

Reviewer#1 (02539405)

This review summarizes the advantages and disadvantages of liver biopsy in the diagnosis, treatment and prognosis of hepatocellular carcinoma. Liver biopsy has been developed for many years. However, as a kind of invasive examination, it is seldom used in clinic. In the diagnosis of hepatocellular carcinoma, non-invasive techniques such as ultrasound, CT or MRI are preferred. However, with increasing knowledge of the phenotypical and molecular characteristics of HCC, molecular targets have attracted more and more attention in the diagnosis, treatment and prognosis of HCC. Liver biopsy warrants a simple key-hole view of the lesion under examination. The pathological data obtained at the morphological, phenotypical and molecular level from these tiny fragments may be incomplete or only partially representative. However, it still represents the best option to get information from the lesion itself. Therefore, it is necessary to re-evaluate the role of liver biopsy in HCC, and this review gives us a detailed description.

So, we believe this review has some scientific significance. However, there are still some shortcomings in this review. For example, liquid biopsy is a new detection method with good prospects, and the authors should compare the advantages and disadvantages of this method with the liver biopsy. Besides, the second paragraph of the conclusion, was superfluous.

We thank the reviewer for the suggestions; we have included a table highlighting the advantages and disadvantages of liquid biopsy. Further we have eliminated the last paragraph of the conclusions as suggested.

Reviewer#2 (00070894)

1. The title reflect the main subject/hypothesis of the manuscript.
2. The abstract seems to be lack of a sentence to summarize the main aspects described in this study.
3. The key words reflect the focus of the manuscript.
4. The background, methods, results, and discussion were of high quality, comprehensively collecting and discussing useful information.
5. Lack of figure and table might be less interpretable. There may be a overall flowchart to describe your aspects of discussion

We thank the reviewer for the suggestions; we have modified the abstract as suggested and include a table

Reviewer#3 (02861225)

Di Tommaso et. al. nicely reviewed the current knowledge on the role of tumor biopsy and biology in HCC. The manuscript is well written, but the following points might be addressed in order to further improve its quality:

- 1) Please elaborate about the different biopsy techniques (role of needle size, true cut vs. aspiration biopsy) and their pros and cons.
- 2) Please discuss histological quality criteria (specimen size, portal fields, ...).

We have included a reference illustrating briefly different biopsy techniques and quality criteria (Page 9)

- 3) Please provide a summarizing table or figure including Pros and Cons of the different approaches towards HCC diagnosis. If you have help from a statistician/mathematician, you could model different scenarios (histological vs. radiological diagnosis) in different cohorts (Europe vs. Asia) and calculate a number needed to treat and number needed to harm, and moreover a cost-effectiveness estimation.

We thank the reviewer for the suggestion, and agree it would be a very interesting study; however, we believe it would be an independent original study that falls out of the purpose of a review paper

- 4) Please acknowledge the patient's perspective and the need for an informed consent during the work-up of diagnosing a hepatoma.

We have included a sentence (Page 9)

Reviewer#4 (00069630)

Due to the development of imaging, liver biopsy as a diagnostic method of HCC is not commonly used now. Only a small number of patients with inconsistent imaging evaluation or the need for careful differential diagnosis were advised for the invasive diagnostic method. However, with the progress of molecular biology, targeted therapy and immunotherapy of HCC, the importance of liver biopsy has been put forward again. In this review, the pros and cons of liver biopsy were analyzed. The role of liver biopsy in gene analysis and molecular target of tumors, as well as the effects of targeted therapy and immunotherapy were emphasized. Finally, as the future development direction of this field, liquid biopsy was put forward. This article systematically expounds the recent research related to liver biopsy, which can be used for reference by clinical and scientific researchers. It is an excellent review article.

We thank the reviewer for the kind words

Reviewer#5 (03195661)

The review submitted by Luca Di Tommaso et al has comprehensively described the role of liver biopsy in the diagnosis of hepatocellular carcinoma (HCC). They reported that the role of liver biopsy in the diagnosis of HCC has been challenged by the ability of imaging techniques. Considering the necessity and risk of biopsy, they concluded that the biopsy should be conducted when the nodule has clinical features of higher risk of misdiagnoses such as the increase of atypical markers with normal AFP or the presence of iCCA risk factors. In addition, a non-invasive modality (i.e. liquid biopsy) rather than biopsy is more feasible to index the targeting immune/chemotherapies in the future.

This review was well written, and it is instructive to readers.

Minor comment: Several multikinase inhibitors, such as sorafenib and regorafenib, have been widely used in clinic, however, these agents are prescribed without biopsy and any target examination, resulting in poor response rate in patients. The authors should discuss this issue. That is to say, in the authors' opinion, is it reasonable to detect the kinase activity or other markers before the targeted treatment?

We thank the reviewer for the comments; we have included a paragraph (Page 10)

Reviewer#6 (02687374)

This manuscript mainly introduces the role of current liver biopsy in diagnosis and molecular treatment of HCC. The authors introduced fundamental diagnosis of HCC, pathological diagnosis of HCC and prognostic markers. Furthermore, pros and cons of liver biopsy use in clinical management of HCC and liquid biopsy in HCC were introduced.

This review is comprehensive, and the author made an appropriate assessment on the current diagnosis of HCC and current risk/benefit balance. The language of this manuscript was quite appropriate, and references were also suitable. Therefore, I recommend accepting this manuscript

We thank the reviewer for the kind words