

## PEER-REVIEW REPORT

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

**Manuscript NO:** 47459

**Title:** Positron-emission tomography for hepatocellular carcinoma: Current status and future prospects

**Reviewer's code:** 03724099

**Reviewer's country:** United States

**Science editor:** Jia-Ping Yan

**Reviewer accepted review:** 2019-04-12 16:49

**Reviewer performed review:** 2019-04-12 17:04

**Review time:** 1 Hour

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	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input checked="" 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 checked="" 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 a comprehensive, well written review on the role of PET in HCC. Few minor comments. 1. Page 3 - please explain multidrug resistance (MDR) to what? 2. Page 3 - change instable to unstable 3. page 2 - consider including hepatologist to the team of



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multidisciplinary team for managing HCC.

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

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

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No

##### ***BPG Search:***

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No

## PEER-REVIEW REPORT

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

**Manuscript NO:** 47459

**Title:** Positron-emission tomography for hepatocellular carcinoma: Current status and future prospects

**Reviewer's code:** 00504119

**Reviewer's country:** Brazil

**Science editor:** Jia-Ping Yan

**Reviewer accepted review:** 2019-04-12 14:51

**Reviewer performed review:** 2019-04-12 17:07

**Review time:** 2 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input checked="" type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" 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 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 novel radiotracers and immuno-PET have showed great potential value for PET imaging and become the focus of current research, which may enhance the ability of PET for HCC. An overview of the advantages and disadvantages for the current PET



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diagnostic status of HCC will be reviewed, and this paper can be very important to this.

#### INITIAL REVIEW OF THE MANUSCRIPT

##### *Google Search:*

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- ☐ No

##### *BPG Search:*

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No

## PEER-REVIEW REPORT

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

**Manuscript NO:** 47459

**Title:** Positron-emission tomography for hepatocellular carcinoma: Current status and future prospects

**Reviewer's code:** 03477256

**Reviewer's country:** Germany

**Science editor:** Jia-Ping Yan

**Reviewer accepted review:** 2019-04-15 07:50

**Reviewer performed review:** 2019-04-15 08:07

**Review time:** 1 Hour

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 checked="" 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 checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

### SPECIFIC COMMENTS TO AUTHORS

1. Can PET differentiate between HCC and intrahepatic cholangiocarcinoma (CCC) ? 2. Which significant value does contrast-enhanced ultrasound imaging still have in daily clinical practice? 3. What about digital angiography ? With this technique even small



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HCC's can be detected. 4. The authors should discuss about the significance of PET-MRI.  
Might this device be of interest and significance in future ?

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##### ***BPG Search:***

- ☐ The same title
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- ☐ Plagiarism
- ☐ No

## PEER-REVIEW REPORT

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

**Manuscript NO:** 47459

**Title:** Positron-emission tomography for hepatocellular carcinoma: Current status and future prospects

**Reviewer's code:** 02530754

**Reviewer's country:** Spain

**Science editor:** Jia-Ping Yan

**Reviewer accepted review:** 2019-04-12 08:44

**Reviewer performed review:** 2019-04-16 08:41

**Review time:** 3 Days and 23 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" 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 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

The present review by L. Ren-Cai and cols. summarize the role of PET-scan in patients with hepatocellular carcinoma and discuss the potential advantages of recently developed radiotracers. The authors provide a nice background including a description

of the available radiotracers. Although the topic is of great interest, there is a very recent review published in WJG which overlaps widely with the present manuscript and therefore the authors should consider redirecting the focus as detailed below. - As outlined above, a recent manuscript addressing this topic was recently published in WJG: "Lee et al. Emerging role of 18F-fluorodeoxyglucose positron emission tomography for guiding management of hepatocellular carcinoma. World J Gastroenterol. 2019 Mar 21;25(11):1289-1306". I would recommend the authors to remove most of the information regarding 18-FDG while expanding the potential applications of newly developed radiotracers. - The review is too optimistic and does not provide a complete viewpoint in some sections. PET scan has well known limitations in HCC assessment. A significant proportion of HCCs does not show increased radiotracer uptake. In these patients, the PET scan may have no role at all. In patients with HCC and positive PET, there is a risk of over-staging which needs to be further discussed. The use of PET as screening may not be cost-effective and its systematic implementation in tumor staging is a matter of debate. Maybe these caveats could be joined in a section of "Limitations of 18-FDG PET-scan in HCC" to be included immediately after the background in order to reinforce the need to develop specific radiotracers (which should be the main focus of the review). - Is there any cost-effectiveness analysis of PET in HCC patients undergoing potentially curative therapies? As far as I know, this is a literature gap that requires further investigations. Please comment. - In page 5, it can be read: "PET scanning has a high sensitivity for detecting metastases but a low sensitivity for HCC". I guess that the authors meant that the sensitivity to detect the primary tumor is reduced but this requires clarification. - I would recommend a summary table including all radiotracers with their supporting evidence in HCC (if available), either to detect intrahepatic or extrahepatic lesions: sensitivity, specificity, predictive values, validation in independent cohorts... It would ease the reading while providing an overview of the strength of the



evidence. - In most scenarios, sensitivity and specificity provides an incomplete evaluation of the precision of a diagnostic technique. Whenever available, predictive values and population of study (BCLC stage, screening vs staging vs evaluation of recurrence) needs to be described. - Figure 3 should be enlarged. In the final version of the manuscript, the image quality should be optimized. - In the conclusion the authors should emphasize the potential clinical role of PET-scan in HCC and more precisely to describe the clinical scenarios where PET-scan should be mandatory vs strongly recommended vs potentially considered vs not useful. This could be also summarized in a table. This information, if based in solid evidence, would be of great interest for the readership. - Pages should be numbered

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

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

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No

##### ***BPG Search:***

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No

## PEER-REVIEW REPORT

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

**Manuscript NO:** 47459

**Title:** Positron-emission tomography for hepatocellular carcinoma: Current status and future prospects

**Reviewer's code:** 03004570

**Reviewer's country:** Turkey

**Science editor:** Jia-Ping Yan

**Reviewer accepted review:** 2019-04-12 08:53

**Reviewer performed review:** 2019-04-19 11:03

**Review time:** 7 Days and 2 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input checked="" 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 checked="" 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 manuscript is a comprehensive, informative review about the current use of PET in HCC. Title, abstract and key words are adequate. Authors benefited from 82 references. Background information, current situation and future prospects about the use of



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18F-FDG PET and new tracers are sufficiently documented. Discussion is highly informative and helpful for clinicians. Figures are perfect. I recommend for publication.

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

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

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No

##### ***BPG Search:***

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No

## PEER-REVIEW REPORT

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

**Manuscript NO:** 47459

**Title:** Positron-emission tomography for hepatocellular carcinoma: Current status and future prospects

**Reviewer's code:** 00039518

**Reviewer's country:** Italy

**Science editor:** Jia-Ping Yan

**Reviewer accepted review:** 2019-04-14 16:45

**Reviewer performed review:** 2019-04-21 21:12

**Review time:** 7 Days and 4 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" 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 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 type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

## SPECIFIC COMMENTS TO AUTHORS

The paper "Positron-Emission Tomography for Hepatocellular Carcinoma: Current Status and Future Prospects" is a well written review about the present role of PET-CT in the diagnosis, staging and prognosis of HCC. Generally speaking, the Authors should

better highlight the limited role of this technique in the present guidelines for the HCC management. The strength of the paper is the excellent overview of the promising perspectives of the new PET-CT applications (dual tracers, immune-PET). I have some concerns that must be addressed by the Authors:

- Abstract: write as follows: ....has improved the ability to detect lesions and has made it possible to achieve great progress
- Introduction, lines 3-4: What does it mean comprehensive treatment? Do the Authors mean multimodal treatments? Please specify
- Introduction, lines 5-6: The Authors write that “partial liver resection and liver transplantation remain the only realistic treatment options for HCC”. Does realistic means curative? In this case , even ablative treatments are included among the curative treatments for HCC.
- Radiotracers: The Authors claim that CuCl<sub>2</sub> PET-CT is useful for the early detection of HCC intracranial metastasis. However, the occurrence of intracranial metastasis in HCC is anecdotal; then, this tracer could be clinically useful only if it is able to early detect extrahepatic HCC metastases independently from intracranial localization. This must be explained
- Section 2. Generally speaking and according to the present EASL guidelines (J Hepatol 2018) , HCC is not a very avid tumour for 18F-FDG PET as uptake is observed in less than 40% of the cases and most well differentiated HCCs are 18F-FDG PET negative. This should be better highlighted in this section.
- Section 2, Paragraph 2.1 : It is not clear to me why 18F-FDG PET-CT has a better sensitivity for extrahepatic metastasis than for intrahepatic HCC. The Authors should comment on this point, even considering that poorly differentiated HCC is largely less frequent than well/moderately differentiated HCC
- Section 2, Paragraph 2.1 The statement “Overall, the staging capacity of 18F-FDG PET-CT is incontestable” must be attenuated as the current guidelines for HCC management do not include PET-CT among the diagnostic and staging techniques for HCC
- Section 2, Paragraph 2.2: All the statements contained in this paragraph (Differential diagnosis) are based on small case series or case reports and

should be changed. Indeed, in my opinion the role of 18F-FDG PET-CT in the differential diagnosis of HCC from other neoplasms and in the extrahepatic staging of HCC remains limited due to the fact that no more than 40% of HCC show an increased uptake of the tracer. Furthermore, it is not clear how this technique can help in the differentiation of malignant from bland portal thrombosis that is usually achieved using CEUS, CECT or even fine needle biopsy of the thrombus - Section 2, Paragraph 2.4: In some of the cited papers the Authors should specify which is the treatment applied (external beam radiotherapy ref. 60, liver transplantation ref 61) - Section 4: The Authors should specify that the role of Dual-phase imaging of 11C-acetate PET in the differential diagnosis of FNH and hemangioma from malignant liver lesions is obviously limited given that this differential diagnosis is easily achieved in most cases using CECT, MRI and even CEUS

## **INITIAL REVIEW OF THE MANUSCRIPT**

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

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No

### ***BPG Search:***

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No

## PEER-REVIEW REPORT

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

**Manuscript NO:** 47459

**Title:** Positron-emission tomography for hepatocellular carcinoma: Current status and future prospects

**Reviewer's code:** 03742333

**Reviewer's country:** United Kingdom

**Science editor:** Jia-Ping Yan

**Reviewer accepted review:** 2019-04-15 01:28

**Reviewer performed review:** 2019-04-21 22:13

**Review time:** 6 Days and 20 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" 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 checked="" type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input 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

I have read with great interest the manuscript entitled "Positron-Emission Tomography for Hepatocellular Carcinoma: Current Status and Future Prospects", submitted to the World Journal of Gastroenterology. In this narrative review, the role of PET for the



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diagnosis and follow-up of hepatocellular carcinoma is explored. The manuscript is well written and the topic of clinical interest. The major criticism is the study design's selection (a narrative review) because the high risk of selection bias; however, the limitations of the studies included are fairly discussed throughout the manuscript. In addition, the manuscript is quite long and the suggestion is to shorten it slightly to improve readability.

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

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

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- ☐ Plagiarism
- ☒ No

##### ***BPG Search:***

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☒ No