



**PEER-REVIEW REPORT**

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 40423

**Title:** Changing role of histopathology in the diagnosis and management of Hepatocellular carcinoma

**Reviewer's code:** 01221925

**Reviewer's country:** Greece

**Science editor:** Xue-Jiao Wang

**Date sent for review:** 2018-06-24

**Date reviewed:** 2018-06-24

**Review time:** 11 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

**SPECIFIC COMMENTS TO AUTHORS**

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. Could



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7901 Stoneridge Drive, Suite 501,  
Pleasanton, CA 94588, USA  
**Telephone:** +1-925-223-8242  
**Fax:** +1-925-223-8243  
**E-mail:** bpgoffice@wjgnet.com  
**https://**www.wjgnet.com

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? 2) The author may wish to suggest an algorithm describing in which cases is liver biopsy a) mandatory, b) potentially necessary, c) unwarranted. 3) The author may wish to describe in more detail the radiological advances in the diagnosis of HCC with emphasis on smaller lesions (<2cm)

#### **INITIAL REVIEW OF THE MANUSCRIPT**

##### ***Google Search:***

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**PEER-REVIEW REPORT**

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 40423

**Title:** Changing role of histopathology in the diagnosis and management of Hepatocellular carcinoma

**Reviewer’s code:** 03538158

**Reviewer’s country:** Japan

**Science editor:** Xue-Jiao Wang

**Date sent for review:** 2018-06-24

**Date reviewed:** 2018-06-25

**Review time:** 1 Day

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer’s expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input type="checkbox"/> No

**SPECIFIC COMMENTS TO AUTHORS**

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.



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Pleasanton, CA 94588, USA  
**Telephone:** +1-925-223-8242  
**Fax:** +1-925-223-8243  
**E-mail:** [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
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**PEER-REVIEW REPORT**

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 40423

**Title:** Changing role of histopathology in the diagnosis and management of Hepatocellular carcinoma

**Reviewer’s code:** 02530754

**Reviewer’s country:** Spain

**Science editor:** Xue-Jiao Wang

**Date sent for review:** 2018-06-24

**Date reviewed:** 2018-06-29

**Review time:** 5 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good		<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	(General priority)	Peer-reviewer’s expertise on the topic of the manuscript:
<input type="checkbox"/> Grade E: Do not publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Minor revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Major revision	<input checked="" type="checkbox"/> General
		<input type="checkbox"/> Rejection	<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

**SPECIFIC COMMENTS TO AUTHORS**

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,



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7901 Stoneridge Drive, Suite 501,  
Pleasanton, CA 94588, USA  
**Telephone:** +1-925-223-8242  
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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. 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. - Another role of histopathological examination of HCC in clinical practice is salvage liver transplantation. I missed this information in the manuscript. - Liver biopsy has limited ability to diagnose well differentiated HCC vs adenoma. Please discuss as a limitation. -Regarding the role of microvascular invasion, there is a systematic review and metaanalysis of its clinical relevance in patients undergoing liver resection or transplantation (PMID:23149850). Consider quoting this paper. - 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. - In page 6, complications of liver biopsy are described based on single center studies with increased sample size (refs 40 and 41). It may well be that complications are underestimated in



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Pleasanton, CA 94588, USA  
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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 institutions are pooled in the analysis. - As a future need, a comment about mVI assessment in liver biopsy specimens would be welcomed.

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