

Format for ANSWERING REVIEWERS



August 25, 2012

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5297-review.doc).

Title: Bridging and Downstaging Treatments for Hepatocellular Carcinoma in the Waiting List for Liver Transplantation

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 5297

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

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Point by point responses to reviewers' criticisms

Reviewer 1: This review article describe an important and controversial issue in the field of liver transplantation such as the clinical impact on dropout from the waiting list, tumour recurrence and overall survival of the bridging and downstaging procedures of hepatocellular carcinoma applied to patients candidates to transplant. This is well written review article and have worth to publish. However, please add the representative or schematic figures. It is helpful for readers.

Response: We added 3 tables concerning advantages and disadvantages of the different bridging and downstaging procedures, the results of the main studies assessing the role of bridging procedures, and the results of the main studies evaluating the downstaging therapies.

Reviewer 2: The manuscript is very detail but purely descriptive. It will be most helpful to add some table to summarize some of the results. Since the title of this manuscript is "Bridging and down staging treatment for HCC in the waiting list for liver transplant", there should be at least 2 table summarizing the outcome of 1. bridging 2. Downstaging. A summary figure of evidence-based approach would also be useful. Even though data is limited, should expand the section on liver transplant outcome since this should be the aim of this review, based on the title. A recommended approach based on the current evidence would greatly enhance this review. Other minor comments: 1. Need to point out the one of the logistic problems with liver resection- the issue with HCC exception should patient need a liver transplant. 2. p.9, line 9: lower than 3 cm should be less than 3 cm

Response: Following the reviewer's suggestions we added 2 tables concerning the results of the main studies assessing the role of bridging and downstaging procedures in HCC patients before LT. As regards the request to expand the section on liver transplant outcome using an evidence based approach, we decided to summarize in Table 2 the currently available results of bridging procedures on drop out rate, HCC recurrence and overall survival after liver transplant, and in Table 3, devoted to the downstaging therapies,

the criteria and rates for successful downstaging, the recurrence free survival and the overall survival of transplanted patients reported in the largest available series. Minor comments 1. The issue of the selection of resected patients who should be considered for salvage liver transplantation has been discussed and expanded in the paragraph Resective surgery; 2. Lower than 3 cm has been substituted with less than 3 cm.

Reviewer 3: The authors reviewed the bridging and downstaging treatment for HCC in waiting list for liver transplantation. This theme is very important but very difficult to describe due to the lack of randomized studies. Furthermore, situation of the patient is much different depending on the patient's factors (liver function, MELD etc) and HCC (tumor) factor (biological feature, location etc), thus very difficult to review about this theme. I think the paper is well written, however, to help the general reader, I suggest the following things. 1. The authors should make tables depending on the methods of the treatment. I think in the table impact on recurrence and survival etc. should be included. Without this, it is very difficult to evaluate which treatment is better. 2. I recommend to make a table or figure which mention the good points and bad points of the therapies. 3. I think biological feature of HCC is also important factor for the future recurrence and survival. The author should include some more comments in Conclusion. 4. Is living-related liver transplantation the one of the choices for HCC patients? If the authors also think so, this must be included in discussion.

Response

1 Following the reviewer's suggestion we decided to add two tables summarizing the currently available main results of bridging (Table 2), and downstaging procedures (Table3). In the tables the main results of both treatment approaches on HCC recurrence and overall survival of transplanted patients are reported.

2 Following the reviewer's suggestions we added one table concerning advantages and disadvantages of the different bridging and downstaging procedure (Table 1).

3 We agree that there is an increasing evidence of the impact of the biological features on the short and long term impact of the bridging and downstaging procedures performed in HCC patients listed for liver transplantation. This has been already partially addressed in the paper in the sections Introduction and Downstaging of HCC beyond conventional liver transplantation criteria. A new paragraph summarizing the results of some recent studies dealing with this topic has been adjoined in the Introduction section

4 We agree that living-related transplant may be an effective treatment option for HCC patients. Considering the object of our review, we expanded the analysis on the results of salvage living donor liver transplantation as rescue treatment after resection and added some references in the paragraphs Resective surgery and Downstaging of HCC beyond conventional liver transplantation criteria. A sentence on the growing role of salvage living-related transplantation as rescue treatment for HCC recurrence after resection has been added in the Conclusion section.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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