Point by point response

Dear Prof. Ze-Mao Gong,

thank you for your e-mail from 25/10/2016 inviting us to resubmit our manuscript to *World Journal for Gastroenterology* for further consideration. Please find enclosed the revision of our manuscript "Eosinophilic cholangitis is a potentially underdiagnosed etiology in indeterminate biliary stricture", which we are resubmitting for publication in *World Journal for Gastroenterology* as an original research article (ESPS Manuscript NO: 30525). We thank the reviewers for very helpful comments and suggestions. As seen below, we provide answers to all comments of the reviewers including consecutive changes to the revised version of the manuscript (highlighted yellow in the revised version).

Reviewer #1:

1. *The author should explain why 56 of 66 patients with inconclusive histological diagnosis were clinically diagnosed more clearly.*

In these 56 cases, clinical data strongly suggested the final diagnosis. E.g. for PSC (n=21), PBC (n=5) and PSC/AIH, autoimmune antibodies were identified. In cases of neoplasia (n=9) or ischemia (n=5), a subsequent histology revealed the diagnosis. Patients with unspecific inflammatory changes associated with choledolithiasis and post surgery were not examined in more detail. The diagnoses of the 56 patients are listed in Figure 2.

2. *The author should explain histological reevaluations of the 56 patients were performed or not.*

In these cases, no histological reevaluations were performed. This information was included in the methods section (page 6).

3. *Long term outcomes of the patients who were diagnosed as eosinophilic cholangitis are interesting matter. If possible, they should be mentioned.*

The two patients with EC treated with bile duct resection had several episodes of transient cholestasis or cholangitis after surgery, which were managed with temporary stent placement if necessary. The patient treated with oral steroids is currently off treatment since 12 months and has not experienced a relapse so far.

This information was included in the results section (page 9).

Reviewer #2:

In the abstract in the first sentence of methods secondary sclerosis should be corrected to sclerosing cholangitis.

The sentence was corrected (page 3).

In the first paragraph of the results where the authors list how histopathology was obtained, I think the reader would benefit from a brief description of how the intraductal bile duct biopsies were taken. This could be described in methods section or discussion as well. Also would be of benefit to know if the physicians

used direct cholangioscopy in any of the cases and if they see an emerging role for this.

Additional information how intraductal biopsies were obtained was included in methods section (page 7): For ERCP, standard duodenoscopes (Olympus V-Scopes, TJF 160VF, TJF-Q180 V; Olympus Europe, Hamburg, Germany) were used and the short-wire technique with locking the wire at the distal end of the duodenoscope was applied. In patient 4, cholangioscopy was used as well (duodenoscope TJF - Q180V, Olympus Medical, Tokyo, Japan).

Furthermore, cholangioscopy as an additional helpful tool was included in the discussion (page 11).

In general it would be of value to know if possible how many if any PSC patients were IGg4 positive as some series place this number at 10%. Is this data available?

We conducted an additional IgG4-staining of our PSC cohort. Unfortunately, in 10/14 cases a sufficient evaluation was not possible since there was not enough tissue left on the paraffin-embedded block of the liver biopsy. The remaining four cases were IgG4 negative. Due to the small sample size, this information was not added to the manuscript.

In the discussion the authors mention that in case reports reviewed up to 40% of the patients had cholecystectomy (CE). It is known that EC can cause symptomatic cholecystitis. How many of the 40% had clinical cholecystitis actually justifying surgery? And for those would did not why was there gallbladder removed?

It is of high interest to determine the rate of possibly unnecessary CE in patients with eosinophilic cholangitis. Eight case reports were identified with CE and sufficient data on clinical assessment. In 3/8 cases CE was performed with clinical suspicion for cholecystitis. In the other five cases, CE was performed because of suspicion for malignancy due to thickening of the gall bladder wall. This underlines the importance of EC in the differential diagnosis of biliary malignancies. The information was included in the discussion (page 11).