

Please note that the page numbers referred to in this response letter correlate to the revised document with changes highlighted. We appreciate the contributions of all editors and reviewers to the improvement of this manuscript.

Comments from the Editors and Reviewers:

Editor Commentary:

1. Cover page sections were modified to meet the appropriate formatting for manuscript submission – review. Most notably, the contributions were updated and an open-access section was added.
2. Abbreviations were updated in both the abstract and manuscript such that they were defined at first usage and then used throughout the paper per editor request.
3. Citations were corrected for both order of appearance and appropriate number of articles per citation as directed in the revision guidelines. Formatting was also updated to comply with WJG standards.
4. Illustrations were updated to be cited in the main body of the paper and a descriptive caption was added on the final page of the document.

Reviewer #1:

1. “Introduction - The authors should describe regarding the difference in BE diagnosis between the USA and the UK although they mentioned on this point later.”

Re:

We thank the reviewer for highlighting this important distinction between definitions the United States and Europe, and agree that this a good point for the reader to keep in mind. The introduction was clarified to reflect that its wording is most consistent with the United States definition, with our further commentary maintained later in the paper.

2. “Tissue acquiring vs. non-tissue acquiring therapy (page 9) and 2nd para on page 12- The authors mentioned the genetic and phenotypic events in BE. Please discuss briefly on the epigenetic alterations including DNA methylation except genetic changes in BE.”

Re:

We agree that the expanding literature on epigenetic alterations is important in elucidating the mechanism of cancer progression in Barrett’s esophagus and has potential for identifying high risk individuals. A brief discussion of epigenetic changes was added to page 14 of the manuscript, including hypermethylation of promoter sequences in tumor suppressor genes, as an evolving area of interest in the progression of Barrett’s esophagus to esophageal adenocarcinoma.

3. “Emerging surveillance modalities (para 1 on page 11)- The authors described that it was initially expected that endoscopic ultrasound (EUS) and CT imaging may provide a useful adjunct role in determining the location of recurrent Barrett’s glands following ablative therapies. This sentence should be deleted because many gastroenterologists may disagree with this.”

Re:

Commentary on the adjunctive role of EUS and CT imaging were modified per reviewers recommendation that this may not be a feeling shared by the gastroenterology community at large.

4. “Current guidelines and Practice Trends for Post-ablation Surveillance. - I think the title of this section should be changed to “Current Guidelines for dysplasia surveillance and practice trends for Post-ablation Surveillance”.

Re:

We thank the reviewer for this recommendation and agree that it adds clarity to the title. We have modified the title of this section to “Current Guidelines for Dysplasia Surveillance and Practice Trends in the Post-ablation Period” to better reflect the contents of the following paragraphs.

Reviewer #2:

1. “In the first paragraph the guideline listed are more consistent with the AGA (2011), ASGE (2012) guidelines and do have distinct differences to the ACG’s (2008) guidelines that I think should either be noted Please clarify the changes in established guidelines over time..”

Re:

We appreciate the reviewer’s attention to this detail and agree that the definition of Barrett’s esophagus has evolved in the guidelines over time. This point is an important one to clarify for the reader, and the introductory paragraph on page 4 has been modified to reflect this. Further expansion on the evolution of Barrett’s definitions is beyond the scope of this article.

2. “The recommendations for endoscopic surveillance “every three months for the first year following ablation, every six months in the second year and annually thereafter” that the ASGE have suggested are not guidelines associated with a level of evidence. Please state this clearly”

Re:

We thank the reviewer for bringing this distinction to our attention, and have added an additional specification to reflect that the ASGE surveillance guidelines were not assigned a level of evidence.

3. “Deficiencies of Current Surveillance Protocols. Buried Metaplasia and Adequacy of Pinch Biopsies - In this first paragraph you depict buried metaplasia as a concern and how the depth of our mucosal biopsies are inadequate for the surveillance of this. You then mention that, “The clinical relevance of buried metaplasia has been called into question since it is protected from acid exposure by the neosquamous epithelium...” Is there any evidence to substantiate this claim? If so please include this. Why does protection from acid exposure matter in terms of risk of future neoplasia/dysplasia? Please explain”

Re:

This statement has been modified on page 11 to better reflect our true meaning. We agree that there is not enough data to support the idea that acid exposure may in some way modify progenitor cells in the esophagus to become metaplastic. Instead, the relevance of buried metaplasia is questioned due to its high prevalence and limited information about true malignant potential. There is also a need for more data comparing the genetic properties and clinical behavior of surface Barrett’s lesions with subsquamous metaplasia.

4. “The next paragraph starting with “Appropriate post-ablation...” deals mainly with the limitations of histologic preparation and inter-observer variation, which I think could be its own section under Deficiencies of Current Surveillance Protocols. This is up to the authors to decide.”

Re:

We appreciate this recommendation. The paragraph has been modified (page 11) to its own stand alone section entitled “Histologic Preparation and Inter-Observer Variation”. We have also modified the prior section to remove commentary about inter-observer variation in the opening sentence, since it will now be discussed in a subsequent heading.

5. “Durability of Response and Recurrence Patterns - In the sentences, “They showed that 90% sustained complete eradication of neoplasia and intestinal metaplasia, with both cancer recurrences occurring near the 5 year cut off”, I would consider removing “cancer” and just leaving “both recurrences occurring near the 5 year cut off.” This is also up to the authors to decide.”

Re:

We chose to change the word “cancer” to “neoplasia”. We did not want to completely remove this reference to emphasize that the recurrences were not of intestinal metaplasia after CE-IM, but instead were high grade lesions.

6. “Because you’ve mentioned Pho et al’s method to detect recurrence “EUS and Neosquamous resection” I would also indicate the method of determining Shaheen’s “rates of eradication” and Gupta et al’ method of determining “rates of recurrence”. This way the reader will know if the durability of response in these studies are determined with an equal method or not (i.e. Neosquamous resection vs mucosal pinch biopsies). This is at the authors’ discretion. Just think it over.”

Re:

We concur about the importance of this distinction to help the reader better understand the nature of these studies. The sentences regarding the Shaheen and Gupta trials (page 12) have been modified to reflect that recurrence was defined using surveillance biopsies for comparison, per the reviewer’s recommendation.

7. Other considerations Cost Effectiveness - Following the sentence “Unfortunately, over-surveillance is currently present in up to 2/3 of patients with NDBE and presents a major area for improved health resource utilization”, if there were a known or estimated cost to this over-surveillance, this would be good to include. I urge the authors to include this.

Re:

We agree that quantifying the financial burden of these additional procedures would be of interest. The studies reviewed did not include a specific cost associated with over-surveillance, however there are cost estimates regarding initial radiofrequency ablation versus surveillance in patients with non-dysplastic Barrett’s esophagus and low grade dysplasia. We have included these estimates on pages 15-16.

8. “Emerging Surveillance Modalities - 2nd paragraph, the sentence “A depth of 333 micrometers or less was associated with a 92% Se, 85% Sp, and 88% accuracy in predicting the presence of residual metaplasia at follow up endoscopy” I think the “less” and “presence” should read as “less” and “absence” or “more” and “presence”. This clarification really needs to be made in a revised ms.”

Re:

This sentence has been modified to “less” and “absence” to better reflect the nature of the findings.