

Dear Editors,

Please find enclosed the edited manuscript in word format.

Title: Endoscopic diagnosis and treatment of esophageal squamous cell neoplasia

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Thank you very much for reviewing our manuscript. The manuscript has been improved according to the suggestions of reviewers. We appreciate the reviewers' comments and suggestions.

Comments from reviewer 1

Thank you for submitting a novel review about current endoscopic diagnosis and treatment of early esophageal squamous neoplasia.

(1) I wonder if there are less perspective about the development of endoscopic diagnosis or treatment of early esophageal squamous neoplasia. Authors listed various treatment strategies with some results of previous studies in this article, but we need more perspective in this review article, I think. For example, I think that the histological assessment of the specimens obtained by endoscopic resection for esophageal squamous neoplasia must be needed to investigate possible lymph node metastases. Then, the ablative therapy

should not be used as the first-line treatment strategy for esophageal squamous cancer, I believe. Therefore, authors should discuss more about their perspective based on the results of previous studies.

Authors' response: We added our perspective regarding the endoscopic diagnosis and treatment of early esophageal squamous neoplasia based on the results of previous studies. We specifically emphasized the importance of endoscopic and histological diagnosis prior to ablative therapy.

(2) Authors demonstrated that screening can lead to a reduction in the incidence of and mortality from esophageal SCCs (page 2 line 14), but I cannot understand why screening procedure could reduce the incidence of esophageal SCCs. Please answer this question or please demonstrate authors' idea about this question.

Authors' response: We made the following changes for increased clarity:

In intervention group, detected lesions were treated according to their stages. Although an initial excess incidence of esophageal SCC was seen in the intervention group possibly related to screening effect, cumulative incidence in the intervention group started to increase after 5 years. The cumulative incidence of esophageal SCC in the screened group became lower than in the control group (4.2% vs. 5.9%, respectively; $P < 0.01$) in full follow-up period of 10 years.

3. There seemed to be several miss typing points in this review, so please revise them.

Authors' response: We carefully reviewed our manuscript and corrected such

errors.

Comments from reviewer 2

The authors summarized many landmark studies on endoscopic diagnosis and treatment of early esophageal squamous neoplasia. Although this review article is well-organized, I have several comments as follows:

(1) (Page 4, Endoscopic detection) As far as I know, Japanese endoscopists inspect the oro- and hypopharynx mainly when inserting scope with making patients a long sounds or under deep sedation.

Authors' response: Thank you for the comment. I agree that Japanese endoscopists inspect the oropharynx when inserting scope which is especially important when the patient is known to have esophageal squamous neoplasia given high risk of synchronous and metachronous lesion at oropharynx. These were added to discussion on *Endoscopic detection* section of the manuscript.

(2) Endoscopic delineation will be essential to achieve complete resection. Lugol chromoendoscopy seems the most reliable technique to delineate early SCC lesions. Although there has been few studies on the endoscopic diagnosis of tumor delineation (horizontal tumor extent), this review article should have the section of "Horizontal extent" between sections of 'WLI vs. IEE vs. LCE' and 'depth assessment'. I recommend the citation of following previous articles, a guideline or a comparative study: Kuwano H, et al. J Surg Oncol. 1992; Inoue H, et al. Endoscopy 2001; Pimentel-Nunes Pedro et

al. Endoscopy 2015 and Dawsey SM, et al. Cancer 1997.

Authors' response: We appreciate this review's comment. We agree that this is very important when assessing the lesion. We added section of "Lateral margin assessment" section and cited the relevant articles.

(3) (Page 4, Depth assessment) Macroscopic types of 0-I and 0-III were described as "protruded" and "excavated", respectively, in the Paris classification. The authors should revise them.

Authors' response: We changed these to "protruded" and "excavated" according to Paris Classification.

(4) (Page 5, other diagnostic modality: Depth assessment) Please describe more issues on the cost of CLE and VLE (volumetric laser endomicroscopy). The instruments will be too expensive to use in the practical endoscopy.

Authors' response: We added discussion mentioning that these are still not widely used and limited to research institutions. Despite recent literature on these advanced imaging technologies, there are issues that need to be solved such as the cost of the procedure, image interpretation training, and standardization of indications. Although it will certainly take time for these modalities to be widely used, we believe that these modalities will become promising with new upcoming research and increased consensus.

(5) (Page 8, Post-endoscopic resection stricture) Two studies initially showed that per-oral administration or topical injection of steroid can prevent

esophageal stricture after ESD. The studies, Hashimoto S et al. *Gastroint Endosc* 2011 and Hanaoka N, et al. *Endoscopy* 2012, should be cited in this paragraph.

Authors' response: We added these two key studies in citation. We agree that these are very important studies that need to be cited in the manuscript.

(6) "Conclusion" will be too long. Please shorten it as possible.

Authors' response: We shortened the conclusion and summarized our discussion points of the manuscript.

Thank you gain for publishing our manuscript in the *World Journal of Gastrointestinal Endoscopy*.

Sincerely yours,

Yuto Shimamura

Takashi Ikeya

Norman Marcon

Jeffrey Mosko