

**Point by point response**

Enclosed please find the revision of the manuscript entitled “Comparing Outcomes for Endoscopic Submucosal Dissection between Eastern and Western Countries: A Systematic Review and Meta-Analysis” to consider for publication in *World Journal of Gastroenterology*. The reviewer comments were much appreciated and have all been addressed in the manuscript and in the point by point response. We would be very happy and proud if this manuscript was published in *World Journal of Gastroenterology*.

Thank you again for your kind consideration of our manuscript.

Yours sincerely

Dane Christina Daoud

## Reviewer's code: 03474116

**1. Authors compared efficacy of ESD including esophageal, gastric and colon cancers between Eastern and Western countries by meta-analysis. In general, requirements of ESD differ among esophageal, gastric and colon cancers. Therefore, authors should divide efficacy into three different organs (esophageal, gastric and colon cancers).**

Answer: We appreciate your critical concerns. ESD outcomes vary according to the lesion location. Thus, in order to answer this question, we decided to stratify the studies by organ and analyzed the same primary and secondary endpoint (**Supplementary Figure S1 - S9**). For the oesophagus, only the pooled proportion of *en bloc* resection showed a significant difference in favour of the Eastern countries. As for gastric lesions, all outcomes were similar except for local recurrence, which was superior in Western countries. Finally, for colorectal lesions, Eastern countries had better curative, *en bloc* and R0 resection rate.

This stratification supports the fact that ESD efficacy varies according to the location of the lesion. Indeed, our results demonstrate that both Eastern and Western countries have similar outcomes for gastric lesions. As for colorectal ESD, which is a more difficult technique, the Eastern world shows better results. This difference could be due to the fact that Western countries still favor EMR for colic lesions and are less experienced.

This sentence was added to the revised manuscript in the methods section, statistical analysis paragraph (8<sup>th</sup> paragraph): "We repeated analysis stratifying by organ (oesophagus, stomach, colo-rectum), by study design (retrospective, prospective) and by country."

This paragraph was added to the revised manuscript in the results section, stratification by organ paragraph (9<sup>th</sup> paragraph): "Because ESD outcomes may vary according to the organ, studies were stratified by lesion location (oesophagus, stomach, colo-rectum). For the oesophagus, only the pooled proportion of *en bloc* resection showed a significant difference in favour of the Eastern countries. As for gastric lesions, all outcomes were similar except for local recurrence which was superior in Western countries. Finally, for colorectal lesions, Eastern countries had better curative, *en bloc* and R0 resection rate. (Supplementary Figure S1-S9)"

This paragraph was added to the revised manuscript in the discussion section, first paragraph: "Our meta-analysis also supports the fact that ESD efficacy varies according to the location of the lesion. Indeed, both Eastern and Western countries have similar outcomes for gastric lesions. As for colorectal ESD, which is a more difficult technique, the Eastern world shows better results. This difference could be due to the fact that Western countries still favor EMR for colic lesions and are less experienced."

## **2. Authors included prospective and retrospective study. Authors should divide efficacy into prospective and retrospective study.**

Answer: Thank you for this very important comment. Indeed, our meta-analysis included a large number of prospective and retrospective studies, mainly in the Eastern group. In order to address the possible bias between both groups, studies were stratified by study design according to their retrospective and prospective design. Stratification by study design was not different from the pooled proportion. The same trend was seen when stratifying by retrospective versus prospective results (**Supplementary Figure S16- S22**). Therefore, this difference between Eastern and Western countries cannot be explained by a difference in study design.

This sentence was added to the method section in the quality assessment and publication bias paragraph (6<sup>th</sup> paragraph): "Quality assessment of the included studies was done by identifying study designs as well as stratifying by study design according to their retrospective or prospective characteristic."

This paragraph was added to the results section in the quality assessment paragraph (11<sup>th</sup> paragraph): "Stratification by study design was not different from the pooled proportion. The same trend was seen when stratifying by retrospective versus prospective results (**Supplementary Figure S16- S22**)."

## **3. How about differences of ESD-related parameters among different Eastern countries?**

Answer: Thank you very much for this comment. In order to answer this question, meta-analyses for primary outcomes were stratified by countries. Pooled proportions for curative, *en bloc* and curative resections were similar among all Eastern countries and Western Countries (**Supplementary Figure S10- S15**).

This paragraph was added in the Results section, in the stratification by country paragraph (10<sup>th</sup> paragraph): “Meta-analyses for primary outcomes were stratified by countries. Secondary outcomes (complication rate and local recurrence) were not stratified because of the limited data available. Pooled proportions for curative, *en bloc* and R0 resections were similar among Eastern countries and Western countries. (Supplementary Figure S10- S15)”

#### **4. How about association with bleeding and use of anti-thrombotic drugs?**

Answer: Thank you very much for this comment. It is an important question. Unfortunately, data regarding association between bleeding and use of anti-thrombotic drugs were incomplete or unavailable in most studies. Future studies should report systematic outcomes for bleeding and use of anti-thrombotic.

This sentence stating this limitation has been added to the revised discussion, 3<sup>rd</sup> paragraph: “Data regarding bleeding and use of anti-thrombotic were not analyzed because they were incomplete or unavailable in most studies. Such limitations seem to be an inherent weakness in the currently published ESD literature and a standardized and detailed reporting of ESD outcomes and use of anti-thrombotic seems warranted for future studies.”

#### **5. Please delete Figures S3-S9. Please add P values in Table 1.**

Answer: For methodological/statistical reasons values listed in Table 1 need to be presented as weighted average and p value cannot be added.

## Reviewer's code: 02446765

**1. The authors compared various outcomes of ESD between Eastern and Western countries. However, outcomes are quite variable according to the organ even in the same center. I would recommend the authors to analyze the data more according to the organ.**

Answer: Thank you for this very important comment. Indeed, ESD outcomes vary according to the organ. This issue was addressed thoroughly given that you are the second reviewer to mention it. Here is the answer given to the previous reviewer:

In order to answer this question, we decided to stratify the studies by organ and analyzed the same primary and secondary endpoint (**Supplementary Figure S1 – S9**). For the oesophagus, only the pooled proportion of *en bloc* resection showed a significant difference in favour of the Eastern countries. As for gastric lesions, all outcomes were similar except for local recurrence, which was superior in Western countries. Finally, for colorectal lesions, Eastern countries had better curative, *en bloc* and R0 resection rate.

This stratification supports the fact that ESD efficacy varies according to the location of the lesion. Indeed, our results demonstrate that both Eastern and Western countries have similar outcomes for gastric lesions. As for colorectal ESD, which is a more difficult technique, the Eastern world shows better results. This difference could be due to the fact that Western countries still favor EMR for colic lesions and are less experienced.

This sentence was added to the revised manuscript in the methods section, statistical analysis paragraph (8<sup>th</sup> paragraph): “We repeated analysis stratifying by organ (oesophagus, stomach, colo-rectum), by study design (retrospective, prospective) and by country.”

This paragraph was added to the revised manuscript in the results section, stratification by organ paragraph (9<sup>th</sup> paragraph): “Because ESD outcomes may vary according to the organ, studies were stratified by lesion location (oesophagus, stomach, colo-rectum). For the oesophagus, only the pooled proportion of *en bloc* resection showed a significant difference in favour of the Eastern countries. As for gastric lesions, all outcomes were similar except for local recurrence, which was superior in Western countries. Finally, for

colorectal lesions, Eastern countries had better curative, *en bloc* and R0 resection rate (Supplementary Figure S1-S9).”

**2. Lots of RCTs were performed in Eastern countries but not in Western countries. Volume of the studies performed in Eastern countries are enormous. So the level of evidence might be quite different between the two groups. How did the authors try to reduce this bias between the two groups?**

Answer: Thank you for this important comment. This issue was also mentioned by the previous reviewer. Here is the answer given to the previous reviewer:

In order to address the possible bias between both groups, studies were stratified by study design according to their retrospective and prospective design. Stratification by study design was not different from the pooled proportion. The same trend was seen when stratifying by retrospective versus prospective results (Supplementary Figure S16- S22). Therefore, this difference between Eastern and Western countries cannot be explained by a difference in study design.

This sentence was added to the method section in the quality assessment and publication bias paragraph (6<sup>th</sup> paragraph): “Quality assessment of the included studies was done by identifying study designs as well as stratifying by study design according to their retrospective or prospective characteristic.”

This paragraph was added to the results section in the quality assessment paragraph (11<sup>th</sup> paragraph): “Stratification by study design was not different from the pooled proportion. The same trend was seen when stratifying by retrospective versus prospective results (Supplementary Figure S16- S22).”

**3. Considering the learning curve, complication rates might be higher in low volume center. Self-learning, duration of observation for experts' procedures, etc might affect the complication rates. Did the authors consider all of these circumstances?**

Answer: Thank you for this very good comment. However, few studies reported systematic outcomes for trainee level. In order to reduce bias from learning curves, we excluded studies with less than 50 patients. Future studies should report systematic outcomes for trainee level.

We mentioned this limitation in the revised discussion. This sentence has been added to the revised manuscript in the discussion section, 3<sup>rd</sup> paragraph: “Because few studies

reported systematic outcomes for trainee level, we decided to exclude studies with less than 50 patients to reduce bias from learning curves and patient selection. Future studies should report systematic outcomes for trainee level.”

**Reviewer’s code: 00001114**

**1. I feel it is difficult to conclude that EMR would be an adequate alternative to ESD from this analysis in the present study. Therefore, I delete the sentences about EMR in Discussion**

Answer: Thank you for this important comment. Since this study does not compare directly EMR outcomes with ESD outcomes, we agree with the reviewers that a direct comparison of the value of EMR with ESD cannot be drawn from the presented study. We modified the discussion accordingly. However, we also feel that because our study shows that ESD results in the Western world are associated with a lower curative, *en bloc*, R0 rate and higher complications rate, EMR might be a good alternative for selected cases depending on the expertise of the endoscopist of the center. (Eg: non-invasive lesions defined to the mucosa).

**2.The authors should replace “ , ” with “ . ” with regard to decimal point in the main text and table. Please revise the number of lesion diameter in Table 1 from 25.65 to 25.7 in Total as well as in Eastern countries and Western countries, respectively, like descriptions in Result section in the main text.**

Answer: Thank you for your comment, we changed coma for point throughout the revised manuscript and revised Table 1.