

Reviewer's comment	Reply
<p>Reviewer 1:</p> <p>Is there any advantages of liver biopsy in HCC, compared with those of imaging modalities? Authors should discuss on them in detail, according to the reported references.</p>	<p>Advantages of liver biopsy in the setting of Imaging limitations, has been detailed in sections on "Imaging limitations" and "Role of tissue analysis in small HCC". Further modifications done as per suggestion. (highlighted page 10- section "Imaging limitations").</p>
<p>Reviewer 2:</p> <p>The manuscript by Prof. Rastogi is a nice review of the current indications and utility of liver biopsy in patients with hepatocellular carcinoma. The topic is of high relevance. Although HCC is the only solid tumor with a specific dynamic radiological behavior, and thus able to be diagnosed in absence of histological assessment, the role of liver biopsy is getting more attention in recent years. Apart from the acknowledged indications of liver biopsy considered within the latest guidelines and elegantly discussed in the manuscript, histological features of HCC may change management in selected patients and may be required for enrolment in randomized controlled trials evaluating new drugs (this may be the only therapeutic options in some patients with advanced disease). The manuscript reads well and is well structured. Tables and figures are pertinent.</p>	<p>I thank the reviewer for encouraging remarks and for summarizing this review so nicely.</p>

<p>The author is kindly invited to consider the following comments: -Although most liver transplant institutions use Milan criteria for selecting candidates for liver transplantation, there are some other less restrictive criteria. Among them, the UCSF criteria have no restriction regarding number of nodules or diameter, but require liver biopsy to rule out poor tumor differentiation. This is a nice example of how liver biopsy may change clinical management. Please consider to include this insight in the manuscript.</p>	<p>Added as per suggestion. (highlighted page 17- section "Biopsy for prognostication"</p>
<p>Another role of histopathological examination of HCC in clinical practice is salvage liver transplantation. I missed this information in the manuscript.</p>	<p>Added as per suggestion. (highlighted page 12, section "Histopathology and Immunohistochemistry for the diagnosis and prognostication of HCC"</p>
<p>Liver biopsy has limited ability to diagnose well differentiated HCC vs adenoma. Please discuss as a limitation.</p>	<p>Added as per suggestion. (highlighted page 11,12, section "Biopsy Shortcomings"</p>
<p>Regarding the role of microvascular invasion, there is a systematic review and meta-analysis of its clinical relevance in patients undergoing liver resection or transplantation (PMID:23149850).</p>	<p>Suggested paper quoted & few details added. (highlighted page 16, section "Biopsy for prognostication"</p>

<p>Consider quoting this paper.</p>	
<p>I sincerely believe that liver biopsy will be boosted in the HCC setting in the near future. Novel drugs and upcoming targeted therapies will be directed against a subpopulation of patients with certain histological features and/or tumor-expression pathways predominance. Liver biopsy will certainly have a central role for the development of personalized medicine in HCC. Please discuss further.</p>	<p>As suggested by other reviewer also, Table 2 showing role of liver biopsy has been inserted. Also, sections- abstract, Imaging limitations, Hisopathology & IHC for diagnosis and prognosis, biopsy for prognostication - additions have been done as per suggestion.</p>
<p>In page 6, complications of liver biopsy are described based on single center studies with increased sample size (refs 40 and 41). In may well be that complications are underestimated in these studies taking into account that the aforementioned centers are widely experienced in this technique. Consider including data extracted from a systematic review in this field (there are several published) in which outcomes from many and heterogenous instituions are pooled in the analysis.</p>	<p>Added as per the suggestions. Highlighted -Page 11, "Biopsy Shortcomings"</p>
<p>As a future need, a comment about mVI assessment in liver biopsy specimens would be welcomed.</p>	<p>Added as per the suggestion. Highlighted - Page 16, 17 section "Biopsy for Prognostication"</p>

<p>Reviewer 3:</p> <p>This is an interesting review paper on the utility of liver biopsy for HCC in today's environment of improved imaging for HCC. The authors does a nice work of describing the debate concerning the utility of biopsy for HCC, including the risks involved.</p>	<p>I thank the reviewer for the appreciation & comments</p>
<p>Could the author please respond to the following questions/comments: 1) Could the author discuss the utility of AFP in diagnosing HCC and in several cases making liver biopsy unnecessary?</p>	<p>Added as per the suggestions. Page 10, after section on Imaging limitations.</p>
<p>2) The author may wish to suggest an algorithm describing in which cases is liver biopsy a) mandatory, b) potentially necessary, c) unwarranted.</p>	<p>Table 2 inserted as per the suggestion. Based on the evidence from published literature, algorithm based on the role of tissue diagnosis is inserted.</p>
<p>3) The author may wish to describe in more detail the radiological advances in the diagnosis of HCC with emphasis on smaller lesions (<2cm)</p>	<p>Few recent details added on page 9 section "Role of Imaging in the diagnosis of HCC" (highlighted)</p>