Dear editor,

Thank you very much for your decision letter and advice on our manuscript (Manuscript ID: 79596, Retrospective Study) entitled “Oral higher doses of prednisolone for prevention of esophageal stricture after endoscopic submucosal dissection for early esophageal cancer and precancerous lesions”. We also thank the reviewer for the helpful comments and suggestions. Accordingly, we have revised the manuscript. All amendments are highlighted in red in the revised manuscript. In addition, point-by-point responses to the comments are listed below this letter.

We hope that the revision is acceptable for the publication in your journal.

Look forward to hearing from you soon.

With best wishes,

Yours sincerely,

Sheng-gang Zhan

Reviewer 1

1. In the introduction, the authors mentioned esophageal stricture in children. Is this relevant to this discussion? Both the background and the treatment of the disease are fundamentally different subjects, and it is doubtful whether it is suitable for quoting.

Response: Thanks very much for your insightful comment. We agree with your comment and have deleted this quote in the manuscript.

2. In the method, there is a statement that EBD is performed if necessary, but in this study, is there not a single case in which balloon dilation was added? Based on past reports and our experience, we cannot believe that oral steroids alone can prevent stenosis.

Response: Thanks very much for your insightful comment. During our follow-up, 14 patients had no feedback of dysphagia symptoms, and no esophageal stenosis observed by endoscopic examination. So there is not a single case in which balloon dilation was added. Because of this, we hope to share this experience, so that more centers will join this study.

3. Why did the author list “0/10” in the result, which should be 14 cases? 10 examples?

Response: Thanks very much for your insightful comment. This was our mistake, the result should be “0/14”, not “0/10”. During the submission period, 4 new cases were followed up for more than 6 months and were included in this study. We made

mistakes in the manuscript revision, and we have revised the manuscript.

4. In the discussion, it is discussed that the evaluation of stenosis is limited to endoscopic observation in the reports so far, as evidence that administration of steroids at the beginning leads to prevention. But other than that, it is really difficult to evaluate, and if the authors argue like this, the authors should include a solid evaluation that can be said to be useful in this study.

Response: Thanks very much for your insightful comment. Esophageal stenosis was defined as the inability of 9.9mm diameter gastroscope (Olympus GIF-Q260J) to pass through the esophageal stenosis. So we evaluate the esophageal stenosis by whether the 9.9mm diameter gastroscope (Olympus GIF-Q260J) can pass through the stricture of esophagus. This is an objective indicator to some extent.

5. In addition, it is assumed that the cause of stenosis is peripheral, but some reports state that the depth of invasion may be related. Isn't it an exaggeration to say that high-dose steroids can be prevented in this content? There is too little evidence to use the word "can".

Response: Thanks very much for your insightful comment. We agree with your comment, and have revised the manuscript.

Oral prednisone (50 mg/day) and prolonged prednisone usage time may effectively prevent esophageal stricture after ESD without increasing the incidence of

glucocorticoid-related adverse events.

6. Furthermore, in this study, there were only two cases of circumferential resection, which makes it difficult to compare with other reports. Considering that point, discussion should be described.

Response: Thanks very much for your insightful comment. We have revised the manuscript.

In our study, we increased the dose of prednisone to 50 mg/day and prolonged the treatment time to 13 weeks. During our follow-up, 14 patients had no feedback of dysphagia symptoms, and no esophageal stenosis observed by endoscopic examination, including the two patients with entire circumference mucosal defects. In addition, the depth of tumor invasion in the two patients with entire circumference mucosal defects was limited within the lamina propria (M2). Studies have shown that the injury of the intrinsic muscle layer was one of the risk factors for esophageal stenosis after ESD for early esophageal cancer and precancerous lesions. Therefore, we paid more attention to avoid the injury of the intrinsic muscle layer as much as possible during ESD operation, which we think was also helpful for the prevention of postoperative esophageal stenosis.

Reviewer 2

1.Under Methods, what is IPCL?

Response: Thanks very much for your insightful comment. IPCL means intraepillary

capillary, which is used to evaluate the classification of early esophageal cancer. The observation of IPCL can help us to predict the depth of invasion of esophageal cancer, so as to determine whether the lesions are suitable for endoscopic treatment. We have revised the manuscript.

Before esophageal ESD, the intraepillary capillary (IPCL) of lesion mucosa observed by magnification endoscopy with narrow-band imaging (NBI-ME) was type B1.

2.The authors defined esophageal stricture as the inability to allow 9.9 mm diameter gastroscope to pass the stricture. I am interested to know if any of the 14 patients who had ESD for lesions >75% circumference had any symptom of dysphagia after the procedure.

Response: Thanks very much for your insightful comment. Regular endoscopic examination was performed at 1, 3, 6 months after ESD and then annually thereafter. And whenever patients felt dysphagia, endoscopic examination was performed on demand. During our follow-up, 14 patients had no feedback of dysphagia symptoms.

3.What kind of diet was the patients advised post-ESD eg. liquid, soft, normal etc? Any of these patients continue to smoke cigarettes and/or drink alcohol?

Response: Thanks very much for your insightful comment. According to the patient's condition, liquid diet will last for 1 weeks, and then soft food will last 1-2weeks. For patients with entire circumferential mucosal defects, the nasojejunal nutrition tube

was placed for 3 days to 1 week of enteral nutrition, followed by liquid diet for 1 week, and then soft food will last 1-2weeks. During the follow-up, two patients continued to smoke cigarettes, but they were trying to quit smoking. No patient continued to drink alcohol.

Reviewer 3

Specific Comments to Authors: I had suggestions about the spelling of some words in the text.

Response: Thanks very much for your insightful comments. We have revised the manuscript.

In 12 lesions, the depth of invasion was histologically limited within the epithelium and lamina propria mucosa, while 2 lesions were limited within the layer of muscularis mucosa without lymphovascular infiltration.

In current study, increasing the dose of oral hormone (prednisone acetate 50 mg/day) and prolonging the treatment time (13 weeks) were effective to prevent esophageal stricture in patients with mucosal defects ≥ 3/4 circumference after ESD.

Reviewer 4

The authors present an study to assess the effectiveness of oral higher doses of prednisolone for prevention of esophageal stricture after endoscopic submucosal dissection .

1. the manuscript lacks any novelty.

Response: Thanks very much for your insightful comment. Esophageal stenosis was one of the main complications of ESD in the treatment of large-area superficial esophageal squamous cell carcinoma and high-grade intraepithelial neoplasia, which really perplexed most digestive physicians. Nowadays, Oral prednisone (30mg/day) was widely used to prevent esophageal stenosis, but the curative effect remians controversial. Studies have reported that patients with entire-circumference resections showed high stricture rates (10/14) by Oral prednisone (30mg/day) . To our knowledge, this was the first attempt to take higher doses of prednisone orally to prevent esophageal stenosis.

2. please write the full term of ESD in the abstract for the first mentioning.

Response: Thanks very much for your insightful comment. We have revised the manuscript.

Esophageal stenosis is one of the main complications of endoscopic submucosal dissection (ESD) for the treatment of large-area superficial esophageal squamous cell carcinoma and precancerous lesions (≥3/4 of the lumen).

3. ESD procedure is not a new one, but when you prefer to explain it, you should provide some related figures for better understanding the process.

Response: Thanks very much for your insightful comment. ESD procedure was shown in figure 1. The extent of the lesion was determined by 0.75% iodine staining

(figure 1A). A dual knife (KD-650Q; Olympus Co, Tokyo, Japan) was used to mark dots around the lesion with a 3mm margin (figure 1B). The 0.9% saline solution containing 0.3% indigo carmine was then injected into the submucosa along the outside of the marked dots and followed by a circumferential mucosal incision with a dual knife (figure 1C) . Submucosal dissection was performed with a dual knife (KD-650Q) from the oral side to the anal side of the lesion under an operating mode (figure 1D). An image obtained immediately after ESD, and the mucosal defect involved more than three-quarters but less than seven-eighths of the esophageal circumference (figure 1E).

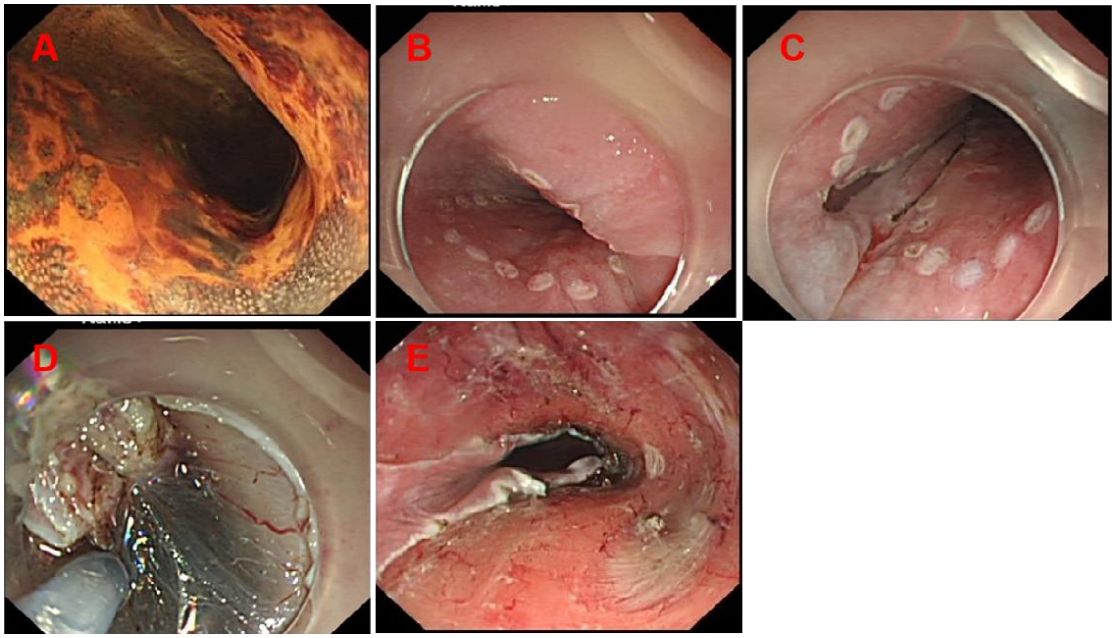

Figure 1: ESD procedure

4.during the first paragraph of result, you mentioned the initial patients and the final cased after applied the eligibility criteria, It's better to add a flow chart for your pathway

Response: Thanks very much for your insightful comment. We have drawn a flowchart.

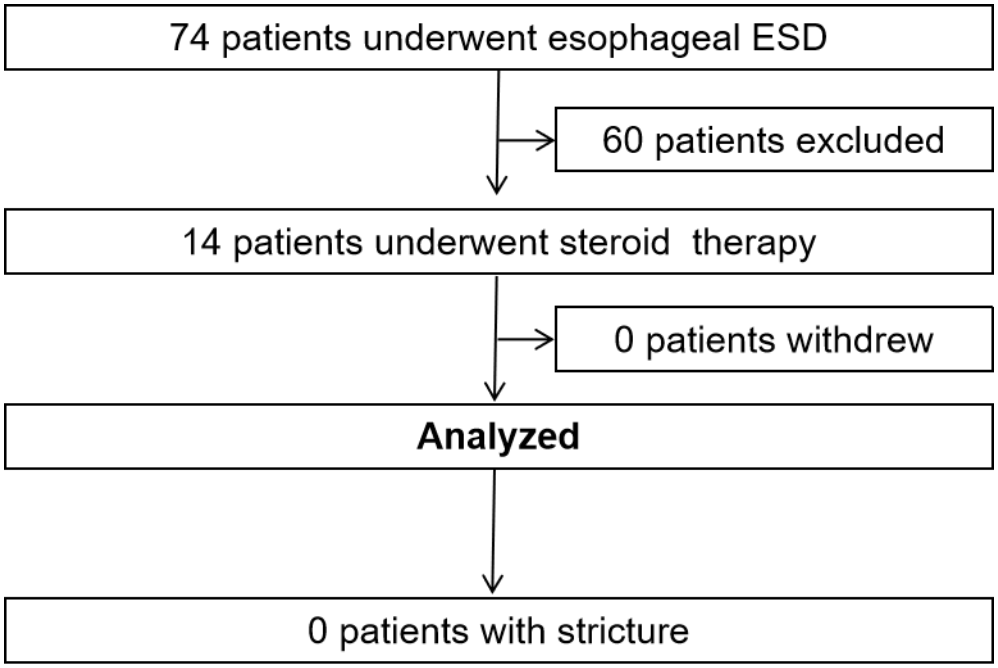

Figure 2: Flow chart.

5.you have claimed that "increasing the dose of oral hormone (prednisone acetate 50 mg/day) and prolonging the treatment time (13 weeks) were significantly effective to prevent esophageal stricture in patients with mucosal defects ⩾ 3/4 circumference after ESD", but you don't have any P.value or effect size; so how do you consider it as "significant".

Response: Thanks very much for your insightful comment. We do agree with your comments, and we have revised the manuscript.

In current study, increasing the dose of oral hormone (prednisone acetate 50 mg/day) and prolonging the treatment time (13 weeks) were effective to prevente

esophageal stricture in patients with mucosal defects ≥ 3/4 circumference after ESD.

6. you have no control group to assess the effectiveness of your therapy in the outcome.

Response: Thanks very much for your insightful comment. In this study, there were only two cases of circumferential resection, which makes it difficult to compare with other reports.