

Format for ANSWERING REVIEWERS



June 9, 2022

Dear Editors,

On behalf of all the authors, I would like to thank you for your consideration of this paper. In the revised manuscript you will find the changes that we made in response to the Reviewers. In this response to reviewer letter we also indicated how we have dealt with the Reviewers' comments.

Please find enclosed the edited manuscript in Word format.

Name of Journal: *World Journal of Gastrointestinal Oncology*

Manuscript Type: ORIGINAL ARTICLE

Percutaneous insertion of a novel dedicated metal stent to treat malignant hilar biliary obstruction.

Francesco Cortese, Fabrizio Acquafredda, Andrea Mardighian, Maria Teresa Zurlo, Valentina Ferraro, Riccardo Memeo, Stavros Spiliopoulos, Riccardo Inchingolo

Invited Manuscript: 03358964

Manuscript ID.: 76726

The manuscript has been improved according to the suggestions of reviewer and Editorial Office's

Comments:

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Major revision

Specific Comments to Authors: Comments to the Authors The authors describe the practice of using two biliary stents antegradely placed through a percutaneous route using US and fluoroscopy as guidance. The stents are placed in a Y- configuration with a stent in stent technique where the second stent is introduced and dilated through the mesh of the first stent. Technical and clinical effects are excellent, and the procedure probably elongates the lives of these patients with malignant strictures in the hilar region of the liver (Bismuth III and IV). The number of patients are 18 and the registration is done over one nine months from Nov. 2020- July 2021. The study is named an observational, single

center study. It is a case series, with no control group. The design is not defined, but from the presentation it seems to be a retrospective study. The researchers have considered technical success, clinical success (relief of jaundice), and secondary endpoints such as stent patency, overall survival, complication rates and stent related complications. The language is of good standard for a scientific journal. The discussion does not include major elements such as the results of ERCP drainage and EUS guided drainage, that represent the standard of care in other centers. This must be included. Tables and images are fine, and illustrate the method well. Figure legends are adequate. The document has no page or line numbers which make it harder to refer to my comments.

Major comments: 1. In the method section and according to the document named: Signed informed Consent form and document(s), there is this statement: Patients were not required to give informed consent to the study because the analysis used clinical data that were obtained after each patient agreed to treatment by written consent. However, as this consent form is not presented as a separate document, I suppose patients consented to the treatment itself with the risks involved, but maybe not to be part of a retrospective or prospective study? The authors should present the consent form in its original format in order to clarify this.

Authors' reply: Thank you for the consideration of this paper and for your comment. We did a retrospective analysis of the data and the original consent form has been added.

2. M&M section: The Helsinki declaration of 1975 has been revised several times since then, and it would be appropriate to refer to the last version.

Authors' reply: A new sentence has been added.

3. Introduction: The authors state that for Bismuth III and IV the outcomes are better with percutaneous approach. The reference is a consensus statement (8). However, there are no references to original studies to confirm this. A better reference would be: Paik WH, Park YS, Hwang JH et al. Palliative treatment with self-expandable metallic stents in patients with advanced type III or IV hilar cholangiocarcinoma: a percutaneous versus endoscopic approach. *Gastrointest. Endosc.* 2009; 69: 55- 62. The main approach to malignant hilar stenoses is to use an endoscopic approach first (ERCP with stenting), and the possibilities to place stent in stent in a Y-configuration or side by side stents are similar with this approach. Why is there no control group who receive this more established treatment, either in parallel or historically. Please consider the following papers for discussion and references: Khashab MA, Valeshabad AK, Afghani E, Singh VK, Kumbhari V, Messallam A, Saxena P, El Zein M, Lennon AM, Canto MI, Kalloo AN. A comparative evaluation of EUS-guided biliary drainage and percutaneous drainage in patients with distal malignant biliary obstruction and failed ERCP. *Dig Dis Sci.* 2015 Feb;60(2):557-65. Doi: 10.1007/s10620-014-3300-6. Epub 2014 Aug 1. PMID: 25081224. Bill JG, Darcy M, Fujii-Lau LL, Mullady DK, Gaddam S, Murad FM, Early DS, Edmundowicz SA, Kushnir VM. A comparison between endoscopic ultrasound-guided rendezvous and percutaneous biliary drainage after failed ERCP for malignant distal biliary obstruction. *Endosc Int Open.* 2016 Sep;4(9):E980-5. Doi: 10.1055/s-0042-112584. Epub 2016 Aug 31. PMID: 27652305; PMCID: PMC5025302. Kongkam P, Orprayoon T, Boonmee C, Sodarat P, Seabmuangsai O, Wachiramatharuch C, Auan-Klin Y, Pham KC, Tasneem AA, Kerr SJ, Romano R, Jangsirikul S, Ridditid W, Angsuwatcharakon P, Ratanachu-Ek T, Rerknimitr R. ERCP plus endoscopic ultrasound-guided biliary drainage versus percutaneous transhepatic biliary drainage for malignant hilar biliary obstruction: a multicenter observational open-label study. *Endoscopy.* 2021 Jan;53(1):55-62. Doi: 10.1055/a-1195-8197. Epub 2020 Jun 8. PMID: 32515005.

Authors' reply: The authors agree with the reviewer that endoscopic options are the first option and the percutaneous approach is reserved for cases in which endoscopy is not possible (usually hilar obstructions). As the comparison between the two approaches was beyond the scope of this study, we

have modified the specific sentence and added the suggested references as follows: “According to currently available data and the ESMO guidelines percutaneous is the recommended approach in cases in which the endoscopic methods are not possible, commonly noted in advanced hilar Bismuth IV obstructions. [8. Mocan et al, 9. Valle JW, Borbath I, Khan SA, Huguet F, Gruenberger T, Arnold D; ESMO Guidelines Committee. Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016 Sep;27(suppl 5):v28-v37. Doi: 10.1093/annonc/mdw324. PMID: 27664259. 10. Paik WH, Park YS, Hwang JH et al. Palliative treatment with self-expandable metallic stents in patients with advanced type III or IV hilar cholangiocarcinoma: a percutaneous versus endoscopic approach. Gastrointest. Endosc. 2009; 69: 55– 62.”

The authors also included the suggested references for discussion as follows: “Although outcomes of endoscopic ultrasound-guided biliary drainage techniques for hilar obstructions are very satisfactory, [Khashab MA, Valeshabad AK, Afghani E, Singh VK, Kumbhari V, Messallam A, Saxena P, El Zein M, Lennon AM, Canto MI, Kalloo AN. A comparative evaluation of EUS-guided biliary drainage and percutaneous drainage in patients with distal malignant biliary obstruction and failed ERCP. Dig Dis Sci. 2015 Feb;60(2):557-65. Doi: 10.1007/s10620-014-3300-6. Epub 2014 Aug 1. PMID: 25081224. Bill JG, Darcy M, Fujii-Lau LL, Mullady DK, Gaddam S, Murad FM, Early DS, Edmundowicz SA, Kushnir VM. A comparison between endoscopic ultrasound-guided rendezvous and percutaneous biliary drainage after failed ERCP for malignant distal biliary obstruction. Endosc Int Open. 2016 Sep;4(9):E980-5. Doi: 10.1055/s-0042-112584. Epub 2016 Aug 31. PMID: 27652305; PMCID: PMC5025302. Kongkam P, Orprayoon T, Boonmee C, Sodarat P, Seabmuangsai O, Wachiramatharuch C, Auan-Klin Y, Pham KC, Tasneem AA, Kerr SJ, Romano R, Jangsirikul S, Ridditid W, Angsuwatcharakon P, Ratanachu-Ek T, Rerknimitr R. ERCP plus endoscopic ultrasound-guided biliary drainage versus percutaneous transhepatic biliary drainage for malignant hilar biliary obstruction: a multicenter observational open-label study. Endoscopy. 2021 Jan;53(1):55-62. Doi: 10.1055/a-1195-8197. Epub 2020 Jun 8. PMID: 32515005.], bilobar drainage with Y-configured SEMS using percutaneous approach is a well-established method for the palliative management of unresectable advanced MHBO in patients with estimated lifetime of more than 3 months[9,22].

4. Another internal approach that has been to use EUS guided biliary drainage with a semi-covered metal stent from the ventricle to the left main bile duct (E.g: Gio-Bor stent). This sometimes allows a similar antegrade cannulation through the papilla with placement of a trans-papillary stent, or it may allow also right sided drainage through the biliary stent from the ventricle.(See attached references above). For drainage of the gall bladder, small LAMS may be placed EUS guided from the duodenum. These alternative approaches should be mentioned and compared based on current literature in the discussion. The main result is a method that results in efficient drainage, with as low invasiveness and risk as possible, without leaving a PTC drain through the skin. Local resources may decide which method to select based on availability and experience.

Authors’ reply: The authors included the suggested references and comments in the discussion. Please see previous comment.

Minor comments: 1. Ref. 18 is a self-reference in the M&M section and describes the endoluminal biopsy of malignant lesions as part of the work-up. In how many patients was this done in the same session as the stenting? Could be reconsidered, or a different reference could be selected.

Authors’ reply: We have changed the ref, avoiding self ref. The endobiliary biopsy was performed in 11 cases; a new sentence has been added.

. Introduction page 4 last paragraph: An end-bracket is inserted after ...50% of the liver volume),.... But there is no start of this bracket, please remove it.

Authors' reply: Done

3. Under "Core tip" the Moving Cell Stent is not referred by name, producer and country, as in the M&M section, this would be appropriate.

Authors' reply: Done

4. There is no mention that in order to place the two stents in its Stent in stent configuration, two separate injection sites passing the skin, peritoneum and liver tissue have to be used in order to angle the stents adequately.

Authors' reply: done

Reviewer #2:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: Dear authors, The Moving Cell Stent (MCS) appears to be a promising new device that will improve the management of patients with unresectable biliary obstruction. I congratulate the authors for the project. A study comparing endoscopic and percutaneous Y-stents will be very good to reinforce the benefit and perhaps a multi-centric study with a higher number of patients. I am here only reinforcing what I believe to be the authors' intention. The text must be revised because the acronym MCS has been changed to MSC in several paragraphs.

Authors' reply: Thank you for the consideration of this paper and for your comment. The changes have been done.

Reviewer #3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Major revision

Specific Comments to Authors: Thank you for the report of new effective SEMS for malignant hilar biliary stricture. My comments were listed below.

Authors' reply: Thank you for the consideration of this paper and for your comment.

1. In page 3, line 22, what does the MSC mean? It is MCS?

Authors' reply: It was a typing error. It has been changed.

2. In page 5, line 1-2, it is written that the outcomes of percutaneous approach are superior to those of endoscopic approach for patients with Bismuth III and IV. The citation is published in 2013. The data might be old? Recently, the SEMSs are improved. Therefore, the outcome of endoscopic approach should have been improved.

Authors' reply: new references have been added. See authors' reply reviewer 1 comment 3.

3. This is the prospective study. Authors should add the information of clinical trial registration.

Authors' reply: This was a retrospective evaluation, so everything has been changed.

4. In stent features, Moving Cell Stent is abbreviated as MSC.

Authors' reply: Changed

5. How is the delivery system of the new SEMS? If the delivery system of the MCS is thick, the other SEMSs with thin delivery system might be suitable for the second SEMS. Could you describe that in the discussion section?

Authors' reply: The second stent should be a MCS because the procedure ends with a kissing balloon dilatation.

6. It is difficult to understand the details of procedure. Could you explain the procedure by putting the figure 2-5 in Figure 2 a-d?

Authors' reply: Done

7. What is the reason of sample size?

Authors' reply: Not sure about the question, but in the limitations of the study, we added the reduced sample size.

8. Could you add the p value in table 4?

Authors' reply: done

9. Why did the authors perform the percutaneous drainage? ERCP and EUS-BD are less invasive than PTBD. Besides, drainage could be achieved by one session of endoscopic drainage. You should discuss this matter in the discussion section.

Authors' reply: See authors' reply reviewer 1 comment 3.

10. In reference 16, the name of journal is wrong. It is "J Hepatobiliary Pancreat Sci".

Authors' reply: Changed

Science editor:

Authors presented a study to evaluate the safety and efficacy of a novel uncovered biliary stent, specifically designed for hilar reconstruction. This is a well written paper regarding new bile duct stent in patients with unresectable biliary disease. Major issues raised by the reviewers are 1) please clarify the type of the study, is it prospective (clinical trial registration number), retrospective or case series, 2) authors should combine Figure 2-5 in Figure 2 A-D, 3) justification of sample size.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade C (Good)

Authors' reply: A: Thank you for the consideration of this paper and for your comment. The requested changes have been done

(2) 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

Gastrointestinal Oncology, 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. 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.

Authors' reply: Thank you for the consideration of this paper and for your comment. The requested changes have been done

Finally, we wish to thank the Editors and the Reviewer for their comments that helped us to increase the value of our paper.

Thank you again for publishing our manuscript in the *World Journal of Gastrointestinal Oncology*.

Sincerely yours,

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