

ROUND 1

REBUTTAL

Manuscript ID 74128 entitled:

"Digital single-operator video cholangioscopy improves endoscopic management in patients with primary sclerosing cholangitis - a retrospective observational study"

Dear Editorial Team and Reviewers,

Thank you for your letter dated March 10th concerning our manuscript (ID 74128, "*Digital single-operator video cholangioscopy improves endoscopic management in patients with primary sclerosing cholangitis – a retrospective observational study*"), which was submitted to the *World Journal of Gastroenterology*.

The manuscript was carefully revised according to the recommendations of the Editorial team and the reviewers. Please find enclosed a detailed point-by-point response to the comments. All revisions are highlighted within the manuscript. We could address all concerns in detail; however, we were motivated to keep our answers and additional text passages as short and conclusive as possible.

We hope that the revised manuscript meets the requirements of the *World Journal of Gastroenterology*.

With best regards,

A. Bokemeyer, M.D.

Reviewer Comments

Reviewer 1

Comment #1:

Thank you for giving me the opportunity to review this interesting article. Bokemeyer A et al. conducted a retrospective observational study regarding digital single-operator video cholangioscopy (SOVC) for the endoscopic management of patients with PSC. Overall, this paper is well-written and informative for readership of the journal because PSC is a relatively rare disease and endoscopic treatment is often difficult for PSC patients. I would like to point out some minor issues and attach the Reviewer's comments as below.

Answer:

Thank you very much.

Comment #2:

I think the importance of this study is to clarify the usefulness of SOVC for patients with PSC. Therefore, I recommend changing the sentence of the aim of this study; from 'To investigate the use of recently introduced ~' to 'To clarify the utility of recently introduced ~', for example.

Answer:

We thank the reviewer for this valuable comment and have changed the sentence accordingly (p. 3, l. 8-9): "...To **clarify** ~~investigate~~ the **utility** ~~use~~ of recently introduced..."

Comment #3:

Insertion of the SpyGlass requires prior or simultaneous EST. But, after EST, reflux cholangitis frequently occurs in patients with PSC. Therefore, I think that the indication for SVOC is very important. During the study period, how many patients with PSC did you perform ERCP? What percentage of patients with PSC required SOVC? How do you think the indication of SVOC for patients with PSC? I think it is not necessarily to perform SVOC in all PSC patients.

Answer:

Thank you for bringing this to our attention. We agree with the reviewer that single-operator video cholangioscopy (SOVC) is not necessary in all patients with primary sclerosing cholangitis (PSC). Likewise, in our centre, SOVCs were not performed in all patients. We added this information to our results section and rearranged information concerning the indication for SOVC use (p. 8, l. 21-27): "... During the study period, 151 ERCs were performed in 72 patients with PSC, and in 30.5% of these ERCs, digital SOVC was additionally carried out (46/151). These 46 cholangioscopies, conducted in 38 PSC patients, were included in the final dataset. ~~46 cholangioscopies were identified that were performed in 38 patients with PSC (Figures 1 and 2).~~ The main indication for SOVC use was the assessment of biliary strictures (80.4%), followed by selective guidewire placement across biliary strictures (13%) and treatment of biliary stone disease (4.3%). ..."

Comment #4:

The authors described in the manuscript that endoprotheses were placed in 10.9% of examinations (Table 2). But, in Table 2, endoprosthesis placement was 0%. Which is correct?

Answer:

We thank the reviewer for this advice and apologize for our mistake. Indeed, in 10.9% of examinations, endoprotheses were temporarily placed. We corrected this mistake in Table 2 accordingly:

Additive procedures during ERC-examination	
(multiple items permitted), n (%)	35 (76.1)
- Balloon dilation of the biliary tract, n (%)	- 7 (15.2)
- New papillotomy, n (%)	- 6 (13.0)
- Conventional transpapillary biopsy, n (%)	- 5 (10.9)
- Endoprosthesis placement, n (%)	- 5 (10.9) 0 (0.0)
Perinterventional application of drugs to prevent AE	
Antibiotics, n (%)	46 (100)
NSAID (Diclofenac/Indomethacin), n (%)	6 (13)
adverse event; ERC: endoscopic retrograde cholangiography; NSAID: nonsteroidal anti-inflammatory drug.	

Comment #5:

Patients with PSC frequently have multiple stenoses and dilatations in biliary tracts. Indeed, the authors described that the most common site of biliary stricture was intrahepatic bile duct (59.1%). Is it possible to advance SpyGlass to intrahepatic stricture site and evaluate the stricture adequately in all patients? How did you maneuver these difficult procedures? You should show technical tips, if possible.

Answer:

We thank the reviewer for this valuable comment. The reviewer is right that it is not possible to advance SOVCs to all intrahepatic stricture sites due to the declining diameter of more proximal localized intrahepatic biliary ducts. In our cohort, the evaluated intrahepatic strictures were localized at the hepatic ducts and up to the segmental ducts as far as SOVC advancement was feasible. To guide cholangioscopy intrahepatically, the use of guidewires can help to advance the cholangioscope to more proximal localized strictures. However, we think that the reviewer addresses an important issue and added the following text passage to our discussion section (p. 11, l. 31-32 and p. 12, l. 1-3): "...As a limitation, digital SOVCs might only be advanced with difficulties to all intrahepatic strictures due to the decreasing lumen of the proximal bile ducts making proximal intrahepatic ducts partially inaccessible for cholangioscopic assessment. To guide cholangioscopy intrahepatically, the use of guidewires can help to advance the cholangioscope to more proximal localized strictures. ..."

Comment #6:

In table 5, biliary stones were successfully extracted in all 8 patients. However, complete extraction of intrahepatic stones is sometimes very difficult due to the distal biliary stricture especially in patients with PSC. How did you extract all intrahepatic stones? You should describe how to overcome these difficulties in more detail.

Answer:

We thank the reviewer for this comment. Indeed, the extraction of intrahepatic biliary stones proximal to biliary strictures might be challenging. Dilation of the

distal biliary stricture might substantially help to extract stones. Furthermore, electrohydraulic lithotripsy might be used for stone fragmentation and, recently, new accessories like dormia baskets have become available that can be introduced over the accessory channel of the Spyscope assisting biliary stone treatment. We added the following text passage to our discussion section (p. 13, l. 20-22): "... Sometimes the extraction of biliary stones proximal to biliary strictures might be challenging. Dilation of the distal biliary stricture might substantially help extract stones. Furthermore, electrohydraulic lithotripsy might be used for stone fragmentation..."

Reviewer 2

Thank you very much for reviewing our manuscript.

Comment #1:

Were the 4 cases diagnosed as malignant by SOVC-guided biopsy diagnosed by the initial examination? If they were diagnosed as malignant on the initial examinations, they may have been bile duct cancer rather than PSC. Also, please explain the location of these biliary strictures. Did you distinguish IgG4-related sclerosing cholangitis?

Answer:

Thank you very much for reviewing our manuscript. All patients who were included in our study had a previously diagnosed PSC, and PSC diagnosis was not initially made during SOVC examination. Likewise, the four patients in whom a malignant bile duct stricture was diagnosed had a previously known PSC disease. We completely agree with the reviewer that bile duct cancer as well as IgG4-related sclerosing cholangitis might mimic a PSC-like disease. However, in our study, patients had a previously diagnosed PSC disease, and other diseases, such as bile duct cancer or IgG4-related sclerosing cholangitis, were not (previously) known in our included patients. In our cohort, malignant strictures were localized at the intra- and extrahepatic crossing in three patients, and in one patient, the stricture was localized intrahepatically. To address the reviewer's concerns, we made the following changes to our manuscript:

- a) Methods section (p. 6, l. 16-19): "... PSC diagnosis was previously known and not initially established during performed SOVC examinations. Biliary tract

cancer was not previously diagnosed in these patients; likewise, IgG4-related sclerosing cholangitis was not known in our patient cohort. ...”

- b) Results section (p. 9, l. 18-21): "... The malignant strictures were localized at the intra- und extrahepatic crossing in three patients, and in one patient the stricture was localized intrahepatically at the left hepatic duct...”
- c) Discussion (p. 12, l. 14-19): "... Histopathological analysis is essential for excluding differential diagnoses including Ig4-related sclerosing cholangitis, which may mimic a PSC-like disease. In addition to radiologic and serological assessment, tissue acquisition for histopathological analysis is important for diagnostic assessment ⁽²⁶⁾, and SOVCs might help to gain sufficient histopathological material for correct assessment...”

Reviewer 3

Comment #1:

This is a single-centre, retrospective, observational trial which describes the endoscopic experience with spyglass (digital cholangioscopy) in primary sclerosing cholangitis. Endoscopic management in PSC is complex, because standard procedures for stricture management, cholangiocarcinoma detection and so on should be put in the context of a rare disease with heterogenous phenotype. Therefore, it is positive to see studies that try to advance the field and add evidence. Yet, as authors correctly mention, their work is limited by the small sample size and lack of validation, since most of their findings could not be 100% safely taken for granted since this is a single centre experience (although being an expert one).

Answer:

Thank you very much.

Comment #2:

Double check misspells.

Answer:

We thank the reviewer for this valuable comment. We have double-checked our manuscript for misspellings. Indeed, we found some and corrected them.

Additionally, our manuscript was again checked by a professional language editing service.

Comment #3:

How many cholangioscopy have followed a previous traditional cholangiography within the same endoscopic section? there might be some bias related to the number of cholangitis post-ERC

Answer:

Thank you for bringing this to our attention. In all our patients, a previous traditional cholangiography was routinely performed before using cholangioscopy. This might be a relevant confounder regarding the rate of postinterventional cholangitis. To clarify this point, we added the following text passage to the limitations of our study (p. 14, l. 29-32 and p. 15., l. 1-2): "...Fourth, in all our patients, a previous traditional cholangiography was performed before the use of digital SOVC, which might have confounded the rate of cholangitis described in our study. However, this setting was our routine clinical practice. Initially, endoscopists performed traditional cholangiography, which revealed findings making further cholangioscopic assessment instantly necessary..."

Comment #4:

Authors should comment why they avoided also anti-reflux stenting to prevent cholangitis.

Answer:

Thank you very much for this comment. According to the recent European guideline considering the role of endoscopy in primary sclerosing cholangitis (Aabakken et al., Endoscopy, 2017), both balloon dilation and stent therapy are suitable for the management of biliary stricture. However, studies suggest a higher rate of complications following stent therapy (e.g., Kaya et al. Am J Gastroenterol, 2001 and European multicentre randomized DILSTENT trial by Ponsioen et al.) and stenting frequently requires another ERC to remove stents within several weeks, which is why our centre prefers to perform balloon dilation therapy and avoid stenting in PSC

patients. The same guideline is inconclusive about the use of anti-reflux stenting in PSC patients, which is why anti-reflux stenting is not a routine procedure in our endoscopic centre.

Comment #5:

On top of stenting vs dilation -were the 6 patients that received indomethacin those who had sphincterectomy?

Answer:

We thank the reviewer for this valuable comment. Rectal NSAIDs, including indomethacin, were not routinely applied at the start of the study. Additionally, of those six patients receiving indomethacin, only one had sphincterotomy. However, considering our results, rectal NSAIDs should be regularly dispensed in all patients with PSC undergoing digital SOVC, which is the current standard of care in our department and part of recent guideline recommendations. The following text passage in the discussion section addresses this point (p. 14, l. 9-12): "In our cohort, rectal NSAIDs were not routinely applied at the start of the study; however, considering our results, rectal NSAIDs should be regularly dispensed in all patients with PSC undergoing digital SOVC, which is the current standard of care in our department and part of recent guideline recommendations."

Comment #6:

Please add accuracy together with sensitivity specificity ppv and npv -what is the reference gold standard to which sn,sp,ppv,npv are referenced to? this for stricture diagnosis and for malignancy within strictures

Answer:

We thank the reviewer for this comment. As requested, we added accuracy data to **Table 4** and to our results' section (p. 9, l. 26-27 and l. 30): "... visual examination of dominant strictures had an accuracy of 90.9% (CI72.8-99.2)..." and "...Histopathological analysis of SOVC-assisted biopsy acquisition had an accuracy

of 83.3% (CI 57.2-83.3)...". Furthermore, we specified our reference standard for the stricture dignity in our methods section (p. 7, l. 19-25): "...The final diagnosis (reference standard) of biliary stricture dignity was based on a detailed evaluation of all available data, including clinical information, cross-sectional imaging reports and histopathological analyses, which could be found in the electronic patient chart. The median follow-up time was 12 months (interquartile range [IQR] 7-27 months); during this time, the patients were followed up by repeated checks of the available electronic medical records."

Comment #7:

Could authors comment on cost of cholangioscopy: if it is superior for the detection of common bile duct stones, is it cost-effective even in MRCP-negative cases?

Answer:

We thank the reviewer for this critical comment. Although there is a lack of data, it might be less likely that a routine use of digital SOVCs for stone detection in PSC patients is cost-effective which might especially be true for MRCP-negative cases. To adress this point, we added the following text passage to our discussion section (p.13, l. 16-19): "... Although the utility of cholangioscopy for stone detection in PSC patients might be superior using digital SOVC, it might be less likely that a routine use of digital SOVCs for stone detection in PSC patients is cost-effective, which might especially be true for MRCP-negative cases..."

Comment #8:

Authors claim that "Our study is the first to evaluate the use of digital SOVC in patients with PSC". This might be true as regards digital SOVC, not cholangioscopy in general. "Spyglass single-operator peroral cholangioscopy seems promising in the evaluation of primary sclerosing cholangitis-related biliary strictures" evaluated safety and feasibility of cholangioscopy in PSC "Prospective evaluation of the clinical utility of single-operator peroral cholangioscopy in patients with primary sclerosing cholangitis" evaluated cholangioscopy in PSC Authors should also specify better

what "the use" mean in the sentence.

Answer:

Thank you for this comment. We completely agree with the reviewer that our report is not the first to generally evaluate cholangioscopic use in PSC patients; however, our study is the first to evaluate the efficacy and safety of SOVCs with digital imaging quality in PSC patients. Therefore, we changed this sentence to the following and specified "the use" of digital SOVCs as suggested (p. 10, l. 31-32 and p. 11, l. 1): "Although a few previous reports evaluated the utility of cholangioscopy in PSC patients in general ^[26, 27], our study is the first to evaluate the efficacy and safety use of SOVC with digital imaging quality digital SOVC in patients with PSC."

Editorial Office's Comments

Science Editor

Comment #1:

This study aims to investigate the use of recently introduced digital single-operator video cholangioscopy (SOVC) for the endoscopic management of PSC patients. The article is well written and informative for the readers. But the manuscript needs improvement. But, this work is limited by the small sample size and lack of validation.

Answer:

Thank you very much. To improve the quality of our manuscript, we carefully revised our manuscript according to the reviewers' suggestions. Furthermore, we agree with the *Science Editor* that our manuscript is limited by a small sample size and lack of validation; however, we think that our results are still innovative and interesting for the readership of the *World Journal of Gastroenterology*. Addressing the editor's concerns, we extended the limitations of our study (p.14, l. 19-26): "...First, our study was retrospective and is limited by a small sample size comprising comprised only 46 procedures; however, it is the first to exclusively evaluate digital SOVC use in PSC patients; furthermore, PSC is a rare disease, making our number of procedures noteworthy. Second, we included cases at only one hospital in our analysis; however, our centre is a large tertiary referral centre offering special endoscopic experience to perform cholangioscopic procedures, and we could ensure that all endoscopists were fully trained, improving the reliability of our results. Nevertheless, our study results are limited by a lack of validation, making future prospective multicentre studies necessary."

Company editor-in-chief:

Comment #1:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.

Answer:

Thank you very much for inviting us to revise our manuscript. We carefully revised our manuscript according to the reviewers' suggestions, Editorial Office's comments, and Criteria for Manuscript Revision and hope that the revised manuscript meets the requirements of the *World Journal of Gastroenterology*.

ROUND 2

REBUTTAL

Manuscript ID 74128 entitled:

"Digital single-operator video cholangioscopy improves endoscopic management in patients with primary sclerosing cholangitis - a retrospective observational study"

Dear Editorial Team, dear Reviewer,

Thank you for your letter dated March 30th concerning our manuscript (ID 74128, "*Digital single-operator video cholangioscopy improves endoscopic management in patients with primary sclerosing cholangitis – a retrospective observational study*"), which was submitted to the *World Journal of Gastroenterology*.

The manuscript was carefully revised according to the re-review of the reviewer. Please find enclosed a detailed response addressing the remaining minor concern of the reviewer. All revisions are highlighted within the manuscript.

We hope that the revised manuscript meets the requirements of the *World Journal of Gastroenterology*.

With best regards,

A. Bokemeyer, M.D.

Reviewer Comments

Reviewer 1

Comment #1:

Please describe the period from the first ERCP performed for PSC diagnosis to the SOVC. In particular, I am concerned about the period until the diagnosis of 4 cases diagnosed with bile duct cancer.

Answer:

Thank you very much for this additional, very valuable comment and we are happy to address this concern. For all patients, we described the period from the first ERC performed for establishing PSC diagnosis to the initial performance of digital SOVC. Furthermore, we assessed the period from initial ERC performed for PSC diagnosis to the digital SOVC which was sufficient to establish bile duct cancer diagnosis in four of our patients. We added this information to our results section (p.9, l. 5-6): "...Considering all patients, the mean period from the initial ERC performed for PSC diagnosis to the performance of the first SOVC was 99.9 months (SE \pm 16.6)...." and (p.9, l. 8-11): "...In 10.5% of patients, a final diagnosis of a malignant biliary tumour was established. In these patients, the mean time from initial ERC performed for PSC diagnosis to the digital SOVC, which was sufficient to establish bile duct cancer diagnosis, was 71.3 months (standard error: \pm 16.6) with a range of at least 11 months up to 150 months..."