Accepted:* 3.3.2014; *Available online* 1.4.2014
Address for correspondence: Deepali Jain, Assistant Professor, Department of Pathology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India. Tel.: +91 11 26594774; fax: +91 11 2658863
E-mail: deepalijain76@gmail.com
Abbreviations: AASLD: American Association for the Study of Liver Diseases; AFP: alpha-fetoprotein; CK7: cytokeratin 7; CT: computed tomography; DN: dysplastic nodules; EASL: European Association for the Study of the Liver; EMA: epithelial membrane antigen; EpCAM: epithelial cell adhesion molecule; FNA: fine needle aspiration; GPC-3: glypican-3; GS: glutamine synthetase; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HSP70: heat shock protein 70; MRI: magnetic resonance imaging; pCEA: polyclonal carcinoembryonic antigen; USG: ultrasonography
http://dx.doi.org/10.1016/j.jceh.2014.03.047

Histology

evidence because of a rate of false positives as high as 20%.[14,15]

Recent prospective studies have reported that up to 67% of new nodules smaller than 2 cm identified during surveillance imaging in patients with cirrhosis are indeed HCC.[16] Although the specificity of contrast enhanced MRI has been reported as high as 96% for hepatic nodules of 1–2 cm in size, a significant proportion of small HCC may appear hypovascular or have atypical features, resulting in a false-negative rate of 20%–38%.[17]

Finally, lesions < 1 cm in diameter may be especially difficult to characterize, even with the best imaging techniques. A lesion less than 1 cm in size should be followed by USG examination repeated at 3 months. These recommendations might be applied to patients with partially developed and fully established cirrhosis and chronic hepatitis B. For all other patients without cirrhosis, the possibility of HCC is much lower; therefore biopsy should be done for definite diagnosis of HCC.[12,13]

In comparison with EASL and AASLD criteria, the consensus statement from the Asian Oncology Summit from 2009 recommends that for any nodule, regardless of size, the characteristic features on contrast-enhanced CT or contrast-enhanced MRI is sufficient for diagnosis of HCC, and obviates the need for biopsy.[18]

Histology

IS TISSUE DIAGNOSIS REQUIRED?

Histologic diagnosis is not necessary when the diagnosis of HCC is determined by diagnostic imaging (Level of evidence 1a, grade of recommendation A). Histologic diagnosis by biopsy is indicated when imaging findings are atypical (Level of evidence 3b, grade of recommendation C).

Fine needle aspiration (FNA) biopsy is not without its complications, though rare. The role and efficacy of FNA of small liver lesions (less than and equal to 2 cm) is actively debated.

Percutaneous FNA biopsy performed under image guidance has been adopted as a safe, effective and minimally invasive procedure for the diagnosis of liver lesions. This technique is especially advantageous in patients with advanced malignancies. However controversies were raised over the role of FNA in the detection of HCC.[19] These include 1) high accuracy, sensitivity and specificity of dynamic imaging modalities,[20] 2) the risk of needle tract seeding[21] 3) intraprocedural hematogenous dissemination[21] 4) need of accurate cytohistological characterization in small well-differentiated hepatocellular lesions.[22] All these reasons preclude use of pre-operative FNA diagnosis of HCC. However false-positive results from imaging techniques have also occurred.[14,15] Now there is a need to decide the strategy accordingly in an individual patient. It has to be weighed whether the risk of futile transplantation is more or the risk of seeding? The risk of seeding is overall lower than that of a futile transplantation.[23] There is no clear evidence of post transplantation recurrence due to biopsy-induced hematogenous dissemination.

The percutaneous transabdominal technique under CT or US guidance is the most popular method for performing liver FNA. The sensitivity and specificity of FNA for detection of liver malignancy are around 90% and 100%, respectively. False positives are rare.[24]

Although liver biopsy is not used as frequently for a definitive histopathological diagnosis of HCC, it has an important role in lesions with atypical features on imaging studies. The ability to discriminate between dysplastic nodules and early HCC has become increasingly important, as the efficacy of treatments for HCC, depends on recognition at an early phase. Hence, guided liver biopsy is now mostly used for lesions with equivocal imaging features measuring over 1 cm. The differential diagnosis includes large regenerative nodule, focal nodular hyperplasia-like nodule, dysplastic nodule, early HCC and classic HCC. The first 2 lesions lack cytologic and structural atypia in contrast to dysplastic nodule, early HCC, and classic HCC.

With the new AASLD guidelines, approximately 52%–56% of patients with nodules 10–20 mm in size will need to undergo biopsy.[25]

Hence, biopsy has been strongly recommended before transplantation in patients with small nodules whose nature is uncertain on imaging and in patients with compensated cirrhosis whose only indication for a costly transplantation is the presence of malignancy.

Overall, the specificity and positive predictive value of tumor biopsy is 100% based on the studies available in literature. However the sensitivity varies from 66 to 93% which depends upon the size of the needle and nodule.[23,26,27] Biopsy results obtained by 21- to 22 gage needle and of nodules ≤1 cm show less sensitivity. Tumor biopsy is excellent for ruling in the diagnosis of HCC. However, negative predictive value of biopsy is relatively low. For ruling out the diagnosis, tumor biopsy is less reliable, especially if the nodule is ≤1 cm. Therefore, patients with negative biopsy findings should continue to undergo careful surveillance with repeated imaging.[23,26–28]

Biopsy is not indicated in following situations: A. if there is a focal lesion in a cirrhotic liver and the patient is not a candidate for any form of therapy B. in decompensated cirrhosis and the patient is on the waiting list for liver transplantation C. if the patient is a candidate for resection.

FNAC OR BIOPSY?

Fine needle aspiration could give a smaller risk of seeding than biopsy. Although the specificity and the positive predictive value of FNAC for focal liver lesions is very high, the sensitivity ranges between 67% and 93% and thus diagnostic accuracy is less than for histology.[29] In addition to distinguish malignant from non-malignant lesions is