Author’s response to reviews

Title: Endoscopic-ultrasound-assisted transmural cholecystolithotomy after placement of a novel, fully covered metal stent: initial feasibility study using a porcine model

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Dear editor,

I would thank you for giving us the chance to resubmit the paper and also thank for the reviewers for reviewing in detail and giving us constructive suggestions. The manuscript has been modified according to the suggestion and submitted to the tracking system. The following is a point-to-point response to the reviewers' comments.

1. The authors emphasize that after creation of this fistula cholecystolithotomy is feasible. However this has not been proved in this study since the authors only performed extraction of soft food material from the gallbladder. Probably gallstones would be much more difficult to retrieve because of its hardness and even a fistulous caliber of only 1 cm could be not enough to allow gallstone extraction. In this sense, I think that this study actually proves the feasibility of the endoscopic creation of a cholecystogastric fistula allowing further extraction of the gallstones or other endoscopic therapy within the gallbladder as the authors say in the discussion. Thus, in my opinion the title and objective of the article should be changed and focused to emphasize not the cholecystolithotomy but the creation of a fistula allowing endoscopic therapy. Something like “EUS assisted transmural cholecystogastrostomy fistula creation as a bridge for endoscopic internal gallbladder therapy using a novel fully covered metal stent”.

A: The title "EUS assisted transmural cholecystogastrostomy fistula creation as a
bridge for endoscopic internal gallbladder therapy using a novel fully covered metal stent" was more accurate and objective. As mentioned in the conclusion, this technique was subsequently enable cholecystolithotomy and other procedures for treating biliary disease. Gallstone was the most common disease of gall bladder and should be treated in most patients. So, we chose the cholecystolithotomy to prove the feasibility. The changes were made in the title.

2• Although this is a relatively novel approach, the study essentially replicates prior similar animal studies by at least three different groups Only one such study is referenced by the authors (Binmoeller & Shah, 2011). Furthermore, clinical application of this novel approach has been reported by several groups (see below). The authors should include all these references and comment on the differences and similarities between their findings and these prior reports. The concept of intervention through the mature, naked fistula as opposed to through the stent intervention is novel articles, although the article by in which treatment of a gallbladder polyp through a cholecistogastric fistula is described should be mentioned and discussed

A: In the year 2013 and 2014, more papers referred to the clinical application of this novel approach have been published. These researches should be included in this reversed manuscript. The related articles were further discussed. The changes could be found in the discussion section. Accordingly, the references were also updated.

3• Several types of metal stents have been used by differente authors for EUS-guided gallbladder drainage. Their authors should provide comparative details between their new stent (is this a prototype?) and stents used by other authors for this purpose.

A: It is a prototype of the newly designed stent. In the recently study, all the lumen apposing stents were designed with 2 large flared ends protrude against the adjacent luminal walls with moderate pressure. The shape of the flare end in this study was differently designed from the others. The blunted ends were kept the mucosa from further injury.

4• Clinically irrelevant gallbladder leakage during dilation of the fistula is described in all animals. Could the authors add some hypothesis of how to avoid this leakage in the discussion?

A: In the study, the leakage was not completely prevented as mentioned in the discussion section “there was bile leakage in all 4 animals when the needle pierced the gallbladder and during the dilation procedure”. A little amount of bile leaked around the fistula, which was presented in the EUS image during the process. However, in our observation, this leakage was not cause severe complications, which was also indicated in other studies including the clinical trial. We cannot deny the potential risk of the bile leakage, so further studies should be focused on the techniques to minimize the leakage, like shortened the procedure time from the creation of the fistula to the stent release. This was added in the discussion.
5. According to the information provided in the article it seems that all cholecystogastric fistulas were closed when the animals were euthanized. Is that true? How do they explain the discrepancy regarding fistula patency with prior published studies?

A: The fistulas were closed in our animal study. This may because all the stents were replaced with four weeks and the animals were euthanized after 2 weeks. However, the study was limited by the number of the animals.

6. Please, complete the information of the cystotome used for dilation: caliber, brand, etc.; where the procedures also performed under fluoroscopy?

A: The information of the cystotome was added in the Materials and methods—Cholecystogastrostomy section. The whole procedure was under the EUS guidance only.