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Prof. Monjur Ahmed, Prof. Florin Burada, Prof. Rosa M Jimenez Rodriguez, and Prof. Pashtoon Kasi, please find enclosed our revised version of the manuscript entitled "**Conservative management of malignant gastric outlet obstruction syndrome - evidence based evaluation of EUS-guided gastroentero-anastomosis**" for consideration for publication on the World Journal of Gastrointestinal Oncology.

We sincerely thank the Editor and Reviewers for their suggestions and the opportunity of resubmitting a revised version of our manuscript.

Please find enclosed a point-by-point response to reviewers in which are underlined all the changes apported in the original version of the manuscript.

All the authors of this manuscript have made a substantial contribution to the material and information submitted for publication and approved the paper submitted. Neither the manuscript, nor portions of the manuscript, have been already published, nor are they under consideration for publication by another journal.

Thank you for your time in considering this revised paper.

Yours sincerely,

Andrea Lisotti, on behalf of all co-authors

RESPONSE TO EDITORIAL OFFICE

Science editor: Please keep the reasonable self-citations (i.e. those that are most closely related to the topic of the manuscript) and remove all other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated.

Re: We thank Science editor for the precious suggestion regarding self-citation rate. We deleted the less relevant references and reduced the self-citation rate accordingly. The entire reference list was then revised, taking into account also Reviewer #3 suggestions.

RESPONSE TO REVIEWERS

Reviewer #1: Scientific Quality: Grade A (Excellent); Language Quality: Grade A (Priority publishing); Conclusion: Accept (High priority). Specific Comments to Authors: This paper is a review of EUS-GE. The authors provide an introduction to the etiology of GOO, various techniques for EUG-GE, and a detailed review of treatment outcomes. Due to the latest treatment, there is no similar treatise. These contents are detailed, well summarized and useful to the reader.

Re: We sincerely thank the reviewer for the positive global evaluation; we tried to make the suggested changes in order to increase manuscript's overall quality.

Minor issues

Reviewer #1: Citations are required for the following texts; high-dose proton pump inhibitors therapy is suggested to decrease the volume of gastric secretions and associated inflammation.

Re: We agree with reviewer #1. We added the following reference: **Bell RCW.** Management of regurgitation in patients with gastroesophageal reflux disease. *Curr Opin Gastroenterol.* 2020 Jul;36(4):336-343. (PMID: 32487853 doi: 10.1097/MOG.0000000000000649)

Reviewer #1: Many EUS-related procedures are performed under intravenous anesthesia without airway intubation. Is airway intubation mandatory for EUS-GE? Please describe the reason you recommend. EUS-GE must be performed under general anesthesia, with airways intubation.

Re: In patients with presumed gastric stasis and presence of ingest in gastric lumen, it is mandatory to prevent aspiration. We consider airway intubation a basic safety issue in this field. We clarified this issue in the text.

Reviewer #1: Patients with GOO often develop severe gastric distension. Is nasogastric tube placement necessary as a pretreatment for EUS-GE?

Re: As stated before, we consider mandatory to prevent ingest or fluid aspiration; therefore, we strongly suggest nasogastric tube placement the days before EUS-GE, in case of gastric distension. We clarified this issue in the text.

Reviewer #2: Scientific Quality: Grade D (Fair); Language Quality: Grade B (Minor language polishing); Conclusion: Major revision. Specific Comments to Authors: Comments to the Author: The purpose of this work, entitled 'Conservative management of malignant gastric outlet obstruction syndrome - evidence based evaluation of EUS-guided gastroentero-anastomosis' is to review the etiologies of gastric outlet obstruction (GOO), an extensive description of the Endoscopic ultrasound-guided gastroenterostomy technique, and comparison with surgical bypass and enteral stenting. Authors concludes that EUS-GE 'has the advantage of being as minimally invasive as enteral stent placements, and of guaranteeing long-term results similar to those of surgery'. On the whole, the paper is well-written but some several issues must be commented.

Re: We sincerely thank the reviewer for the detailed assessment of our manuscript; we hope to deal with all the precious suggestions Reviewer #2 made.

Reviewer #2: The first part of the paper is fully dedicated to GOO (epidemiology, clinical aspects, management). Maybe it should be more summarized.

Re: We agree with Reviewer #2 that the first part of the manuscript is quite redundant. We tried to shorten the text and summarized findings.

Reviewer #2: EUS-GE: different variant of techniques are explained, but some important technical aspects are missing. * How to finds the Treitz area, and to select correctly the proximal jejunum?

Re: We thank Reviewer #2 for the concise but detailed description he provided. We added in the text the following sentence. "In patients with no previous abdominal surgery, after the identification of the mesenteric vessels, the echoendoscope should be turned (either clockwise or anticlockwise) to find the Treitz area and first proximal jejunal limb."

Reviewer #2: EUS-GE: different variant of techniques are explained, but some important technical aspects are missing. * How to perform the puncture (pure cute, high power > 140W).?

Re: The use of a pure cut setting with high power is suggested. In our experience, using the ERBE Vio3 electro-surgical unit, we use AutoCut effect 5 power 100 W. We detailed this topic in the text.

Reviewer #2: EUS-GE: different variant of techniques are explained, but some important technical aspects are missing. * In case of misdeployment or maldeployment of LAMS, which rescue options should be take in mind, or recommended?

Re: We added this paragraph.

Misdeployment

In case of LAMS misdeployment, the use of a preloaded guidewire could provide an effective access to the punctured limb. However, in case of a "proximally misdeployed" stent (with the distal flange into the peritoneum and the proximal flange in the stomach), we suggest removing the stent and restarting the procedure. The site of puncture could be closed with through-the-scope clip. In our experience, no complication has occurred. In case of a "distally misdeployed" stent (with the distal flange into the jejunal limb and the proximal flange into the peritoneum), the presence of a preloaded guidewire could be useful for a salvage procedure; on the other hand, peritoneal exploration (either with laparoscopy or with a NOTES procedure) seems required to rescue the EUS-GE.

Reviewer #2: EUS-GE: different variant of techniques are explained, but some important technical aspects are missing. * All the paper is focused on one unique LAMS (AXIOS), but other commercial LAMS are disposable.

Re: We amended the text thanks to the precious suggestion. We mentioned also the recently commercialized Hot-SPAXUS stent manufactured by Taewoong Medical.

Reviewer #2: Which information is known about LAMS removal or timing to check the stent? Recently, some complications related to a long-term of LAMS placement, as perforation due the traumatic hitting of distal flange against the contralateral jejunal wall. Please state your opinion based in this case series reported.

Re: Since no large study reporting EUS-GE long-term outcomes is available, there is no robust evidence in the field. Long term complications due to LAMS traumatism on the contralateral wall could be hypothesized, based on pancreatic fluid collection drainage experience. Reviewer #2 underlined an unsolved issue in EUS-GE patients management. We added in the text a brief paragraph accordingly.

In our humble experience, no long-term

Reviewer #2: Regarding the limitation 'The main limitation of EUS-GE is the position of the target small bowel loop; if the latter is too distant from the gastric wall, it may not be punctured under EUS-view' - it only should occur in case of post-surgical scenarios. In cases with no previous surgeries of the upper GI tract, following the mesenteric vessels from the gastric cavity and turning clockwise/anticlockwise, the Treitz area and first proximal jejunal loop is easily identified. And 'Moreover, it is a safe puncture is not feasible if the target loop is not enough distended; sometimes, despite a large amount of water injected into the small bowel, the target loop collapses because of peristaltic movements pushing water forward', this may be prevented administering a spasmolytic.

Re: We thank Reviewer #2 for the precious technical suggestion in the field; based on a personal experience, it is not always easy to correctly identify the target loop. We modified the text, including these precious suggestions. We rephrased: "The main limitation of EUS-GE is the position of the target small bowel loop; if the latter is too distant from the gastric wall, it may not be punctured under EUS-view. However, the above-described correct identification of the Treitz's area from the mesenteric vessels could reduce this issue in patients with not surgically modified anatomy. Moreover, it is a safe puncture is not feasible if the target loop is not enough distended; sometimes, despite a large amount of water injected into the small bowel, the target loop collapses because of peristaltic movements pushing water forward. Once again, the use of spasmolytic agents could represent a key factor to achieve the goal."

Reviewer #2: This statement as conclusion. 'EUS-GE has the advantage of being minimal invasive as an endoscopic procedure, but with long-lasting effects similar to those achieved by SGJ', up to date it is not prudent. Limited scientific evidence based mainly in retrospective series, not guarantee or recommend this assertion.

Re: We agree with Reviewer #2 that robust data corroborating this finding are lacking; however, a recent American Gastroenterology Association statement proposed a similar conclusion. We slightly modified the conclusion, underlying the need of evidence-based data on long-term outcomes. "EUS-GE has the advantage of being minimal invasive as an endoscopic procedure; weak evidence suggest that EUS-GE could provide long-lasting effects with lower recurrence rates^[44]. Large high-quality evidence are still required in this field."

Reviewer #3: Scientific Quality: Grade C (Good); Language Quality: Grade C (A great deal of language polishing); Conclusion: Major revision.

Re: We sincerely thank the reviewer for the detailed assessment of our manuscript; we hope to deal with all the precious suggestions Reviewer #3 made.

Reviewer #3: 3rd paragraph in “Motility disorders” part in “ETIOLOGY” section, Authors write “Moreover, alteration of gastric motility could complicate thoracic and abdominal surgery by disruption of the vagus nerve..”. What does this sentence mean? Are thoracic and abdominal surgery the causes of gastric dysmotility? This sentence is likely to represent the opposite meaning.

Re: We thank Reviewer #3; we have rephrased the sentence in order to make it clearer. Vagus nerve could be damaged after surgery; this damage could result in gastric dysmotility. We clarified the text.

Reviewer #3: 3rd paragraph in “Mechanical obstruction” part in “ETIOLOGY” section, Authors write “However, this figure is probably lower..”. The figure is lower than what? Please indicate an object for comparison.

Re: As requested by Reviewer #2, introduction was shortened and the misspelled sentence was deleted.

Reviewer #3: 5th paragraph in “Mechanical obstruction” part in “ETIOLOGY” section, The term of “Carcinoids” is incorrect. It should be revised as “neuroendocrine neoplasms”. Table 1 also should be revised.

Re: We totally agree; we substituted the term “carcinoids” with “NENs” accordingly.

Reviewer #3: 3rd paragraph in “CLINICAL MANIFESTATIONS AND DIAGNOSIS” section, Authors write “gastric lumen full of ingests..”. “ingest” is an uncountable noun, isn’t it?

Re: We congratulate Reviewer #3 for the excellent language skills; this insightful suggestion has been taken into account to increase the manuscript quality.

Reviewer #3: 4th paragraph in “CLINICAL MANIFESTATIONS AND DIAGNOSIS” section, “may be difficult to diagnose with endoscopic biopsies” should be revised as “..difficult to be diagnosed..”.

Re: We congratulate Reviewer #3 for the excellent language skills; this insightful suggestion has been taken into account to increase the manuscript quality.

Reviewer #3: The heading of “MANGEMENT OF MALIGNANT GOO” has a spelling error. “MANAGEMENT” is correct.

Re: We checked and corrected this typo.

Reviewer #3: 2nd paragraph in “EUS-GUIDED GASTROENTEROSTOMY (EUS-GE)” section, Can LAMS really be used for EUS-guided hepaticogastrostomy (EUS-HGS)? I think LAMS cannot be used in EUS-HGS because of intervening liver parenchyma between intrahepatic bile duct and stomach. On the contrary, LAMS is useful for EUS-guided choledochoduodenostomy (EUS-CDS) gallbladder drainage.

Re: Of course, LAMS cannot be used for EUS-HGS. Dedicated biliary stents (such as the “Giobor” stent form Taewong) are specifically designed for this indication, but they cannot be defined LAMS. We thank Reviewer #3 for the identification of this incorrect statement. We amended the text.

Reviewer #3: 4th paragraph in “EUS-GUIDED GASTROENTEROSTOMY (EUS-GE)” section, “peri-gastric varices” is incorrect in spelling. Please revised as “peri-gastric”.

Re: We checked and corrected this typo.

Reviewer #3: 3rd paragraph in “Pre-operative management” part in “EUS-GUIDED GASTROENTEROSTOMY (EUS-GE)” section, Authors write “large amount of ingests”. “ingest” is an uncountable noun, isn’t it?

Re: We checked and corrected this typo.

Reviewer #3: In “Anterograde EUS-GE-the “rendezvous” method” in “Techniques” part, Authors write “The guidewire can be captured in the duodenum or proximal jejunum by coiling of the second wire within the dilatation balloon itself..”. What is “the second” wire?

Re: We totally agree that the description of all the EUS-GE techniques are unclear. We failed to reach a clear and concise depict. We rephrased all the chapter and make it shorter and schematic.

Reviewer #3: In “Anterograde EUS-GE-the “rendezvous” method” in “Techniques” part, Reference 34, which was written by Kawakubo et al. is inadequate. This paper is describing EUS-RV for biliary drainage.

Re: We thank Reviewer #3. All the reference list was updated thank to Editor’s and Reviewers’ suggestion.

Reviewer #3: In “Anterograde direct method” part, This part is hard to be understood. Authors mention at first “This technique is helpful in presence of a complete luminal obstruction not transitable with an endoscope or a guidewire.” However, at last, authors say “it is almost impossible to fill a duodenal or jejunal loop if the stenosis is so tight to prevent the passing of a guidewire”. It is likely to be confused. How can the jejunum/duodenum beyond the stricture be dilated? Please mention precisely how to inject the solution into this area.

Re: We totally agree that the description of all the EUS-GE techniques are unclear. We failed to reach a clear and concise depict. We rephrased all the chapter and make it shorter and schematic.

Reviewer #3: In “EUS-guided double balloon-occluded gastrojejunostomy bypass (EPASS)” part, Text in this part is also confused. Do you understand this technique precisely? A dedicated double-balloon tube can be inserted over the 0.025-inch guidewire. A preloaded 0.089-inch guidewire and/or over-tube can help the balloon tube advancement avoiding loop formation in the gastric fornix. Please read Prof. Itoi’s article attentively.

Re: We totally agree that the description of all the EUS-GE techniques are unclear. We failed to reach a clear and concise depict. We rephrased all the chapter and make it shorter and schematic.

Reviewer #3: In “Outcomes of EUS-GE for malignant GOO” part, “Malignant GOO may benefit of palliative therapy based on..” What does it mean? Do you mean “Malignant GOO may benefit from palliative therapy based on..”?

Re: We rephrased the sentence in order to clarify it.

Reviewer #3: In “Outcomes of EUS-GE for malignant GOO” part, “Since the first description of EUS-GE in a pig model in 2002 [9]..”. Reference 9 is incorrect. Please revise.

Re: We thank Reviewer #3. Several changes in reference list caused this error. Of course, 2002 description refers to Fritscher-Ravens A et al. *Gastrointest Endosc*. All the reference list was updated thank to Editor's and Reviewers' suggestion.

Reviewer #3: In "Outcomes of EUS-GE for malignant GOO" part, Authors write various techniques about EUS-GE, such as direct EUS-GE, the balloon-assisted technique, hybrid rendez-vous, EPASS technique, the double balloon-assisted EUS-GE. These term are different from those which described in "Techniques" part. So it is be confused. What is the direct EUS-GE? Authors used the word "direct" in "Direct EUS-GE-traditional/downstream method" and "Antegrade direct method" in "Techniques" part. Moreover, what is the double balloon-assisted EUS-GE? Is this different from E-PASS? Please explain.

Re: We thank Reviewer #3. We rephrased and clarified these issues, in order to make the text more understandable. Since all techniques are summarized in table 3, we deleted most of the description to make the text more readable and fluent.

Reviewer #3: In the last paragraph in "Outcomes of EUS-GE for malignant GOO" part, Authors write about the long-term outcome of EUS-GE, however, long-term outcome is not described actually; only success rate and AEs were noted. Why not?

Re: As recently stated in an American Gastroenterology Association position paper [clin Gastroenterol Hepato], EUS-GE is reported to present with fewer symptoms recurrence and need for reintervention compared to enteral stenting. These findings were extrapolated from dr. Chen et al.'s manuscript [44] published on *Surgical Endoscopy* in 2017, where the Authors observed "Symptom recurrence and need for re-intervention, however, was significantly lower in the EUS-GE group (4.0 vs. 28.6%, (p = 0.015)."

However, we agree that a single retrospective study provides weak evidence in the field and we rephrased the conclusions accordingly.

Reviewer #3: In 3rd paragraph in "Comparison of EUS-GE with enteral stenting" part, "EUS-GE not only showed a statistically significant better initial clinical success (95.8% vs 76.3%, P=0.042) and a lower rate of procedure failure requiring reintervention (32% vs 8.3%, P=0.021), but also a lower incidence of AEs compared to enteral SEMS placement (40.2% vs 20.8%)." The rate of procedure failure and AEs of EUS-GE and enteral stenting were reversed?

Re: Reviewer #3 did a remarkable check of our manuscript. All the Authors sincerely thank him/her for the precious support.

Reviewer #3: In 3rd paragraph in "Conclusion" section, "Moreover, it is a safe puncture is not feasible.." is likely to be grammatically incorrect.

Re: We checked and rephrased the entire sentence accordingly.