

RESPONSE LETTER

Manuscript NO: 33267

Dear Editor,

Thank you for this kind opportunity to resubmit our article. We appreciate the valuable comments of the Editor and the reviewers, and hope that we have been able to address all questions and make the additions requested into the manuscript.

The paper is submitted in .doc format, and figures have been submitted as .ppt to enable editing. References have been checked and modified according to the instructions. The order of some references has been changed due to additions. Reference No. 14 has been changed, since the original text is no longer available (Ishii et al. Hepatogastroenterology 2014). The manuscript has been in a new language review at Nature Publishing Group. All changes including language revision have been highlighted.

Since we now use a new version of SPSS statistical package, all data was re-analyzed. Bonferroni corrections have also added. There were no significant changes to previous results, and all changes are highlighted.

The study has been supported by grants of Sigrid Jusélius foundation, State Funding and Gastroenterological Research Fund.

Here are comments to the reviewers:

The submitted manuscript by Boyd et al. is an interesting study evaluating clinical and laboratory characteristics of PSC patients in order to identify subjects with biliary dysplasia that could benefit from early liver transplantation. The subject is of interest. However a few issues need to be addressed before coming to final conclusions. - The population in study is not sufficiently described by the Authors and this makes the paper difficult to follow.

- We have now described the population in more detailed way to make it easier to follow, see the "Materials and Methods - Patients"-section.

How was the histological diagnosis reached in patients that were not transplanted?

- The histological diagnosis was verified from histological samples in 12/15 patients (of these samples, 2 were provided in autopsy, 2 were provided during attempted and cancelled LT, and 8 with core-needle biopsy or surgical sample). Among the rest three of them, diagnosis was verified with imaging and cytology in 2 patients and imaging only in 1 patient. We have tried to describe this more clearly in "Results – Cholangiocarcinomas".

What was the indication for liver transplantation in the various groups?

- Indication for liver transplantation was suspicion of biliary neoplasia in 12/16 patients with low-grade dysplasia, 7/10 patients with high-grade dysplasia and in 4/4 patients with CCA. In other patients, indication for liver transplantation was end-stage liver disease or severe symptoms. This has been stated in "Materials and Methods - Patients".

What was the correlation between suspicious brush cytology and presence of (low and high) dysplasia or cholangiocarcinoma after transplantation?

- Brush cytology was suspicious in 11/16 patients with low-grade dysplasia, 8/10 patients with high-grade dysplasia, and in 4/4 patients with CCA. We have added this information more in detail in "Results"-section.

What is the surveillance protocol used?

- The surveillance protocol we used has now been referred to in "Introduction". The frequency of ERCs and BCs depends on previous ERC and BC findings. If suspicious cytology is seen, a new ERC is performed within 3 months. Otherwise a new ERC is performed after 1-5 years depending on the severity of ERC changes.

The title of the manuscript is misleading and does not reflect the content of the study.

- We have now modified the title to better reflect the content of the study.

References for Figure 1 and 2 should be added in the text.

- We have added the references for both figures and they are highlighted in "Materials and Methods".

The paper is novel and the subject is so interesting. The figures are good and eye-catching. My comments: 1) There should be more details about the methods i.e. They have mentioned about the flow cytometry but not described anything about it. 2) The patients groups has not been clarified.

- We have now described flow cytometry in more detail. The patient groups have been described in more detail in "Materials and Methods – Patients".

We hope that we have been able to address the referee and Editor comments adequately and that the paper in its present form is suitable for publication in WJG.

Kind regards,

Sonja Boyd