Peer Review File

Article Information: https://dx.doi.org/10.21037/jgo-21-117

Reviewer A

Comment 1: This review manuscript was covered with almost all category on Barrett's esophagus.
Reply 1: Thank you for taking the time to provide a thoughtful review of our manuscript and for your kind words regarding the breadth of our review.
Changes in the text: N/A

Comment 2: However, important factor is early detection and therapy for early stage.
Reply 2: We completely agree. Early detection and therapy for these indications are incredibly important and therefore we have added the topics you suggested we cover below.
Changes in the text 2: We have added a new section on the topics you suggested. This new section can be found in section 7 titled "Imaging for Early Detection of Barrett's Carcinogenesis" (Lines 523 – 551).

Comment 3: It is not enough how to detect early stage of BEA, for example: NBI, Magnified NBI, acetic acid sprayed endoscopy.
Reply 3: Thank you for noticing that we inadvertently omitted all of these further detection modalities. The various different forms of early detection modalities via gross inspection of diseased tissue are very important topics to discuss in this review. All of these sections you have suggested have been added to this manuscript.
Changes in text 3: We have added a new section called "Imaging for Early Detection of Barrett's Carcinogenesis" with seven subsections discussing these various screening modalities. This new section can be found in section 7, subsections I-VI.

Comment 4: Please add the references about early detection modalities.
Reply 4: Thank you for this suggestion to expand on adding references about the various early detection techniques.
Changes in text 4: We have added 9 new references to this new section on early detection modalities (Page 17-18, Lines 590-637).

Reviewer B

The authors of the study reviewed current methods of BE monitoring and therapeutic strategies for patients who have progressed to cancer. Novel diagnostic tools (serum markers, cytology, genomics, transcriptomics, etc.) are comprehensively described. This literature review is well-written and address a relevant and rapidly growing public health concern.
Thank you for taking the time to provide a thoughtful review of our manuscript and for your kind words regarding the breadth of our review. We have addressed your comments and suggested revisions below – all of which we thought were pertinent to include in our review.

Comment 1: A brief section regarding pathophysiology of BE in GERD patients is needed (molecular pathway by which the normal squamous mucosa of the distal esophagus is transformed into a columnar mucosa / stem cells that give rise to BE).

Response 1: Thank you for the suggestion, this information was lacking in the original submission and is definitely important to mention to provide a holistic review of disease progression!

Changes in the text 1: We have included a new section, *Section 4: Pathophysiology of Malignant Transformation of Normal Esophageal Epithelium* (pages 6-7, lines 199-240), that provides hypotheses for cell transformation based off of marker and cellular pathway trends. We have also included information about changes in the microenvironment of BE tissue as compared to normal esophageal tissue with regards to immune cell activity and microorganism presence.

Comment 2: Section 4. Tissue retrieval techniques. Routine endoscopies. The authors quote reference 20 (a review from 2012) many times. For instance: "If high-grade dysplasia is diagnosed, then the recommendation is the patient should be screened every 3 months". This is outdated. The authors should follow instead the ACG clinical guideline for diagnosis and management of Barrett's esophagus (Shaheen NJ).

Response 2: This is now Section 5, and we have updated this information with additional, more recent references and have fully described the ACG guidelines for routine surveillance or therapeutic intervention recommendations for BE by Shaheen, *et al*.

Changes in the text 2: We added 6 more recent peer-reviewed papers as references to this section and added the ACG guidelines by Shaeen, *et al* have been added to this section (Section 5, Subsection I) to make this part of the manuscript better reflect the current standard of care for BE monitoring cadences and subsequent management protocols.

Comment 3: Novel endoscopic ablation therapies for BE should be included in the review.

Response 3: We agree, including endoscopic ablation therapies would provide more information to readers and is pertinent to this manuscript.

Changes in the text 3: We have added an ablation techniques section discussing cryoablation and radiofrequency under Section 8, lines 640-653.

Comment 4: There is no mention of the role of anti-reflux in patients with BE. This is a very controversial topic that should also be discussed.

Response 4: Thank you for this suggestion. Anti-reflux surgery is a relevant and controversial area that would provide valuable perspective to the paper's subject matter.

Changes in the text 4: We have added a subsection within the Therapy section to state and describe the role of anti-reflux surgery in patients with BE — found in Section 8, subsection II (lines 655-669).

Comment 5: Section 6 therapy. There is a section for chemoradiation, but NOT for perioperative chemotherapy (more often used in EAC patients). ACCORD and FLOT trials should be briefly discussed.

Response 5: Thank you for the advice. We decided to cover the results of the ACCORD and FLOT trials. We also included patient results of the MAGIC trials as well.
Changes in the text 5: We added a perioperative chemotherapy section in Section 8, Subsection III (lines 671-683).

Comment 6: Immunotherapy: Good data regarding the use of Nivolumab is currently available for resectable locally advanced esophageal cancer (Checkmate-577 trial) and might be worth including it also.
Response 5: Great point. We wrote this manuscript before these data were published along with the subsequent FDA approval. This is definitely something that needs to be included in this review.
Changes in the text 5: We have added in information and the Checkmate trial results from the recent publication regarding the use of Nivolumab for EAC under the Immunotherapy section IV (lines 748-754). We also made sure to note the recent FDA approval for Nivolumab in that same section.

Reviewer C

Comment 1: The authors have collected a broad amount of topics in regards to diagnosis, prevention and Therapy of EAC, and each of the parts include the necessary facts and details.
Response 1: Thank you for the kind words in regard to our manuscript. We appreciate your thoughtful review of our work and feel your suggested revisions were all reasonable and after incorporation into our revised manuscript, we feel your peer-review has made this paper to be a much stronger, and better laid out review.
Change in text 1: See below for details on changes to text with respect to Reviewer C's recommendations.

Comment 2: Nevertheless, the structure of the review is somewhat confusing as it does not reflect the title and jumps between technology, molecular biology and treatment approaches.
Response 2: After further review, we agree that the overall layout of the review article was not in a meaningful chronological state and we have reformatted the layout of the paper to reflect your suggestions, which we think makes more sense and follows the title and abstract better.
Changes in text 2: We reformatted the paper closer to the order recommended in Comment 3.

Comment 3: I suggest performing a clear separation according to the title by:
Diagnoses of BE or EAC, especially the diagnosis and requirements (CT, PET-CT, EUS) for EAC have not been mentioned as well as the different endoscopic techniques (NBI, acid or new techniques) should be mentioned.

Prevention of Cancer:
- molecular understanding and Biomarker
- Technology
- pathology (please acknowledge the "indefinite for dysplasia" should not be used anymore)

Surveillance of BE
- Biomarker

Treatment of EAC
- Endoscopic treatment (EMR, ESD, RFA)
- Surgery
- chemotherapy
- targeted therapy

Response 3: This was a great suggestion, as imaging modalities have played a role in diagnosing staging of these diseases which should be acknowledged. We also agree the ordering of sections does not follow the title and therefore we agree with this Reviewer that the sequence in which the sections are presented are confusing and therefore were rearranged to the specifications provided above – to the best of our ability. Upon further review, we agree with this referee that the term "indefinite for dysplasia" is outdated and should not be used in this review.
Changes to text 3: In tune to the suggestion, we have added a new section, *Section 7: Imaging for Early Detection of Barrett's Carcinogenesis* (lines 590-637), including the imaging modalities as well as endoscopic techniques and their uses in these applications. As mentioned before, we have rearranged the sections of the paper to follow a more sensical clinical sequence, as suggested by reviewer C. We also removed all mentions of the term "indefinite for dysplasia".

Comment 4: Risk Factors (the authors are not mentioning at all, the recent developments in the prediction of progression by epidemiological factors resulting in risk stratification of patients.
Response 4: Thank you for this suggestion. We agree that the discussion of epidemiological risk factors' role in risk stratification of patients would provide great value to the paper.
Changes to the text 4: We have added a synopsis of epidemiological factor-based risk stratification in our discussion of Pathophysiology of Malignant Transformation of Normal Esophageal Epithelium — found in Section 4, Subsection I (lines 200-215).