

Format for ANSWERING REVIEWERS

December 4, 2021



Dear Editor:

Please find enclosed the edited manuscript in Word format (file name: 71668-revised manuscript.docx).

Title: Biliary metal stents should be placed near the hilar duct in distal malignant biliary stricture patients

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The manuscript has been revised according to the reviewers' suggestions:

1 The format has been updated.

2 Revisions have been made according to the reviewers' suggestions.

Reviewer 1: This article is a retrospective comparative study about the appropriate positioning of the SEMS used for endoscopic biliary drainage. The aim of this study to determine which position was ideal for SEMS placement was pretty reasonable, but its execution was lacking in significant parts, such as missing data and a discrepancy between the study design and the analyzed results. Therefore, this article is far from containing any new information of significant value, and I do not recommend this paper for publication. If it is even to be considered for publication, major revision is required.

Response: First, thank you very much for reviewing our manuscript. We have revised the manuscript according to your comment.

Comment 1: This article classified the causes of SEMS dysfunction into ingrowth, overgrowth, ingrowth and overgrowth, top edge closed by the CBD wall, and dislocation. The main cause of SEMS dysfunction in this article was overgrowth. However, It did not include sludge formation (encrustation) or food debris in the causes of SEMS dysfunction. Sludge formation is usually the most crucial cause of SEMS dysfunction, and Its incidence as the cause of SEMS dysfunction is higher than that of overgrowth in both covered and uncovered SEMS and that of ingrowth in covered

SEMS in almost all randomized controlled studies between covered and uncovered SEMS. (Isayama et al. Gut 2004;53:729-734, Telford et al. Gastrointest Endosc 2010;72:907-914, Krokidis M et al. Cardiovasc Intervent Radiol 2010;33:97-106, Kitano et al. Am J Gastroenterol 2013;108:1713-1722) I can not understand why this article did not include sludge formation as the cause of SEMS dysfunction. This fact is a serious flaw in the results of this article.

Response: Thank you for this valuable comment. We believe that the obstruction of sludge or food debris is important for comparisons between uncovered SEMSs and covered SEMSs. However, we thought the obstruction of sludge or food debris was not related to the position of the top edge of the SEMS. To accurately evaluate SEMS dysfunction caused by tumor invasion, we excluded obstruction by sludge and food debris from SEMS dysfunction.

However, I agree with your comment. Therefore, I have added data on obstruction by sludge or food debris to the limitations section (Lines 291-299, supplementary figure 2). When SEMS obstruction by sludge or food debris was also defined as SEMS dysfunction, the patency period was significantly longer in the Hilar group than in the Lower group.

Comment 2: As the authors mentioned in the discussion section, the type of SEMS is too heterogeneous, and the axial force and radial force are too different among SEMSs. These can only affect the results of this article. This fact is a severe flaw in the study design of this article. The authors stated in the discussion section that a closed top edge by the CBD wall could be prevented by using a longer SEMS. However, a closed top edge by the CBD wall occurs only in the SEMS with higher axial force. Please clarify in the result section which stents cause it.

Response: Thank you for this comment. In the cases in which the top edge was closed by the CBD wall, the SEMSs used were the Zilver 635, WallFlex, Niti-S large cell, and HANARO stents (Lines 218-220). Therefore, these SEMSs were not always those with higher axial forces, except for the WallFlex stent.

More in-depth discussion of the relation between closure of the top edge closed the CBD wall and axial force has been included (Lines 252-257).

Reviewer 2: Generally, the topic is very interesting. Biliary drainage is an age old question, and concerns are mainly the necessary, safety, and efficacy, as well as materials. As everyone knows location is an important factor of patency and efficacy, but no literature have been published on this issue. This paper revealed that “a longer patency period could be achieved by positioning the SEMS near the biliary hilar duct”, which is of importance in clinical. In addition, the manuscript is well designed. However, there are several minor problems.

Response: First, thank you very much for reviewing our manuscript. We have revised the manuscript according to your comment.

Comment 1: Definition of “near” remains blur and is of controversy,, which need a wider consensus.

Response: Thank you for this comment. As you described, “near” is an unclear term. When the USEMS was placed through the upper CBD within 2 cm from the junction of the right and left hepatic ducts, the case was included in the Hilar group. Otherwise, the case was included in the Lower group (Lines 136-139). This definition has been added in the abstract (Lines 73-75).

Comment 2: The study period is 10 years, which is too long in my opinion. During this period, great changes have happened on biliary drainage, such as indications, material (metal vs. plastic; cover vs. uncover; et al) and technique (PTBD vs. EBD vs. other), which would affected the location of the tube and in turn have an unavoidable impact on the patency, safety, and efficacy of the biliary drainage, as well as location. Please make further analysis to strength your conclusion; if not, please emphasize it in the Discussion.

Response: Thank you for the valuable comment. We compared the procedure year between the Hilar group and the Lower group. We divided the year of the procedure into the first five years (2011-2015) and the later period (2016-2021). The results showed that the procedure year was not significantly different between the Hilar group and Lower group (Lines 180-181, 188-189, 207, Table 2). In addition, the patency period was not significantly different between placement procedures performed in the first five years and in the later period (Supplementary figure 1K). The procedure year did not significantly influence SEMS dysfunction according to the Cox proportional hazard model (Table 3).

Comment 3: References in the "Introduction" are a little timeworn, please update the latest publications.

Response: Thank you for this comment. We have added citations that were published after 2019 (Reference numbers 10, 11, 22).

Comment 4: In the introduction, the main theme of this study (the position but not technique of stent) was a little inadequate, compared with other background.

Response: Sorry for the confusing context. We want to state that biliary SEMS placement is desirable for treating unresectable DMBO in the introduction. Afterwards, we want to clarify that the ideal position of the SEMS needs to be considered. Therefore, we have added an additional sentence (Lines 114-116).

Comment 5: Please clarify the origin of "DMBO", distal bile duct, duodenum, and pancreatic?

Response: Thank you for this comment. I have added the origin of the DMBO in Table 1.

Comment 6: As shown in Fig2, the length of the tube was also one of factors of patency in my opinion; while, on the other hand, axial force related to the tube should also be discussed in the Discussion.

Response: Thank you for this valuable comment. The influence of axial force has already been discussed in the discussion section (Lines 279-290). However, the influence of axial force on the top edge closed by the CBD wall was also pointed out by reviewer 1 (comment 2 of reviewer 1). Therefore, I have added the relevant data and consideration of the type of SEMS used that have the top edge closed by the CBD wall to the results (Lines 218-220) and discussion (Lines 252-257). In the cases of closure of the top edge by the CBD wall, the SEMSs used were the Zilver 635, WallFlex, Niti-S large cell, and HANARO stents. These SEMSs were not always stents with higher axial forces, except for the WallFlex stent. When a short SEMS is placed near the top edge of the DMBO, the axial force might be enhanced by the biliary stricture. Using longer SEMSs overcomes this problem because the axial force decreases with increasing distance between the top edge of the SEMS and CBD

stricture. In fact, a biliary obstruction was relieved by placing a second SEMS near the biliary hilar duct.

Reviewer 3: Endoscopic ultrasound-guided biliary drainage (EUS-BD) using a self-expandable metallic stent (SEMS) has been widely performed to treat distal malignant biliary obstruction after unsuccessful endoscopic retrograde cholangiopancreatography (ERCP). However, the appropriate positioning of the stent remains unclear. The aim of the study is to determine the ideal position for SEMS placement. A total of 127 patients with biliary obstruction between the junction of the cystic duct and Vater papilla were enrolled in this study. The conclusion is a longer patency period could be achieved by positioning the SEMS near the biliary hilar duct. Although this study is retrospective, it has reached clinically useful conclusions. A large number of patients were included. Congratulations to the authors for completing such a study.

Response: First, thank you very much for reviewing our manuscript. We are honored by your kind words.

Science Editor:

Comment 1: The key findings The manuscript is a retrospective study to evaluate the ideal position for SEMS placement in patients with distal malignant biliary obstruction. The key point of this study is the stent patency period became significantly longer when the SEMS were placed from near the biliary hilar duct. The topic is within the scope of the WJG.

Response: First, thank you very much for handling our manuscript.

Comment 2: The limitations and/or shortfalls, if any, of the underlying review process

1) Heterogenous SEMS company

Response: Thank you for this comment. I have discussed the heterogenous nature of the SEMS companies in regard to the differences in axial force. I have revised the manuscript according to the reviewer's comments (Reviewer 1: comment 2 and response, Reviewer 2: comment 6 and response).

2) Not RCT

Response: Thank you for this comment. This is a limitation (Lines 277-279).

3) Too low dysfunction rates of Hilar group

Response: Thank you for this comment. Insertion of the SEMS near the biliary hilar duct dramatically prevented SEMS dysfunction. However, we did not include obstruction by sludge or food debris as SEMS dysfunction to properly evaluate the relation between SEMS dysfunction and tumor invasion. Therefore, I have added data on obstruction by sludge or food debris to the limitations section (Lines 291-299, supplementary figure 2). This revision was performed according to comment 1 from reviewer 1.

4) Unlike the rapidly developing stent, the study enrolment period is too long. There was no comparison with only the most recent data.

Response: Thank you for this comment. We investigated the influence of the procedure year based on Comment 2 from Reviewer 2. We compared the year of the procedure between the Hilar group and the Lower group. We divided the year of the procedure into the first five years (2011-2015) and the later period (2016-2021). The results showed that the procedure year was not significantly different between the Hilar group and Lower group (Lines 180-181, 188-189, 207, Table 2). In addition, the patency period was not significantly different between placement procedures performed in the first five years and in the later period (Supplementary figure 1K). The procedure year did not significantly influence SEMS dysfunction according to the Cox proportional hazard model (Table 3).

5) No evaluation for sludge formation

Response: Thank you for this comment. As described in the response to comment 3), we have added the data relevant to sludge formation.

Comment 3: Whether the methods used are sound for evaluating the hypothesis: It was a pity that the study did not proceed as RCT, but it was well designed to confirm the study aim.

Response: Thank you for this comment. We are honored by your kind words.

Comment 4: Whether the results can be obtained with those methods and are justified: Results were well organized, and the conclusion was drawn from the methods. However, I think that some data should be sent to the Supplement, and the main result should be only left in the main text for emphasis. Figure 4 was too complex and provided too much information to the readers.

Response: Thank you for this comment. We left the comparison of patency period based on the four factors significantly different between the Hilar group and Lower group in Figure 4. The comparison of patency period based on other factors is now shown in supplementary figure 1.

Comment 5: Whether the interpretation of the results and the conclusions drawn are sound: It's OK.

Response: Thank you for this comment. We are honored by your kind words.

Comment 6: The relative contribution of the work to the field or topic being reviewed: This retrospective study is very interesting and provided an important issue for appropriate stent position in the distal malignant biliary obstruction. Because the long-term patency of inserted stent is essential for cancer patients with biliary obstruction, this study has some limitations, including study design such as not RCT.

Response: Thank you for this comment. The fact that this study was not an RCT is a limitation (Lines 277-279). As such, we have revised the limitations according to the reviewer comments (277-299).

Company Editor in Chief: 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.

Response: Thank you for this comment. I have re-edited the manuscript according to your instructions.

Sincerely,
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