Hochiminh City, May 14, 2019

Dear Professor Ruo-Yu Ma,

We would like to thank you very much for your kindness to allow us to revise our manuscript. We would like to respond to the reviewers' comments and your kind suggestions as followed:

Editor' comments to author:

Thank you for your kind instructions. We have carefully revised the manuscript following your instructions.

Reviewers' comments to author:

Reviewer 1

1. Please provide the web site address regarding Ref #1 in the section of Reference.

   Thank you for your kind suggestion. The web site address has been added in the revised manuscript.

   Addition in manuscript: Globocan. https://gco.iarc.fr/. 2018

2. Please insert Ref #1 after the sentence of "But it is the third leading cause of death due to cancer as the majority of patients have been detected in advanced stages" in the section of INTRODUCTION in Page 5.

   Thank you for your kind suggestion. Ref#1 has been cited accordingly as suggested.

3. In "II.1 HISTOLOGICAL APPROACH" or "OLGIM (Operative Link for Gastric Intestinal Metaplasia) Staging System", the Kyoto global consensus on H. pylori gastritis strongly seems to recommend not only the OLGA grading system but also OLGIM or GC risk stratification in the CQ14.

   Thank you for your kind comment. We have revised the section accordingly.
   Change in manuscript: The Kyoto global consensus on *H. pylori* gastritis strongly recommends that the OLGA and OLGIM (Operative Link for Gastric Intestinal Metaplasia) grading systems should be used for GC risk stratification[10].

4. In Page 8, please provide full spelling for "UGIE"

   Thank you for your kind comment. We have revised the section accordingly
   Change in manuscript: esophagogastroduodenoscopy (EGD)

5. In "Gastric dysplasia and the risk for gastric cancer development ", regarding LGD, I feel there is a problem about the difficulty of differentiation between gastric adenocarcinoma and low-grade

adenoma/dysplasia (LGA) on endoscopic forceps biopsy (Dig Endosc. 2018 Mar;30(2):228-235). Please comment on this problem.

Thank you for your wonderful suggestion. We have added a section to discuss about this important issue in the revised manuscript.

Addition in manuscript: Notably, there is a remarkably histological discrepancy between biopsy and material obtained from endoscopic resection. A recent study from Japan found that a substantial proportion of biopsy-proven gastric LGD specimens were diagnosed as GC after endoscopic resection[40].

6. In "II.3 NON-INVASIVE APPROACH" Page 18, regarding the last sentence, "The measurement of serum PG I and sPGr alone or in combination with H. pylori serum antibody (HpAb) test, and/or Gastrin-17 has been investigated to identify high-risk individuals". Please provide references.

   Thank you for your kind suggestion. Appropirate reference has been cited accordingly as suggested.

7. Please delete "(Kim GIE 2016)" that is Ref 66 in Page 21.

   Thank you for your kind suggestion. We have deleted these words as suggested.

8. In Page 22, please provide full spelling for "UGIS".

   Thank you for your kind suggestion. We have revised the word to "upper gastrointestinal series (UGS)".

9. Please provide the reference instead of (Kim, 2016) in the last sentence in Page 26, Line 9.

   Thank you for your kind suggestion. Appropirate reference has been cited accordingly as suggested.

Reviewer 2

1. Title: What is the meaning of western and eastern points of view? It does not express the meaning that explained in the text. Please revise the title into for example: "comparison of western and eastern methods" and so on.

   Thank you for your kind suggestion. We would like to revise the title as suggested. "perspectives" has been used instead of "points of view".

2. Before II, the aim of study should be explained.

   Thank you for your kind suggestion. We have revised the manuscript strictly according to the instructions of the Editor.

3. After II.1, the subtitles have no number such as: II.1.1 and II.1.2 and …

Thank you for your kind suggestion. We have revised the manuscript strictly according to the instructions of the Editor.

4. In III section, again, subtitles have no numbers: III.1 ….

Thank you for your kind suggestion. We have revised the manuscript strictly according to the instructions of the Editor.

5. The comparison of western and eastern countries?

Thank you for your kind suggestion. We have added a section to give readers an overview about the comparison of approach methods used in Eastern and Western countries. The comparisons in detailed have been discuss under sections subtitled with the words "Western countries" and "Eastern countries" in the sections "Indentifying high-risk individuals for gastric cancer development" and "Lessons from Eastern and Western perspectives and the possibility to develop an integrated resource-sensitive approach"

Addition in manuscript: There are several approaches to identify these subjects including noninvasive methods, esophagogastroduodenoscopy and histology. The histological examination is traditionally required for the diagnosis of precancerous gastric lesions. However, endoscopy, especially with modern endoscopic technologies, and biomarkers have been reported to have acceptable accuracy for histological diagnosis of precancerous gastric lesions. Currently, the main approach in Western countries is histological-based while that in Eastern countries with high prevalence of GC is endoscopic-based.

6. Strategy: without any connecting sentence of paragraph.

Thank you for your kind suggestion. The according paragraphs have been carefully revised.

Change in manuscript: Biopsy strategy: obviously, endoscopically visible gastric lesions suspected of precancerous gastric lesions and GC should be biopsied. But the strategy of taking mapping biopsies may be different depending on the local resources (Figure 4). In regions with high resources, it is recommended to take mapping biopsy at mucosal sites according to the Sydney protocol for patients with endoscopic findings suggesting of chronic gastritis[10]. The biopsy specimen from angularis angular is essential in order not to downgrade OLGA and OLGIM gastritis stage and miss the high-risk individual[82]. Specimen from each site should be put into separate container. Whenever available, IEE should be used for detecting and taking targeted biopsy[50]. Regarding histological assessment, the OLGIM and OLGA staging systems should be applied[9, 10].

However, a recent Korean study found that only about one quarter of patients with GC in this high-risk population had high-stage OLGA and OLGIM gastritis. Therefore, these staging systems may not be sensitive indicators for GC in Asians as reported in Western populations and local validation is required[83]. The GIM subtype analysis may be considered but is not a necessity as the presence of incomplete GIM is significantly associated with extensive GIM, which is an easier documented marker[32, 33, 84].

In regions with limited resources, mapping biopsy is also recommended and specimen from each site should be put into separate container as above mentioned. In some developing countries, the cost for histological examination is not currently reimbursed and the cost increment for additional containers could not be afford by many self-paid patients [4]. As patients with extensive gastric atrophy and/or GIM have higher risk of GC development[32, 34, 35], a reasonable option is to take 5 biopsies at mucosal sites according to the Sydney protocol and put them into 2 separate containers for antrum and corpus. Another option is to define high-risk patients based on EGA severity alone given that well-trained endoscopists are available.

7. Where is discussion and conclusion?

Thank you for your kind suggestions.

- As this is a minireview, the discussion has been integrated into the body of the section "Lessons from Eastern and Western perspectives and the possibility to develop an integrated resource-sensitive approach". The discussion was based on the ideas already mentioned in previous sections as well as some additional references.
- We have added the conclusion section as you kindly suggested.

Addition in manuscript: The characteristics of individuals with high risk for GC development have been well recognized. There are several strategies attempting to identify these individuals including non-invasive, endoscopic, histological or combined approaches. The main approach in Western countries is histological-based while that in Eastern countries with high prevalence of GC is endoscopic-based. Although some approaches have demonstrated to be cost-effective and be able to reduce GC mortality, these could not be widely applied as limited resource is an important barrier in many regions, Basing on the current evidence from both of Western and Eastern perspectives, an integrated and resource-sensitive approach could be develop for real-life practice.

Once again, we would like to express our sincere thanks to you for helping us to improve the scientific quality of the manuscript.

With the warmest regards,

Dr Duc Quach