

ANSWERING REVIEWERS

Dear Editor,

We appreciate the opportunity to revise our manuscript entitled “Endoscopic Submucosal Dissection of Gastric Tumors: A Systematic Review and Meta-analysis” for consideration for publication in the *World Journal of Gastrointestinal Endoscopy*. We have responded to the editor’s comments as well as reviewer’s suggestions, and updated our manuscript to address important issues raised in the review. We believe this has significantly improved our manuscript.

The manuscript has not been previously published in whole or in part, nor is it under consideration for publication elsewhere.

We look forward to hearing from you.

Sincerely,

Diane Levine, MD

Below are our responses to reviewers’ comments:

ESD is the natural evolution of endoscopy and a few will doubt its potential. Not surprisingly, Asia dominates this field. The article is very interesting and well written. English is at a level of native speaker. It is also properly constructed, having followed the principles of meta-analyses. The number of studies and patients included is also very satisfactory. There are only a couple of minor comments. Really wonder, is google translator reliable enough for non-english papers? Authors are very correct about the possible causes of heterogeneity but it’s also quite obvious that it’s difficult to compare series done with the technology of early 2000 with current technology. It would be also worthwhile, especially for western doctors, if authors could give an estimate of the number needed to overcome the learning curve.

Response: We appreciate the favorable comments made by the reviewer on our manuscript.

On the issue of the Google translator, we relied very little on the translator as almost all the articles in foreign language we came across had abstract and center of study translated in English and we were able to find a more updated study from the same center with full text in English. We also had a native Chinese speaker (Ms. Tianyu Tang) who helped to double-check the Chinese articles that were initially considered for inclusion. Subsequently, all (except one) were excluded from our final analysis. In a sensitivity analysis, exclusion of this study in foreign language did not change any of our estimates.

Evidence from prior studies indicates that at least 30 studies will be required to overcome the learning curve. We have added this important information to our revised manuscript as thus (page 11, lines 25-27): “Furthermore, the proficiency of the ESD procedure takes some time to acquire as prior studies have suggested that it takes at least 30 procedures for a beginner to overcome the learning curve”.

If the authors give any detail for complications it will be more valuable. (Is this technique need any learning curve?)

To address this important point, we have now done a more detailed analysis of the complications/adverse outcome of the procedure by evaluating for potential sources of heterogeneity for each adverse outcome. This information has now been included in the revised manuscript as thus (pages 9, lines 8-21): *“Evaluation for potential sources of heterogeneity showed that the rate [95% CI] of immediate perforation was significantly lower with epithelial (2.7% [2.2-3.6%]) compared with subepithelial tumors (8.9% [2.7-15%]) (p=0.02) and has declined by 0.29% [0.05-0.54%] per year over the duration of study (p=0.02). Similarly, the rate [95% CI] of immediate bleeding has declined by 2.3% [0.72-3.9%] per year over the duration of study (p=0.007). Lastly, we found that the rate [95% CI] of delayed bleeding increases by 1.3% [0.07-2.5%] for every 10 year increase in age.*

.... The rate [95% CI] of recurrence decreases by 0.4% [0.1-0.7%] for every 10 year increase in age (p=0.01) and there was a trend towards higher rate in Western countries (5.1% [0.5-11%]) compared with Asia (0.5% [0.3-0.6%]) (p=0.06).”

Yes, the technique requires a learning curve. Evidence from prior studies, indicates that at least 30 studies will be required to overcome the learning curve. We have added this important information to our revised manuscript as thus (page 11, lines 25-27): *“Furthermore, the proficiency of the ESD procedure takes some time to acquire as prior studies have suggested that it takes at least 30 procedures for a beginner to overcome the learning curve”.*

The authors did the largest assessment of the published gastric ESD studies. However, you included subepithelial tumors which involved the muscularis mucosa. Don't you think that there exists difference concerning R0 resection and complication between true epithelial neoplasm and subepithelial tumor? Is it also true between intestinal and schirrhous type gastric adenocarcinoma? Perhaps subgroup analysis would help and both two situations may become to be another confounder, not limit to case volume and experience

Response: We would like to thank the reviewer for pointing out this interesting point. In our revised analysis, we did not find any significant difference in R0 resection when we compared studies involving only epithelial tumors with studies involving only subepithelial tumors (p=0.6). However, there was significant difference in the rates of immediate perforation which we have now indicated in the revised manuscript as thus (pages 9, lines 8-10): *“Evaluation for potential sources of heterogeneity showed that the rate [95% CI] of immediate perforation was significantly lower with epithelial (2.7% [2.2-3.6%]) compared with subepithelial tumors (8.9% [2.7-15%]) (p=0.02)”.*

Unfortunately, most of the studies included mixed population of intestinal and non-intestinal tumors and so we were not able to explore the difference in outcome between intestinal and non-intestinal tumors in a head-to-head comparison.