Peer Review File

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Reviewer A

Friedel present a review on the diagnosis and treatment of Barrett´s esophagus.

The review is well written with interesting concepts.

I suggest 2 points that must be addressed to improve the manuscript:

1) There is no real "methods". Practically all the text is under the heading "methods".

Reply: Yes, I agree with this observation. I implemented changes as per the suggestion.

2) There is no mention on the role of PPI and antireflux surgery in the prevention of BE progression.

Reply: I have added a paragraph in reference to these topics.

Reviewer B

Personally, I do not think this manuscript addressed the title of the paper. This manuscript provide a very brief overview of screening, surveillance, pathology, alternative screening strategies and treatment (resection and ablation). Theses are not really in line with the unmet needs of Barrett's.

Breaking the title into 2 parts, in my opinion, the unmet need for diagnosis is:

1) Is screening for BE even effective? There are a lack of studies out there on a screening cohort of patients with reflux.

2) Does screening for BE lead to improved esophageal mortality long term? We do not know this. But certainly, the authors should discuss more critically that screening and subsequent surveillance could lead to detection of earlier stage esophageal cancers.

3) Is screening patients with reflux the right approach? A recent study by Eluri et al in the Am J gastro 2023 and a subsequent editorial by Joel Rubenstein suggested that screening patients

who responds to PPI probably provides better diagnostic yield that screening those who are taking PPI, because those who take PPI who responds are probably more likely to have true acid reflux.

Reply: In the reviewer preface, several issues were raised. I appreciate the comments about the title but I prefer to keep it as is. Screening for Barrett's has not been clearly shown to be efficacious. I try to bring this out in the manuscript. This is topical since the Spechler/El-Serag AJG (April) editorial states this. There is only limited data for lesser EAC mortality (Codipilly) in those in a BE screening cohort and I mentioned this. I read the Eluri/Rubenstein works after my submission. I feel that using PPI response to determine screening for BE is suspect and will exclude appropriate subjects for screening. It is accepted that Barrett's epithelium is less sensitive than the normal squamous epithelium with lesser tendency for heartburn.

The unmet need for surveillance include:

1) Discuss the BOSS trial study and the anticipated results and perhaps, some of the flaws in study design. The results are due to be released next year. This study will provide some evidence towards whether even surveillance of BE is the right approach.

Reply: I mentioned the BOSS trial.

2) Another unmet need for treatment is, can we endoscopically treat T1b lesions? The PREFER trial from Amsterdam would hopefully shed light on this. Some tertiary centres are even performing EMR as the definitive treatment for low risk T1b lesions (lack lymphovascular invasion, well differentiated). In fact, the PREFER trial is also investigating whether higher risk T1b lesions can be treated endoscopically.

Reply: I mentioned the PREFER trial.

3) Is RFA the best form of treatment? We don't know. Cryotherapy and APC are alternatives but given the solid evidence for RFA, it makes it difficult to conduct and trials which could have a head-to-head comparison with RFA.

The above are probably more important points which addresses the title of the unmet needs in BE treatment and diagnosis.

Personally, the section of screening deficiency can remain, but to critically discussed the points above.

The section of screening and surveillance is nothing new and can probably be removed.

The section on Pathology is also of low relevance and can be removed. If the author decide to retain this section, I would expand more on the use of p53, WATS and tissue Cypher. Currently, the summary of the evidence for these technologies are too brief (only 1-2 sentences).

The section on alternative screening technologies can be retained, but only if more details about the different technologies can be expanded upon.

The section of resection and ablation can be removed. If planning to include a section on this, I would critically discuss the points above (unmet need for surveillance).

Additional points

Some of the references are old and are from narrative reviews, which are not ideal. For example, reference 3 is extracted from a narrative review and it would be better if the author could cite proper data. Similarly, Reference 4 is from 1996, and clearly does not reflect current costs.

Sentence 14-15 which stated that esophagectomy as an option for HGD. This is not current practice and almost every centers would recommend an ablation. The citation 9 is clearly an out of date citation stemming from 2011. There are many other later recommendation which should have been cited here instead, ie ACG 2022 guidelines, ESGE or even the BSG guidelines. None of these guidelines recommend oesophagectomy for HGD.

Reply: RFA is the gold standard in Barrett's ablation in my opinion and I think that is the literature consensus. I perform RFA personally as well as liquid nitrogen and nitrous oxide balloon cryotherapy. APC has been around for years and has never been considered mainstream in Barrett's ablation and arguably somewhat dangerous. In my opinion liquid nitrogen application is more involved than RFA. This and the present need for the nasogastric tube which hinders precise application makes liquid nitrogen less desirable. Cryo- balloon literature has been performed mostly at university centers and it is unclear if this data is generally applicable. Currently the balloon can treat only small areas at a time. I agree we need more comparative analysis but I don't think that's forthcoming anytime soon.

I respectively will keep the sections that this reviewer wanted truncated or removed. I think they are necessary for a narrative review of this topic. I did expand however on the areas that were suggested including pathology and alternative therapy. I replaced the two references that was somewhat dated. I agree esophagectomy is a last resort for high-grade dysplasia Barrett's subjects. However, there are instances where this may be an option. We have a multidisciplinary conference at my institution and occasionally the consensus is to offer surgery as an option. This

would be typically in a younger patient perhaps with a family history of EAC and with extensive multifocal and refractory BE dysplasia.

Reviewer C

This manuscript is a good summary of screening, diagnosis, endoscopic treatment, and prospects for Barrett's esophagus (BE). However, in spite of the review article about BE, this article is far too much regional. Please consider revising them.

Major comments

1. Page 2, lines 4-5, the author stated that BE rises from esophageal squamous mucosa, low-grade dysplasia arises, and finally high-grade dysplasia or EAC arises, but is this true? Since many EAC cases do not have evidence of IM, which is required for the diagnosis of BE in many guidelines, there is an ongoing debate as to whether the origin of EAC is really BE. The author needs to describe origin of EAC and BE in detail citing the latest reports. (e.g. [Science. 2021; 373: 760-767.])

Reply: I believe the consensus is that Barrett's esophagus emanates from intestinal metaplasia which is derived from squamous epithelium deleterious transformation. I am aware that a proportion of specimens from esophageal adenocarcinoma subjects does not reveal intestinal metaplasia/Barrett's esophagus. I mentioned this briefly and the implication would be that screening for and surveillance for Barrett's and surveillance in Barrett's is not worthwhile which would be a sobering conclusion and I don't think accepted at this point. I did mention briefly the concept above.

2. Page 2, lines 13-15, the author described BE and EAC risk factors. However, there is no mention of aging, the most well-known risk factor for both BE and EAC. A detailed discussion of risk factors would make the entire paper more persuasive when discussing the following paragraph about a screening of BE. The author should mention more about the risk factors of BE and EAC such as GERD, hiatal hernia, medications (PPI, NSAIDs, statin), bile acid, and Helicobacter pylori infection. If possible, it would be preferable if the BE and EAC could be listed separately in the table.

Reply: Age as a BE predisposing factor is elaborated upon. I listed the relevant predisposing and mitigating factors in a table. There is scant literature on PPI in terms of prevention of Barrett's and I mentioned briefly about PPI role in slowing Barrett's progression. There was an interesting hypothesis that PPI may actually promote Barrett's by changes in the bile salt pool. An UDCA/PPI study did not show any benefit for UDCA. There is limited data concerning the

protective effect of breast-feeding, hormone replacement therapy and oral contraceptives. There is also modest data on promoting BE via drugs that lower esophageal sphincter pressure. This would include particularly the xanthines. I did not think the supporting data was robust so I only listed aspirin/NSAID's and statins.

3. Like page 2 lines 13-15, page 4 lines 14-16, and page 5 lines 6-8, the author repeatedly uses the phrase "Guidelines ・・・". However, only one reference is cited in either paragraph. It is not seemed to be adequate for review article. The definitions of BE differ across various guidelines, readers are confused as to which guidelines the author is referring to. This is a very important point in describing BE. If you are writing a review article about BE, for either paragraph, please cite at least three unbiased regional guidelines for BE or EAC (e.g., U.K., U.S., EU, Asia-pacific, and Japan). Also, please describe the differences, if any, between each guideline.

Reply: The guidelines from the three American societies and the BSG are remarkably similar in terms of surveillance recommendations. I do not think it worthwhile to tease out differences between them. There is limited data from Asia perhaps reflecting lesser prevalence and less complicated Barrett's. One article suggested implementation of Barrett's screening guidelines in Japan. I added references for the different society guidelines.

4. Page 4, line 17, the author says "EMR is usually performed via band ligation". Is it really performed worldwide? To my knowledge, while several guidelines described the usefulness of EMR, few guidelines specify EMR with band ligation. Please reconsider this paragraph.

Reply: I modified my statement regarding the method of EMR. My impression in the U.S. is that band ligation is more prevalent but the literature for this is scant.

Minor comments

1. Many abbreviations are not defined when it first described. For example, BE, EAC, HGD, LGD, NDBE, GERD, IMEAC, GEJ, and so on. Please review all abbreviations again.

2. Page 1 line 11 "maanagement" may be misspelled. Please confirm.

3. Some references are missing the journal names. Correct references 38 and 47, and please confirm all references again.

Reply: I appreciate the minor comments and made the necessary changes and added a glossary that may be added at the editor discretion.