

October 12, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: **19485-Revised manuscript**).

Title: Approach to the endoscopic resection of duodenal lesions

Authors: Jonathan P. Gaspar, MD, Edward B. Stelow, MD, Andrew Y. Wang, MD

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 19485

The manuscript has been improved according to the suggestions of reviewers:

1 Revision has been made according to the reviewers' suggestions (whenever possible).

(1) Comments from reviewer 00030598:

My comments are as follows: In this review paper, Gaspar JP and Wang AY provide updated features regarding the types of duodenal lesions, endoscopic assessment and the role of endoscopic ultrasound in duodenal lesion resection that may help physicians or endoscopists to appropriately manage these duodenal lesions.

Authors' response: We appreciate this reviewer's comment and assessment of our paper.

This is a well-written paper and there seems to be no serious criticism regarding the methodology but the authors need to make a caution in some suggestions. There are limited data for high-definition narrow-band imaging or chromoendoscopy to evaluate the mucosal pit of duodenum to differentiate neoplastic lesions. As the authors mentioned the data for NBI is not as robust for duodenal neoplasia and the "Kudo" pit pattern had not been well described in duodenum. This should be mentioned in the discussion.

Authors' response: We appreciate this reviewer's wisdom regarding being cautious with some of our suggestions. As the reviewer noticed, we did disclose the issue of limited data being available regarding the use of NBI and the "Kudo" pit pattern in the duodenum to evaluate for neoplasia. We have reiterated this important point later in our discussion about "Post-resection endoscopic surveillance."

In the conclusion section, the author mentioned "Early adenocarcinomas that invade only the superficial duodenal submucosa could potentially be treated by endoscopic

resection, as in other parts of the luminal GI tract, in the proper clinical context.” How deep of the submucosal extension is allowed? Could you provide sufficient reference to support this point of view?

Authors’ response: Thank you for this comment. We have modified this statement and are trying to make it more clear that we are not generally recommending resection of submucosally-invasive duodenal adenocarcinomas. We have added a reference in support of this section.

This is a comprehensive review of the endoscopic assessment for duodenal lesions. It is helpful from novice level to competence level of therapeutic endoscopy. In my opinion, I suggest to remove the “Role of endoscopic ultrasound in duodenal lesion resection” before the “Endoscopic assessment”

Authors’ response: We appreciate this reviewer’s comments and suggestions. However, given the conflicting suggestion of the other reviewer below (comment #5), we have chosen to leave this section in place, as it is.

In “Bruenner’s gland adenoma or hamartomas” section, please clarify what kind of endoscopic removal is considered.

Authors’ response: Thank you for this suggestion. We have elaborated on how Bruenner’s gland tumors could possibly be removed, depending on their morphology.

In “Solitary Peutz-Jeghers polyp” section, in many instances Peutz-Jeghers polyp do not present in isolation. Is a more extensive workup needed to exclude Peutz-Jeghers syndrome?

Authors’ response: We appreciate this comment, and we have suggested evaluation to exclude Peutz-Jeghers syndrome in situations where a solitary Peutz-Jeghers polyp is suspected.

(2) Comments from reviewer 00029045:

This is a review reporting commonly encountered duodenal lesions and the approach to the endoscopic resection of these lesions. I have the following comments on this paper:

1. Distinction between the terms polyps and lesions is unclear. I believe that Au used the term “lesions” for sub-epithelial neoplasms that generally appear as polypoid lesions, however. Probably the term duodenal neoplasms could be preferred.

Authors’ response: We appreciate this reviewer’s careful reading of our manuscript and suggestion. We chose the term “lesion,” which is used in our title, as not all of

these lesions are polyps (e.g., subepithelial lesions) and not all of these lesions are neoplasms (such as Bruenner's gland tumors or lipomas). Polyps are typically sessile or pedunculated lesions (and can be neoplastic or non-neoplastic). Given the variety of findings that we are describing, we believe that use of the term "lesion" as a general term is very applicable.

2. I believe that a Table summarizing Types of duodenal lesions should be useful.

Authors' response: Thank you for this very insightful comment. We agree with the reviewer and have added a table (Table 1) that describes the types and characteristics of various duodenal lesions that can be encountered on upper endoscopy, which we hope will be helpful to the reader.

3. Figures are nice. Histology of different lesions is mandatory.

Authors' response: We are pleased that the reviewer likes our figures. We had considered including histology of different lesions; however, the title and the intent of our manuscript is the "Approach to the endoscopic resection of duodenal lesions." As such, our focus was on the endoscopic appearance of duodenal lesions as well as on the inclusion of images depicting the resection of duodenal lesions. As our manuscript includes many different duodenal lesions, we believe that by trying to cover the histopathology of all of these lesions would be very difficult to do. Lastly, as we are advanced endoscopists, our expertise is on the endoscopic appearance and approach to the resection of duodenal lesions, and not on the histopathological diagnosis of these lesions.

To do our best to address this reviewer's concerns, we have added a co-author, Dr. Edward B. Stelow, who is an expert GI pathologist at our institution, who has helped us to get several examples of histopathology that illustrate some of the duodenal lesions that we describe in this manuscript.

Furthermore, we have included the excellent reference by Bal et al, entitled "Primary duodenal neoplasms: a retrospective clinico-pathological analysis," which was published in the World J Gastroenterol in 2007. This excellent manuscript (which was recommended by this reviewer later in comment #7) has outstanding photomicrographs of histology from duodenal lesions.

4. Treatment options should be better related to non-ampullary and ampullary neoplasms.

Authors' response: We have clarified treatment options as they pertain to non-ampullary and ampullary mucosally-based lesions (typically adenomas) by the addition of Table 2.

5. Role of EUS could be better reported previous of endoscopic resection techniques.

Authors' response: We appreciate this reviewer's comments and suggestions. However, given the conflicting suggestion of the other reviewer (who suggested that we remove this section altogether), we have chosen to leave this section in place, as it is. Clearly, there is some variability among experts regarding the use of EUS in the management of certain duodenal lesions.

6. A table summarizing outcomes of the literature of the different techniques should be included.

Authors' response: We appreciate this reviewer's suggestion. We have also endeavored to address this suggestion by the addition of Table 2 (also mentioned above). In Table 2 we have stratified different methods of endoscopic resection for mucosally-based duodenal lesions (which are typically adenomas) by the appropriate size, by type of lesion (non-ampullary vs. ampullary), by the ability to perform piecemeal resection, and by the (subjective) degree of difficulty. As there are very few prospective (even fewer prospective comparative) studies on the outcomes by resection method, it would be difficult to compare efficacies (of say cap-EMR to cap-band-EMR to conventional EMR to underwater EMR). In fact, a recent publication in *WJG* in 2015 by Marques et al (that included Naohisa Yahagi, a noted expert in the field of ESD) concluded that the present "literature is insufficient to draw definitive conclusions about duodenal EMR and ESD. Thus, we did not list efficacies for different resection techniques in this table as comparisons of retrospective data could be biased.

7. Please add the following references: 1. Bal A, Joshi K, Vaiphei K, Wig JD., Primary duodenal neoplasms: a retrospective clinico-pathological analysis. *World J Gastroenterol.* 2007 Feb 21;13(7):1108-11. 2. Marques J, Baldaque-Silva F, Pereira P, Arnelo U, Yahagi N, Macedo G. Endoscopic mucosal resection and endoscopic submucosal dissection in the treatment of sporadic nonampullary duodenal adenomatous polyps. *World J Gastrointest Endosc.* 2015 Jun 25;7(7):720-7. doi: 10.4253/wjge.v7.i7.720. Review. PubMed PMID: 26140099; PubMed Central PMCID: PMC4482831. 3. De Palma GD. Endoscopic papillectomy: indications, techniques, and results. *World J Gastroenterol.* 2014 Feb 14;20(6):1537-43. doi: 10.3748/wjg.v20.i6.1537. Review. PubMed PMID: 24587629; PubMed Central PMCID: PMC3925862. 4. De Palma GD, Masone S, Siciliano S, Maione F, Falletti J, Mansueto G, De Rosa G, Persico G. Endocrine carcinoma of the major papilla: report of two cases and review of the literature. *Surg Oncol.* 2010 Dec;19(4):235-42. doi: 10.1016/j.suronc.2009.06.003. Epub 2009 Jul 7. Review. PubMed PMID: 19586767. 5. De Palma GD, Luglio G, Maione F, Esposito D, Siciliano S, Gennarelli N, Cassese G, Persico M, Forestieri P. Endoscopic snare papillectomy: a single institutional experience of a standardized technique. A retrospective cohort study. *Int J Surg.* 2015 Jan;13:180-3. doi: 10.1016/j.ijsu.2014.11.045. Epub 2014 Dec 10. PubMed PMID: 25498490.

Authors' response: We very much appreciate this reviewer alerting us to these very

important publications. We have added each of these publications to our manuscripts and believe that these new references have significantly strengthened our review.

2 References were updated and minor edits to the text were made

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

Sincerely yours,

Jonathan P. Gaspar MD
Edward B. Stelow, MD
Andrew Y. Wang, MD, FACC, FASGE