

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Clinical Cases

**Manuscript NO:** 39010

**Title:** For initially unresectable hepatocellular carcinoma: Conversion therapy and the suitable timing for subsequent salvage surgery

**Reviewer's code:** 02944278

**Reviewer's country:** Italy

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2018-03-30

**Date reviewed:** 2018-04-03

**Review time:** 4 Days

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 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

Interesting paper, subject actually matter of debate. Good introduction and good description of therapeutic options

## INITIAL REVIEW OF THE MANUSCRIPT

### *Google Search:*

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
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### *BPG Search:*

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- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ [Y] No

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Clinical Cases

**Manuscript NO:** 39010

**Title:** For initially unresectable hepatocellular carcinoma: Conversion therapy and the suitable timing for subsequent salvage surgery

**Reviewer's code:** 02822478

**Reviewer's country:** India

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2018-03-30

**Date reviewed:** 2018-04-06

**Review time:** 7 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 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
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<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 type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input type="checkbox"/> No

### SPECIFIC COMMENTS TO AUTHORS

The authors have reviewed the value of downstaging and salvage surgery for initially unresectable HCC. A table providing details of the type of salvage therapy used and associated rate of successful resection may be provided.

## INITIAL REVIEW OF THE MANUSCRIPT

### *Google Search:*

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## PEER-REVIEW REPORT

**Name of journal:** World Journal of Clinical Cases

**Manuscript NO:** 39010

**Title:** For initially unresectable hepatocellular carcinoma: Conversion therapy and the suitable timing for subsequent salvage surgery

**Reviewer's code:** 02939463

**Reviewer's country:** Taiwan

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2018-03-30

**Date reviewed:** 2018-04-08

**Review time:** 8 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 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 checked="" type="checkbox"/> Grade D: Fair	<input checked="" 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 checked="" 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

The indication of pre-operative treatment, the treatment selection and the timing of salvage surgical resection are critical issue that are not standardized for downtaging treatment of HCC. The authors performed a systemic review and provided their

opinions related to the topics. 1. Eligibility criteria for downstaging and the definition of downstaging determined the success rate of downstaging treatment. The authors need to analyze the outcomes accordingly to clarify the effectiveness of different downstaging protocol. 2. The authors presented different methods to evaluate residual liver volume, liver function and liver stiffness. The advantage and shortcomings of these methods should be analyzed and discussed. 3. The authors proposed that salvage surgery should be performed after TACE when (1) after CR both in radiology and AFP; (2) PVT has disappeared as confirmed radiologically and no extrahepatic metastasis occurs; and (3) corresponds to the Makuuchi criteria. The criteria is hard to reach when the tumor size is  $> 5$  cm, or when major vascular invasion presents. The author should provide the possibility of successful downstaging under such criteria. 4. Viable tumors during pathological examination is frequent after TACE, even in radiological complete response tumors. The authors suggest removing the tumors even after TACE. If this is true, TACE procedure without increasing the residual liver volume cannot increase the resectability of HCC. More evidence and clear explanation for this suggestion is recommended. 5. The increased liver volume after portal vein embolization (PVE) is not proportional to the improvement of liver function. Decision for safe liver resection after PVE should be different from that in patients without PVE. The authors reviewed criteria for successful liver resection both after PVE and without PVE. They suggested liver resection is safe when FLR is  $>25\%$ . The conclusion is not fully supported by the references. 6. The authors recommended SIRT “for patients with insufficient FLR, vital structures invaded by tumors or a heavy tumor burden”. Other downstaging treatments can also be used under the same circumstances. The authors did not define the specific role of SIRT. 7. In theory, sequential TACE and PVE provide a safe and effective method of HCC downstaging. The authors need to clarify the eligibility criteria in compares with TACE or PVE only. 8. The full text of PLF



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should be supplied. 9. Spelling errors are found in this article. English editing is necessary.

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

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

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- ☐ Plagiarism
- ☐ [Y] No

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Clinical Cases

**Manuscript NO:** 39010

**Title:** For initially unresectable hepatocellular carcinoma: Conversion therapy and the suitable timing for subsequent salvage surgery

**Reviewer's code:** 02353723

**Reviewer's country:** Italy

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2018-03-30

**Date reviewed:** 2018-04-23

**Review time:** 24 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 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 checked="" 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 checked="" 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 manuscript of Zhang et al. presents several important problems, so that an initial comment about their aim is difficult to be done. They did not insert the page number, therefore it was difficult to trace the comments. The title is cryptic since it is explained





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neither what is the purpose of the manuscript nor that it is a review. The abstract summarize and reflect the work described in the manuscript In the abstract there are plenty of abbreviations that are not defined In the first line of the abstract they report that the manuscript is a review, but they should specify the type of review (in this case they presented a narrative review). Once again, in the first line it is not clear what the authors mean for “The aim of this review was to investigate conversion therapy ..”. The first paragraph of the methods should be rewritten “Conversion therapy and salvage surgery were briefly defined and then we proceed to the literature retrieval of these topics” The preoperative types of liver volume and function assessment are just the summary of common parameters or scores known in the literature. This should be not considered a search but merely a list. In the following sentence (line 10-11) the authors probably meant that they provided a careful search of conversion therapies and savage surgery strategies reported in the literature The key words are not correctly listed. For example “Hepatocellular carcinoma; Initially; Unresectable” should be substituted with “Unresectable hepatocellular carcinoma” The manuscript adequately describes the background and present status while the aim is not well explained. In addition, the following sentence is repetitive and should be removed “It has been reported that initially unresectable HCC patients undergoing conversion therapy followed by salvage surgery have a 5-year survival rate of 57%, comparable to the rate in patients who underwent liver resection immediately after presenting with resectable tumors[8]”. The methods describing the procedure used to select papers from the literature are very insufficient. The research objectives are achieved by the experiments used in this study. However, the contributions that the study has made for research progress in this field is limited by the nature of the paper. The manuscript interprets the findings highlighting the key points clearly and logically. The findings and their applicability/relevance to the literature are stated in a clear and definite manner. Part of the discussion is reported in



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the results section where the authors make comments on the various techniques used. Apart from authors' comments the issue treated is of relevance to clinical practice. Figures should be improved (the figure is hardly legible). Tables are sufficiently good. References are appropriate. The style, language and grammar are accurate, but there are many typographical mistakes (words not followed by space). As far as the research methods and reporting, the authors did not insert the PRISMA 2009 Checklist

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

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

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

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- ☐ No

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Clinical Cases

**Manuscript NO:** 39010

**Title:** For initially unresectable hepatocellular carcinoma: Conversion therapy and the suitable timing for subsequent salvage surgery

**Reviewer's code:** 02353723

**Reviewer's country:** Italy

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2018-06-28

**Date reviewed:** 2018-07-01

**Review time:** 3 Days

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
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<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 was substantially improved, but it is my opinion that it still needs major changes.

I would start with the title. Conversion therapy and suitable timing for subsequent salvage surgery for initially unresectable hepatocellular carcinoma: what is new?

In the Abstract –Results section- the authors report the definition of Conversion Therapy that is not mentioned in the manuscript.

Introduction: “Thus, hepatectomy is currently the first-line curative therapy, but only 10% to 30% of lesions are resectable at the time of diagnosis.” Where is the reference ????

In the following paragraph the definition of conversion therapy should be added. I would suggest “Therapy that may render some unresectable tumors surgically approachable and may also contribute to better outcome. (Advances in systemic therapy for hepatocellular carcinoma. James J. Harding, ... Ghassan K. Abou-Alfa, in Blumgart's Surgery of the Liver, Biliary Tract and Pancreas, 2-Volume Set (Sixth Edition), 2017).

The last sentence of the introduction, defining the aims, should be similar to that of the abstract, which stars “To review ...”.

I suggest to move the three paragraph following the introduction (pre-operative assessment, liver volume tests and liver function tests, which are not included in the aims) after the “Conversion therapy for initially unresectable HCC” paragraph, since they correspond exactly to the first point (1) assessment of the patient’s condition, including tumor stage, liver function, FLR, and body tolerance.

In the paragraph dedicated to TACE, in the first part dedicated to the description of the technique, I would add the reference “Facciorusso A et al. Transarterial chemoembolization: Evidences from the literature and applications in hepatocellular carcinoma patients. World J Hepatol 2015;7:2009-19.”

The initial part of the discussion is too negative. It should be better to suggest some concepts that are reported by the same authors about the factors to consider for the assessment of resectability. The sentence should be changed as following: “Firstly, the definition of unresectable is still subjective once T1 and T4 stages are excluded. However,



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the distribution of the nodules to both hepatic lobes, the presence of high alpha-feto levels, and the vascular involvement are substantial tumoral parameters that help in the evaluation of resectability beside residual liver function and patients general conditions. Moreover, the limit of unresectability depends on the level of the hospital and the experience of the operator or their expertise in surgery.”

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

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

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- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ [Y] No

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

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ [Y] No