Peer Review File

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Reviewer A

The authors briefly reviewed general concepts before treatment and comprehensively reviewed therapeutic options. I have only one suggestion to improve the manuscript and minor comments:

Comment 1: The authors presented a very interesting flowchart on treatment options. I would like to learn from the authors if there is no role for antireflux surgery in patients with low grade dysplasia, especially in combination with endoscopic therapy
Reply 1: It has been stated and demonstrated in studies that antireflux surgery in combination with endoscopic therapy might prevent progression and possibly regression of dysplastic and metaplastic changes in the esophagus. However, such studies include small numbers of patients and short follow-up therefore was not able to address long-term success. Because this is still difficult to prove and the supporting evidence is inconclusive, further evaluation with larger controlled trials and longer-term follow-up is necessary to better define the success of this approach for preventing low-grade dysplasia's progression to esophageal cancer.

dos Santos RS, Bizekis C, Ebright M, *et al.* Radiofrequency ablation for Barrett's esophagus and low-grade dysplasia in combination with an antireflux procedure: A new paradigm. *The Journal of Thoracic and Cardiovascular Surgery*. 2010;139(3):713-716.

Reviewer B

I would like to thank the authors for their contribution to esophageal cancer treatment research. With interest I have read this manuscript which is overall complete, well-written, well-structured and clear.

Major comments:
Comment 2: There are numerous overview articles on the treatment of Barrett's. Could you perhaps add elements to make this review more unique? Should we use RFA, MPEC, APC, cryo or PDT in clinical practice? Do patient/endoscopic/histologic factors influence treatment options?
Reply 2:No response.

Minor comments:
Comment 3: Line 48: wouldn't "Epidemiology" be more suitable as the title for this paragraph?
Reply 3: I agree and will make this change.

Comment 4: Line 56: please use more recent references, including meta-analyses, to support the text on risk factors for BE. Optionally add the risk factors for progression of BE to esophageal adenocarcinoma.
Reply 4: In 2019, a systematic review and meta-analysis was performed to assess the correlation of

the risk of BE in the general population based on the number of risk factors while controlling for potential confounders. 49 studies through October 2018 were analyzed (307,273 individuals, 1,948 with BE). The results of the analysis revealed the prevalence of BE for several populations as: low-risk general population, .8%; GERD, 3%; GERD plus presence of any other risk factor, 12.2%; family history, 23.4%; age >50, 6.1%; obesity, 1.9%; and male sex, 6.8%. When controlling the study region, age, and gender in a meta-regression, there was a positive linear relationship between the number of risk factors and the prevalence of BE.

Qumseya BJ, Bukannan A, Gendy S, *et al.* Systematic review and meta-analysis of prevalence and risk factors for Barrett's esophagus. *Gastrointestinal Endoscopy*. 2019;90(5):707-717.

In another systematic review and meta-analysis performed in 2018, 20 studies (including 74,943 patients) were analyzed to detect the risk factors associated with the progression of BE with and without LGD to BE with HGD or EAC. They found that the risk factors for the progression of BE included increasing age, male sex, ever smoking, longer BE segment length, and LGD. Alcohol use and obesity was not associated with risk of progression. Therefore, they concluded that patients with these risk factors should undergo more intensive surveillance or endoscopic therapy.

Krishnamoorthi R, Singh S, Ragunathan K, *et al.* Factors Associated With Progression of Barrett's Esophagus: A Systematic Review and Meta-analysis. *Clinical Gastroenterology and Hepatology.* 2018;16(7):1046-1055

Comment 5: Line 77: there is no proof that the development of esophageal adenocarcinoma always follows the GERD - intestinal metaplasia – dysplasia sequence. Intestinal metaplasia is not always present in gross resection specimens (possibly due to, e.g. rapid transformation, tumor overgrowth, different histologic types). Please provide a more balanced elaboration on this matter using recent and valuable references.

Reply 5: Of the patients with GERD, about 10–15% will develop BE. The normal esophageal squamous mucosa transforms into simple columnar epithelium is provoked chronic injury from recurrent reflux. Studies have shown that the duration of reflux symptoms was an important factor for BE development. The damage that acid causes to the esophageal epithelium creates dilated intercellular spaces that causes an increase in the trans-epithelial permeability allowing for larger molecules to diffuse across. This exposes basal layer stem cells to reflux fluid that induces a cascade of events leading to cell edema and eventual cell death. Phenotypic transformation of squamous cells into columnar mucosal cells then occurs due to a combination of tissue reparative processes in the setting of an acidic environment. Two pathways exist for the transformation of columnar epithelium to BE, gastric differentiation or intestinal differentiation. Gastric differentiation consists of the formation of parietal cells within glands. Intestinal differentiation consists of the formation of goblet cells within the columnar epithelium that is induced by intestinalizing gene expression. Intestinal differentiation is unfavorable in comparison due to its capability of further progression to epithelial dysplasia and adenocarcinoma. With this information in mind, it is important to note that BE is the strongest predicting factor of EAC even though only a small percentage of patients with BE will develop cancer.

Schlottmann F, Molena D, Patti MG. Gastroesophageal reflux and Barrett's esophagus: a pathway to esophageal adenocarcinoma.

Comment 6: Line 81: I think a schematic figure of cells would be more informative to explain intestinal metaplasia and goblet cells than photos. If you want to include a macroscopic image, please use one that clearly shows the difference between squamous cell epithelium and salmon-colored mucosa and highlight the GEJ, circumferential, and maximum extent.
Reply 6: I will replace the gross image with this schematic figure.

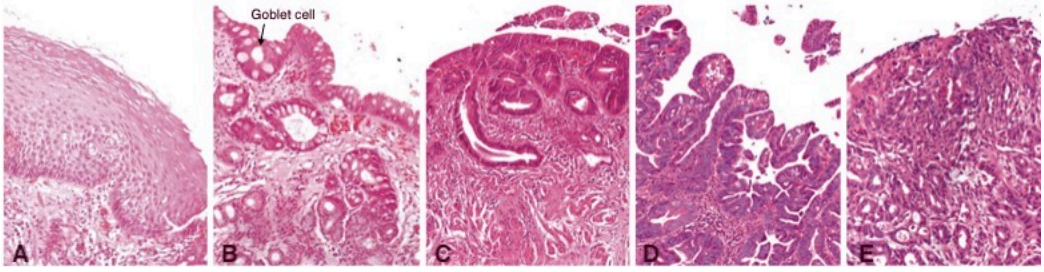

Figure 1: Transition of normal squamous epithelium to intestinal metaplasia, dysplasia and adenocarcinoma. A. normal stratified squamous epithelium. B. Barrett's esophagus without dysplasia with the presence of goblet cells. C. BE with low-grade dysplasia D. BE high-grade dysplasia. E. esophageal adenocarcinoma.

Ong CA, Lao-Sirieix P, Fitzgerald RC. Biomarkers in Barrett's esophagus and esophageal adenocarcinoma: predictors of progression and prognosis. *World J Gastroenterol*. 2010;16(45):5669-5681.

Comment 7: Line 204: could you report on the risk of progression to esophageal cancer after EMR instead of the mean remission time? Also, you are referring to a single-center retrospective study; could you refer to a prospective study? For example, the study by Pech et al. published in Gut in 2008.
Reply 7: In 2000, a prospective study was conducted on 64 patients with Barrett's esophagus (61patients with early carcinoma, 3 patients with high-grade dysplasia) to investigate the role of endoscopic mucosal resection. They were divided into 2 groups. Group A consisted of 35 patients that met the criteria for low risk (macroscopic types I, IIa, IIb, and IIc, lesion diameter up to 20 mm, mucosal lesion, histological grades G1 and G2 and/or high-grade dysplasia). Group B consisted of 29 patients that met the criteria for high risk. Complete remission was achieved in 97% of the patients in group A and in 59% in group B. In a mean follow-up of 1 year +/- 8 months, recurrent or metachronous carcinomas were found in 14%. Only one major complication occurred, spurting bleeding, that was managed endoscopically.

Ell C, May A, Gossner L, et al. Endoscopic mucosal resection of early cancer and high-grade dysplasia in Barrett's esophagus. Gastroenterology. 2000 Apr;118(4):670-7.

Comment 8: Line 293: but efficacy is very disappointing compared with RFA.
Reply 8: Agreed. There is a consecutive case series of 86 patients at a single center that was done to compare effectiveness, safety, and cost of photodynamic therapy (PDT) and radiofrequency ablation (RFA) in treatment of Barrett's dysplasia (BD). 33 patients with high-grade dysplasia (HGD) had treatment with porfimer sodium photosensitzer. 53 patients with BD (47 with LGD, 6

with HGD) had RFA. The complete histological resolution response of BD was 54.5% with PDT versus 88.7% with RFA. They concluded that RFA had higher rate of complete histological resolution response without any serious adverse events and it was also less costly than PDT for endoscopic treatment of BD.

Ertan A, Zaheer I, Correa AM, *et al*. Photodynamic therapy vs radiofrequency ablation for Barrett's dysplasia: efficacy, safety and cost-comparison. *World J Gastroenterol.* 2013;19(41):7106-7113.

Do you think it would be helpful to include this study for a comparison view of the two treatments?

Reviewer C

Comment 9: Result information should be described in the Abstract.
Reply 9: I'm not clear on what result information you are referring to? I included the types of studies in my methods in the abstract section.

Comment 10: Discussion section might be too short.
Reply 10: Although there is a strong association between GERD and BE, its development into cancer is a rare dysplastic process that is not completely understood. Nonetheless, surveillance and treatment early on is imperative to preclude this from occurring. Such methods include PPIs, endoscopic mucosal resection, endoscopic submucosal dissection, radiofrequency ablation, multipolar electrocoagulation, argon plasma coagulation, cryotherapy, photodynamic therapy, and esophagectomy. Every patient is unique in not only the pathology that leads to their diagnosis, but how they will respond to the treatment they undergo. Careful evaluation of dysplastic mucosa and management with one of the vast treatment modalities that are available is fundamental in mitigating its potential to become cancer.
