

## ANSWERING REVIEWERS



April 25, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 2665-review.doc).

**Title:** Transplantation versus resection for HCC with compensated liver function after downstaging therapy

**Author:** Lei Jianyong, Yan Lunan, Wang Wentao

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

**ESPS Manuscript NO:** 2665

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

### Reviewer #1:

1. Response to comment: (This study included patients with well compensated liver disease (Child's A and B / MELD score around 8), and understandably none of the patients had severe decompensation. I think this should be clearly stated in the paper's Title, Methodology (inclusion and exclusion criteria) and Conclusions)

Response: It is really true as Reviewer suggested, and we have added this information into the paper's Title, Methodology (inclusion and exclusion criteria) and Conclusions.

2. Response to comment: (The authors did not explain on which basis patients were selected for either liver resection or liver transplantation; the selection criteria for each modality should be clearly clarified in the Methodology.)

Response: We are very sorry for our negligence of this, and we have added this information in the Methodology: Resection was firstly considered for cirrhotic patients with well preserved liver function, liver transplantation was used if subtotal hepatic resection was not anatomically feasible and the living or deceased donor liver graft can be available, the patients with Child Class C were introduced to accept LT and excluded from our study.

3. Response to comment: (Almost all of the patients included in this study had HBV-induced chronic liver disease. In such patients, the new antiviral agents can easily control disease progression. It is also well known that controlling viral replication halts disease progression and decreases the risk of tumor recurrence or developing new lesions. That might have significantly contributed to the good outcome after resection in this study group, especially if you compare it to other parts of the world where HCV is the mostly common cause of liver cirrhosis. I think that this argument should be highlighted in the discussion)

Response: It is really true as Reviewer suggested that controlling viral replication halts disease progression and decreases the risk of tumor recurrence or developing new lesions, so we have added these information in the “Methodology and Discussion”.

4. Response to comment: (The authors correctly identified the weakness of this study, which are lack of randomization and small sample size. Therefore, I think the conclusions are overstated. The conclusions should clearly state that “in selected group of patients with compensated liver disease” liver resection “might” offer better or similar outcome over liver transplantation; and that ““ further randomized studies on a larger number of patients is warranted before drawing any conclusions”)

Response: We have made correction according to the Reviewer’s comments: the conclusion change to be that In selected group of HCC patients who accepted successful downstaging therapies and be with compensated liver function (child class A or B), liver resection might offer better or similar outcome over liver transplantation; and that further randomized studies on a larger number of patients is warranted before drawing any conclusions.

5. Response to comment: (In the result, and under Major postoperative complications and mortality, the authors stated that “The patients who died in both groups did not have any proof of HCC in the explanted liver, and they were excluded from the recurrence rate calculation”. Does that mean the tumor was entirely eradicated by the down staging treatment? Please clarify)

Response: We are very sorry for our incorrect writing, and this sentence should be: The patients who died in hospital after liver resection or LT did not have any proof of HCC recurrence in the liver (no imaging evidence about the recurrence when the patient died in hospital), and they were excluded from the recurrence rate calculation. And no patient’s tumor was eradicated by the down-staging treatment.

## **Reviewer #2:**

1. Response to comment: (If two different groups of patients selected for the study in the Methodology will affect the reliability of the result? Please clarify)

Response: Considering the Reviewer’s suggestion, we have added the information about the selected method in our study: Resection was firstly considered for

cirrhotic patients with well preserved liver function, liver transplantation was used if subtotal hepatic resection was not anatomically feasible and the living or deceased donor liver graft can be available, the patients with Child Class C were introduced to accept LT and excluded from our study. Meanwhile, we have compared the baseline data (Table 1 and 2) between these two groups, and found no significantly difference between two groups, so there is no selection bias in our study.

2. Response to comment: (The presence of the intrahepatic micrometastases and extrahepatic micrometastases was the very important risk factor affecting recurrence and survival in HCC patients after LT or LR. However, the author did not include such micrometastases in the risk factors for tumor recurrence in the result. I hope that the author should pay attention to it in the result and discussion)

Response: We are very sorry for our negligence of the intrahepatic micrometastases and extrahepatic micrometastases, we have collected the information and reanalysis the risk factors for tumor recurrence, and we found out that the intrahepatic micrometastases and extrahepatic micrometastases was not the risk factor for tumor recurrence. That's because there is no extrahepatic micrometastases for all patients who accepted LT or resection after successful down-staging therapy.

3. Response to comment: (In the discussion, the authors also admitted that "So a larger multicenter study comparing an larger number of patients with HCC after successful downstaging therapies in both groups (LR and LT) would be ideal." Now that there are lack of randomization and small sample size selection in the study , the conclusion drawn in this study should be cautious and narrow)

Response: We have made correction according to the Reviewer's comments: the conclusion change to be that In selected group of HCC patients who accepted successful downstaging therapies and be with compensated liver function (child class A or B), liver resection might offer better or similar outcome over liver transplantation; and that further randomized studies on a larger number of patients is warranted before drawing any conclusions.

4. Response to comment: (In the conclusion, the authors stated that "Due to the higher postoperative morbidity and similar survival and tumor recurrence-free rates, the LT should not be considered as the primary treatment for patients with HCC that meets the Milan criteria after successful downstaging therapy." LR is the treatment of choice in noncirrhotic patients and in cirrhotic patients with well-preserved liver function. In patients with advanced cirrhosis and tumor extent within the Milan criteria, liver transplantation is clearly the best option. For advanced-stage HCC patients, successful downstaging does not mean the elimination of the pre-neoplastic cirrhotic background. If an underlying chronic liver disease exists, making a decision on which method should be selected is difficult. Treatment decisions must be individualized. I think that these problems should be taken into account in the methodology and conclusion)

Response: We have re-written the conclusion according to the Reviewer's suggestion, and we have added some information in the methodology.

5. Response to comment: (What does this word " HR " in Introduction mean? Is it a

clerical error or a different meaning?)

Response: We are very sorry for our incorrect writing, it should be LR(liver resection).

### **Reviewer #3:**

1. Response to comment: (Your 5 year recurrence-free survival after liver resection is about 60%. In most reports, 5 year recurrence rates are said to be around 50-70% which translates into 5 year RFS of 30-50%. Yet, this would be the main advantage of transplantation over resection and can explain why in your study resection is equal or even superior to LT. Please comment on your high 5year recurrence free survival rates)

Response: As Reviewer suggested that, our 5 year recurrence-free survival after liver resection is higher than other reports, one of the main reason for this higher rate was the pre-operative successful down-staging therapies. In our another report, which is accepted by another journal(Journal of Gastrointestinal Surgery) and will be published recently, we found out that Successful down-staging therapies can provide a selection on HCC patients and are associated with better operative outcome. And in the discussion, we have discussed about the reason for the high recurrence-free survival rate in the discussion.

2. Response to comment: (Your overall survival numbers are excellent especially regarding the fact that only advanced HCC after successful downstaging have been included. The rate of successful downstaging is 58% and seems very high. Please characterize the pre- and post-downstaging tumor number and size in more detail.)

Response: Considering the Reviewer's suggestion, we have added the data about the pre- and post-downstaging tumor number and size in more detail in table 2. And The rate of successful downstaging ranged from 24 to 69% in other reports (Gordon-Weeks AN, Snaith A, Petrinic T, et al. Systematic review of outcome of downstaging hepatocellular cancer before liver transplantation in patients outside the Milan criteria. Br J Surg.2011;98(9):1201-8). In our study, the inclusion criteria for down-staging was the modified UCSF down-staging protocol, the eligibility criteria for down-staging were as follows: a single tumor with a diameter up to 8 cm, two to three tumors with individual diameters up to 5 cm and a total diameter up to 8 cm, and no vascular invasion by imaging criteria. Our inclusion criteria for down-staging is stricter than other reports, so our rate of successful downstaging is higher than others.

3. Response to comment: (What is the survival of your total cohort including those patients that could not be downstaged successfully? Please consider providing an intention to treat analysis of all patients.)

Response: Thanks for your good advice! But our study was a retrospective

research, the main aim of our study was just to compare the results of LT and LR in patients with HCC that met the Milan criteria after successful downstaging therapy. So we think the intent-to-treat analysis is not necessary in our this study. But coincidentally, we are preparing an intent-to-treat analysis in our another study to include those patients that could not be down-staged successfully, so I can not provide the intention to treat analysis of all patients at here.

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

Sincerely yours,

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