

December 14, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 22820-Brief article.doc).

**Title:** Liver transplantation for hepatocellular carcinoma beyond the Milan criteria: A review

**Author:** Dong-Wei Xu, Ping Wan, Qiang Xia

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

**ESPS Manuscript NO:** 22820

The manuscript has been improved according to the reviewer's and editor's suggestions (All the revisions have been highlighted in the updated vision):

**1 Two tables has been added according to editor's suggestions.**

Thanks for your suggestion, we added 2 tables to summarize and compare the different criteria to help the readers with all the different classifications. In Table 1(**Page 14**), we summarize the selection criteria in different centers for HCC beyond the MC. Table 2(**Page 15**) was based on different serum tumor markers and their cut-off.

We have made use of a language editing service provided by a professional English language editing company (American Journal Experts), and the editorial certificate was attached.

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

(1) **Comment:** A table or 2 summarizing existing expansions of Milan criteria may be helpful to potential readers.

**Response:** According to the reviewers' comments, we added 2 tables to summarize and compare the different criteria to help the readers with all the different classifications. In Table 1(**Page 14**), we summarize the selection criteria in different centers for HCC beyond the MC. Table 2(**Page 15**) was based on different serum tumor markers and their cut-off.

(2) **Comment:** What is the opinion of the Authors on differences in qualification of patients for LDLT and DDLT? Should selection criteria differ?

**Response:** Thanks for your question, on the issue, we think that for patients within the MC, the long-term survival rate was comparable between DDLT and LDLT. However, to further verify the value of LDLT in HCC recipients exceeding the MC, more case-controlled research with larger patient number are needed to be conducted to propose a more appropriate selection criteria.

According to your good suggestion, the statement above was added in the part of "LDLT VERSUS DDLT FOR HCC BEYOND THE MC" (**Page 12, Line 20**).

(3) **Comment:** I would elaborate more about the theoretical advantages and disadvantages of LDLT vs. DDLT.

**Response:** Thanks for your comment. According to comment, related content have been improved, as follow: There are several advantages including reducing the pretransplantation waiting time of patients with HCC, alleviating the ischemia-reperfusion injury because of shortened ischemic time, providing a an optimal donor graft for those with end-stage liver disease and even a timely graft for patients with fulminant hepatic failure promote the development of the approach. Although LDLT is criticized for its higher rate of surgical complications post-transplantation(biliary complications, vascular complications) than DDLT<sup>[75, 76]</sup>, it has been generally recognized by most studies that LDLT could achieve a comparable long-term survival rate in adult patients compared with DDLT<sup>[77-79]</sup>. (**Page 11, Line 23**).

(4) **Comment:** Please add some information on the prognostic value of complete pathologic response after neoadjuvant treatment.

**Response:** Considering your good suggestion, we changed the beginning of the section of "HCC DOWSTAGING ADJUVANT THERAPY BEFORE LT" into "Downstaging has been proved to be an effective way for patients with advanced HCC to reduce the tumor stage to fulfill the MC and achieve a complete pathologic response (cPR) by undergoing neoadjuvant therapies such as transarterial chemoembolization (TACE), radiofrequency ablation (RFA) and percutaneous ethanol injection." (**Page 10, Line 13**). What's more we added the following part into this section: "Vatche et al.<sup>[62]</sup> performed a retrospective review of 501 patients who received neoadjuvant therapies and found that compared with recipients without cPR, patients with cPR had significantly lower MELD scores and significantly superior 1-, 3-, and 5-year recurrence-free and disease-specific survival." (**Page 10, Line 24**) and "Several studies regarded that TACE mediates its effect by inducing complete histological necrosis, with reported rates of cPR in 27% to 57% of patients with TACE <sup>[68, 69]</sup>." (**Page 11, Line 5**)

(5) **Comment:** The authors provided some information on the prognostic value of static AFP concentrations. What about the dynamic changes of tumor markers?

**Response:** According to your good suggestion, we added the following part in the section of "BIOMARKERS USED TO PREDICT HCC RECURRENCE AFTER LT": "Xu et al.<sup>[31]</sup> investigated the AFP data before and after LT in 97 patients and reported that post-transplant AFP levels that did not decrease to

$\leq 20$  ng/ml within 2 months were indicative of higher risk of recurrence. Another study conducted by Hanouneh et al.<sup>[32]</sup> confirmed patients beyond the MC with tumor growth  $<1.61$  cm<sup>3</sup>/month experienced less recurrence than those beyond the MC with tumor growth  $>1.61$  cm<sup>3</sup>/month.”. **(Page 8, Line 14)** And “Another study also showed that increased NLR was associated with worse overall survival and recurrence-free survival <sup>[44]</sup>” **(Page 9, Line 14)**. And “Chung et al.<sup>[48]</sup> also confirmed that the intra-operative decline of CRP was related to the occurrence of gross post-transplant outcomes”. **(Page 9, Line 23)**

**(6) Comment:** Please add some information on the choice of appropriate surgical technique, and whether it should differ in patients within and beyond MC.

**Response:** Thanks for your question, we think that the surgical technique may be divided into DDLT and LDLT. Currently, DDLT recipients are mainly from Western countries and approximately 70% of LDLT recipients are from Asian countries due to the shortage of deceased donation, which was caused by many social and cultural reasons. For patients within the MC, the long-term survival rate was comparable between DDLT and LDLT. However, to further verify the value of LDLT in HCC recipients exceeding the MC, further case-controlled research with larger patient number needs to be conducted to propose more appropriate selection criteria. According to your good suggestion, the statement above was added in the part of” LDLT VERSUS DDLT FOR HCC BEYOND THE MC” **(Page 12, Line 20)**.

**(7) Comment:** The focus of the paper was to review advances in LT beyond the Milan criteria. The authors describe various extended criteria and disclose their advantages and drawbacks. In addition they list biomarkers used in assessing the grade of HCC. The last chapter of the paper is about downstaging of HCC for LT. Remarks - There is not much new in the paper, but it may give the clinician more background in accepting HCC patients on the LT list. - The authors underline the Asian criteria, which may work better in Asian patients with viral hepatitis induced HCC than in alcohol cirrhosis of the western countries. - There is nothing new in biomarkers, AFP, PIVKA-II or NLR. The value of CRP may also be challenged. - The use of PET is also contradictory in HCC. - The TACE and RFA are widely used to treat small HCCs of patients on the waiting list. The role of downstaging instead is poorly evaluated. - LDLT arises risks for the donor, and the method should not be used for cases with poor prognosis. - The value of posttransplant adjuvant treatment with sorafenib or mTORinhibitors is still unproven.

**Response:** Thanks for your comments, according to the issues that you concerned, first, we added 2 tables to summarize and compare the different criteria to help the readers with all the different classifications. In Table 1**(Page 14)**, we summarize the selection criteria in different centers for HCC beyond the MC. Table 2**(Page 15)** was based on different serum tumor

markers and their cut-off in different selection criteria.

Second, we added more information about the advantages and disadvantages of LDLT vs. DDLT. **As is shown in Page 11, Line 23**, “There are several advantages including reducing the pretransplantation waiting time of patients with HCC, alleviating the ischemia-reperfusion injury because of shortened ischemic time, providing a an optimal donor graft for those with end-stage liver disease and even a timely graft for patients with fulminant hepatic failure promote the development of the approach. Although LDLT is criticized for its higher rate of surgical complications post-transplantation(biliary complications, vascular complications) than DDLT<sup>[75, 76]</sup>, it has been generally recognized by most studies that LDLT could achieve a comparable long-term survival rate in adult patients compared with DDLT<sup>[77-79]</sup>.”

Third, we also added information of dynamic changes of tumor markers in prognostic value in HCC patients. The following part was added in the section of “BIOMARKERS USED TO PREDICT HCC RECURRENCE AFTER LT”, “Xu et al. <sup>[31]</sup> investigated the AFP data before and after LT in 97 patients and reported hat post-transplant AFP levels that did not decrease to  $\leq 20$  ng/ml within 2 months were indicative of higher risk of recurrence. Another study conducted by Hanouneh et al. <sup>[32]</sup> confirmed patients beyond the MC with tumor growth  $<1.61$  cm<sup>3</sup>/month experienced less recurrence than those beyond the MC with tumor growth  $>1.61$  cm<sup>3</sup>/month.”. **(Page 8, Line 14)** And “Another study also showed that increased NLR was associated with worse overall survival and recurrence-free survival <sup>[44]</sup>” **(Page 9, Line 14)**. And “Chung et al.<sup>[48]</sup> also confirmed that the intra-operative decline of CRP was related to the occurrence of gross post-transplant outcomes”. **(Page 9, Line 23)**

At last, we add information on the prognostic value of complete pathologic response after neoadjuvant treatment. “Downstaging has been proved to be an effective way for patients with advanced HCC to reduce the tumor stage to fulfill the MC and achieve a complete pathologic response (cPR) by undergoing neoadjuvant therapies such as transarterial chemoembolization (TACE), radiofrequency ablation (RFA) and percutaneous ethanol injection.” **(Page 10, Line 13)**. “Vatche et al.<sup>[62]</sup> performed a retrospective review of 501 patients who received neoadjuvant therapies and found that compared with recipients without cPR, patients with cPR had significantly lower MELD scores and significantly superior 1-, 3-, and 5-year recurrence-free and disease-specific survival.” **(Page 10, Line 24)** and “Several studies regarded that TACE mediates its effect by inducing complete histological necrosis, with reported rates of cPR in 27% to 57% of patients with TACE <sup>[68, 69]</sup>.” **(Page 11, Line 5)**

**3 References and typesetting were corrected, and the order of references was updated.**

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

Sincerely yours,

A handwritten signature in black ink, appearing to read 'Qiang Xia'.

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