

ANSWERING REVIEWERS

Name of journal: World Journal of Meta-Analysis

ESPS manuscript NO: 74428

Title: Is there a role for liver transplantation in the treatment of hepatocellular carcinoma in non-cirrhotic liver?

Reviewer #1: The review paper presents current knowledge about the role of liver transplantation (LT) candidates in treatment of hepatocellular carcinoma (HCC) in non-cirrhotic liver. We ask the authors to clarify in more detail the possibilities and criteria for primary surgical resection from the position of the type and stage of underlying liver disease, and location, number and size of tumors. Does potential distinct hepatocarcinogenesis and underlying liver disease have impact on different outcome of LT in patients with and without cirrhosis or is it just effect of more advanced stage. Please provide further comments on our current knowledge on this topic. Does downstaging with loco-regional therapy (as in cirrhotic LT candidates) and rescue LT after primary resection, could have role in stratification of best LT candidates for HCC patients without cirrhosis. What are the results in published studies, of primary staging by radiological methods (CT, MR,) in relation to explant staging of HCC. The title, abstract, manuscript organization, discussion, tables and references are appropriate. Language requires significant polishing to achieve precision, clarity and grammatical correctness.

Answers:

Resectability criteria were added in the Resectability Determination session

In the introduction section, the impact of distinct hepatocarcinogenesis and underlying liver disease on patients outcomes was highlighted.

Reviewer #2: This minireview aims to focus on LT performed for HCC in non-cirrhotic liver and define indications, outcomes and factors influencing recurrence or survival. The review is conducted in a non-systematic fashion, with a few relevant manuscripts in the field missing in the bibliography and have not been analysed in the manuscript (e.g. A systematic review by Houben et al dated 1999 included 16 series, while this paper focusses on 6 manuscripts, (Table 1)). The manuscript analysed by the Authors as the backbone data for this study (again included in Table 1 and mentioned in the text) seem to be cited incorrectly or inappropriately: - Ref 19: 8 patients from this series are mentioned to be included while in the original manuscript there is mention of: "Thirty-six patients (3.6%) underwent liver transplant for anatomical irresectability in noncirrhotic liver--five of them with tumor recurrence after previous resection" - Ref 20: It is not clear whether the analysed transplants were effectively for HCC on healthy liver. The original manuscript mentions: "OLT were performed when tumor extension or the presence of underlying liver disease precluded PHx". Clearly indicating that there could have been an underlying liver disease and the individual data do not appear to be present in the text for an accurate subgroup analysis - Ref 21: this is a systematic review itself and can not be cited as an individual series or its data to be presented among other series - Ref 22: The Authors report a 27% 5-year survival for non-cirrhotic patients, when the original manuscript does not appear to report such data in the text

Answers:

All the outlined errors and improper use of references were corrected.

Reviewer #3: Liver transplantation (LT) for the treatment of patients with hepatocellular carcinoma (HCC) in non-cirrhotic liver (NCL) is a topic of major interest. In this mini-review the authors aimed to discuss and analyze available data on LT for NCL-HCC, in order to help clinicians for decision-making process regarding the role of LT in NCL-HCC treatment. The review is of interest and well presented, however, to further improve the manuscript some issues would deserve further details and should be addressed. -Background: the authors should describe how the changing scenario of HCC is impacting on HCC treatment. It has been reported that in the last decades there was a progressive expansion of non-viral cases and, namely, of "metabolic" hepatocellular carcinoma in non cirrhotic patients, as recently described (The evolutionary scenario of hepatocellular carcinoma in Italy: an update. *Liver Int.* 2017 Feb;37(2):259-270). -Further, it would be recalled the role of different etiologies in HCC development, curative treatment, and recurrence risk after liver transplantation. It has been reported a role of alcohol intake as independent predictor in non-cirrhotic subjects with chronic HBV infection of HCC development, as previously described (Natural course of chronic HCV and HBV infection and role of alcohol in the general population: the Dionysos Study. *Am J Gastroenterol.* 2008 Sep;103(9):2248-53), and extremely variable HCC recurrence risk and survival are in patients with successfully treated HCV-infected patients (A meta-analysis of single HCV-untreated arm of studies evaluating outcomes after curative treatments of HCV-related hepatocellular carcinoma. *Liver Int.* 2017 Aug;37(8):1157-1166.).

Answers:

The recent suggested references from reputed journals were added.