

ANSWERING REVIEWERS



April 6, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 17189-edited_nde.doc).

Title: Managements of recurrent hepatocellular carcinoma after liver transplantation: a systematic review.

Author: Nicola de'Angelis, Filippo Landi, Maria Clotilde Carra, Daniel Azoulay

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 17189

The manuscript has been improved according to the suggestions of reviewers:

1) Format has been updated according to the Journal guidelines for a systematic review.

2) Revision has been made according to the suggestions of the reviewer. Hereafter, the authors' reply (A) to each reviewers' comment/question (Q).

Reviewer #1

Q: This manuscript conducted a comprehensive review from the literature up to January 2015 to analyze the efficacy (survival) and safety of treatments for recurrent hepatocellular carcinoma (HCC) in patients with liver transplantation (LT). A total of 61 studies were selected including 13 case reports, 41 retrospective case series, and 7 retrospective comparative studies. Based on these literature, the authors concluded that the management of recurrent HCC in LT patients is challenging and associated with poor prognosis independently of the type of treatment. The study contents of this manuscript meet the mission of WJG, and the topic can provide comprehensive data and knowledge for future clinical trials on LT for patients with HCC. The methods of searching databases reasonable, the analysis for the data is reliable, and the writing is fluent. Because this is a review manuscript, no ethic issues is concerned. According to these features, I am recommending you to receipt and publish it.

A: Thank you for your supportive comments on our manuscript.

Reviewer #2

Q: This is an interesting systematic review describing the management of post transplant HCC recurrence. As mentioned by the authors, the articles used for the review are mostly retrospective, hence the results have to be considered keeping the impact of various bias in mind.

A: We agree with the reviewer and we highlighted in the manuscript, especially in the discussion (limitation section) the need of caution before drawing definitive conclusions since the overall level of evidence is low.

Q: Minor comments 1. Did the authors look at recurrence rates with underlying etiology of liver disease?

A: It was not possible to distinguish the rate of survival by the different liver etiologies in the majority of the included articles.

Q: Did the pattern of recurrence depend on HCV /HBV status and any impact of serological status and antivirals post transplant especially on late recurrence?

A: Similarly, this information was missing in the majority of the studies, thus it is not possible to conclude. However, the HCV/HBV infectious status was not recognized as predictive of HCC recurrence in previous studies or reviews aimed to assess the prognostic and predictive factors of HCC recurrence in transplanted patients.

Q: 3. Was there a impact of pre tx downstaging on recurrence, pattern of recurrence and outcome of recurrence?

A: Although this was not the objective of the systematic review, other papers previously demonstrated that the pattern of recurrence, e.g. early or late HCC recurrence, is a predictor of survival. In fact, early HCC recurrence is associated with shorter survival rates. We mentioned it in the discussion section, as uniformly reported in the included studies. Conversely, no data are available on the impact of downstaging on the treatment outcomes. We collected the information about the classification as Milano In or Milano Out HCC wherever available, but it was not possible to pool this data together and draw some conclusions.

We agree with the reviewer that this information would have been highly interesting for the readers. Unfortunately these are the limitations of the current literature; we thus added these points as suggestions and objectives for future research (highlight comments).

3) Typesetting was corrected.

4.) Figure 1 (the flow chart of study selection) has been upbaded also as a separate word file that can be easily edited.

5) Since authors are non-native speakers of English, we provided a language certificate by a professional English language editing service, namely American Journal Experts (Certificate Verification Key: C8D7-864D-D801-6E16-7404)