Reviewer's report

Title: Impact of Stem Cell Marker Expression on Recurrence of Hepatocellular Carcinoma Post Liver Transplantation

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Reviewer: Michael Oertel

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The aim of the studies by Zeng et al. was to determine whether TACE-treated tumors have an increased expression of markers which are expressed in cancer stem cells, and whether these markers can be used to predict HCC recurrence. In a retrospective study, the authors used paraffin-embedded liver sections of explanted HCC liver tissues derived from patients who underwent liver transplantation. The study group was divided into a group of patients that were treated by TACE using doxorubicin and lipidol (n = 18) and into a group of patients who did not receive treatment prior to liver transplantation (n = 22). Liver sections were stained for CD44, CD90, CD133 and EpCAM and the staining intensity was scored. All markers were higher expressed in tumor cells, compared to the surrounding tissue. CD133 and EpCAM were higher expressed in the TACE vs. non-TACE group. Four/18 patients in the TACE group had tumor recurrence, all of them in EpCAM high patients (4/11); only one recurrence occurred in the non-TACE group.

Comments:

1. The paper is well written and the obtained data are adequately presented.

2. The authors showed evidence that high EpCAM expression in HCC specimens is associated with higher tumor recurrence in patients with TACE treatment prior to liver transplantation. The weakness of the present study is that the results were derived from a relatively small patient group. These data have to be confirmed in large-scale studies.

3. Till now, several markers were used to identify or characterize stem cells or cancer stem cells. The major problem is that there are no unique markers for these specific cell types. The suggested markers for cancer stem cells (e.g., EpCAM) are also expressed on hepatic progenitor cells (which are known to be activated in cirrhotic liver) or differentiated epithelial cells. Therefore, it will be very interesting to further determine the expression profile of the EpCAM-positive cells in these tissues, using simultaneous immunohistochemical techniques. For instance, was there any immunohistochemical analyses for cytokeratin 19 performed?

4. The authors mentioned in the Results section, that there was more fibrosis observed in the TACE-treated tumors vs. the non-treated group. How was that
5. In the abstract, the sentence “Four of seven EpCAM high patients recurred within 2 years while 0 of 11 EpCAM low patients recurred.” It should be “Four of eleven EpCAM high patients recurred within 2 years while 0 of 7 EpCAM low patients recurred.” In addition, in Figure legend 3, “0/11” should be replaced with “0/7”.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests