October 03, 2021

Re: Submission of a Revised manuscript to the WORLD JOURNAL OF GASTROINTEROLOGY

Prof. SUBRATA GHOSH, AGAF, FCAHS, FRCP (C), FRCPC, FRCPE, MD, Full Professor
Editor-in-Chief

Dear Prof Subrata Ghosh,

Thank you very much for giving us the opportunity to revise our *invited review* (Manuscript number: 71354)

We would be grateful for the consideration of our revised manuscript "*Surveillance strategies for precancerous gastric conditions after H. pylori eradication: there is still need for a tailored approach*" (by Endrit Shahini and Marcello Maida) for publication in the ***World Journal of Gastrointerology***.

The authors have read and complied with author guidelines, and they all have seen and approved this manuscript for publication. None of the authors had a conflict of interest to disclose concerning this manuscript.

We are grateful to the Editors for their precious contributions and comments. We have revised our manuscript accordingly for grammar, style, structure and we hope that you will now find it suitable for publication in the ***World Journal of Gastrointerology***. In case of final acceptance, we agree to make this manuscript open-access.

The changes in the manuscript are identified in track change mode. Below you can find a point-by-point reply to the reviewers. We used red to denote revised or inserted text.

Thank you for your precious time.

We are looking forward to receiving your decision in due time.

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Reply to Reviewers:

1. **Reviewer #1: The authors provided useful conclusions for clinical practice and future study. The proofs are sound and the reviewing of published studies is profound. As far as I am concerned, this manuscript should be accepted with high priority.**
   Thanks to the reviewer for the appreciation of our paper.

2. **Reviewer #2: In this letter, authors conclude that "Additional studies are yet required to sharpen the hazard stratification of patients with the greatest chance of gastric cancer evolution" and conduct a comprehensive analysis. However, there are some issues that need to be explored in this letter.**

   Dinis-Ribeiro M et al showed that "…have a negative family history for GC do not require surveillance". Does the author agree with this view?

   We thank the reviewer for his precious comments. We partially agree with the Dinis-Ribeiro M affirmation "*The majority of patients with IM, those who during high-quality endoscopy were shown to have IM of limited severity and extent, confined to the antrum, and have a negative family history for GC do not require surveillance*" since the endoscopic follow-up should be individualized according to the presence even of other comorbidities, genetic and racial factors that can be additional gastric cancer risk factors as we wrote (page 6) "…*Moreover, multiple and evolving racial, ethnic, and immigration factors, may affect the risk of gastric neoplasia…*". To further support our opinion we have added the following sentence "…*Notwithstanding, maybe this affirmation seems to neglect the feasibility of genetic/epigenetic/racial factors, personal habits and underlying comorbidities (i.e., alcohol consumption, smoking, autoimmune and metabolic diseases), that can hold distinctive malignant potential, theoretically affecting subsequent endoscopic surveillance*".

   The authors suggest that "further studies are still needed to refine the risk stratification of patients with the highest risk of gastric malignancy development". Can they give a brief explanation?

   We specified this concept in the page 6 and changed the sentence "we believe that further studies are still needed to refine the risk stratification of patients with the highest risk of gastric malignancy development" into "…*further large prospective multicenter studies are still needed to identify additional risk factors of gastric malignancy development*".

The risk of gastric neoplasia is affected by race, ethnicity and immigration, the authors note. Then, in terms of people's life and rest, whether its impact on gastric neoplasia can't be ignored, whether there is research significance?

GC screening with endoscopy have been considered amenable in individuals who are immigrants from regions associated with a high risk of gastric cancer (East Asia, Russia, or South America) or who have a family history of gastric cancer (*Kim GH, Liang PS, Bang SJ, Hwang JH. Screening and surveillance for gastric cancer in the United States: Is it needed? Gastrointest Endosc. 2016 Jul;84(1):18-28*).

Particularly, there are marked racial and ethnic differences in non-cardia and cardia gastric cancer prevalence within the United States.

Specifically, non-cardia cancer incidence is higher in minorities and changes by community socioeconomic status, but cardia cancer incidence is higher in non-Hispanic whites and does not differ substantially by community socioeconomic status (*Gupta S, Tao L, Murphy JD, Camargo MC, Oren E, Valasek MA, Gomez SL, Martinez ME. Race/Ethnicity-, Socioeconomic Status-, and Anatomic Subsite-Specific Risks for Gastric Cancer. Gastroenterology. 2019 Jan;156(1):59-62.e4*).

Compared with biennial and no screening, screening endoscopy with continued surveillance only when indicated was cost effective for non-Hispanic blacks, Hispanics, and Asians. Hence, endoscopic non-cardia gastric cancer screening for high-risk races and ethnicities have been judged to be cost effective in the United States (*Saumoy M, Schneider Y, Shen N, Kahaleh M, Sharaiha RZ, Shah SC. Cost Effectiveness of Gastric Cancer Screening According to Race and Ethnicity. Gastroenterology. 2018 Sep;155(3):648-660*). Accordingly, we added the mentioned references to the paper.

The authors suggest that cost-effectiveness strategies for H. pylori positive patients should be better optimized. Are they thinking in terms of long-term surveillance or short-interval endoscopic surveillance?

We intend mainly in the short term and consequently in the long term surveillance. Therefore, to better explain this concept, we modified the sentence "These aspects should be examined in the next future to establish and optimize the most cost-effective strategies for recognizing H. pylori-positive patients with PGC." into the following sentence *"… to establish and optimize the most cost-effective strategies for recognizing and managing H. pylori-positive patients with PGC in the short- and long-term follow-up."* (Core tip and page 6).

3. **Reviewer #3: The authors have submitted a letter article on the review by Weng CY et al. I agree with the authors on the importance of risk stratification of gastric cancer. Even with a high-resolution endoscope, if morphological changes do not appear, genetic and epigenetic changes in epithelial cells cannot be detected. In addition, the report by Asada et al.1), which examined the relationship between methylation abnormalities and ectopic gastric cancer, is extremely important as a predictor. The authors need to mention this point a little. Asada K, Nakajima T, Shimazu T, et al. Demonstration of the usefulness of epigenetic cancer risk prediction by a multicentre prospective cohort study. Gut. 2015 Mar; 64 (3): 388-96.**

   We thank very much the reviewer for his meaningful suggestions. Accordingly, we have added the mentioned relevant concept (page 5-6) as well the specific reference "…*Notably, even with a high-resolution endoscope, if morphological changes do not appear, genetic and epigenetic changes in epithelial cells cannot be detected[8]. Specifically, epigenetic alterations (i.e., aberrant DNA methylation), accumulate in cancers and also in normal-appearing tissues surrounding cancers[8]. Indeed, cross-sectional studies prove that aberrant methylation levels in normal tissues may be associated with cancer risk, particularly in chronic inflammation-associated cancers. Additionally, the relationship between miR-124a-3 DNA methylation abnormalities and similar trends for EMX1 and NKX6-1, have been judged extremely relevant predictors of developing authentic metachronous GCs[8]*".