

**For reviewer 1:**

I appreciate your kind and careful comments on our paper.

**Minor comments**

**#1 You should mention the kinds of electrosurgical unit and selected setting, which might affect the clinical outcome of ESD. If the setting of electrosurgical unit were changed during dissection due to fibrosis, you should mention the difference of the setting.**

--> We think that your comment is very important. The electrosurgical unit used in this study was the VIO300D (ERBE, Tuebingen, Germany). Mucosal incision was carried out using the Endocut I current (effect 2, cut duration 4, interval 3), and submucosal dissection was done with the swift coagulation current (effect 3, 40 W). Hemostasis of visible vessels was done using the soft coagulation current (effect 3, 60 W). We did not change the setting of electrosurgical unit during dissection due to fibrosis. As your comments, we added sentences into the method like below.

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Hemostasis during ESD and ablation of visible vessels at the post-ESD ulcer site were achieved using hemostatic forceps (Coagrasper; Olympus Co, Tokyo, Japan). **For the electrosurgical unit, the VIO300D (ERBE, Tuebingen, Germany) was used. Mucosal incision was performed using the Endocut I current (effect 2, cut duration 4, interval 3), and submucosal dissection was carried out with the swift coagulation current (effect 3, 40 W). The visible vessels were ablated using the soft coagulation current (effect 3, 60 W).**  
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**#2 Traction method was reported to be useful for shortening the procedure time or prevention of adverse event including perforation. If possible, you should mention the usage rate of traction method.**

--> We are very thankful for your kind comments on our paper. However, this study is

retrospective, we did not evaluate the usage rate of traction method.

**#3 Did longer procedure time affect the rate of aspiration pneumonia? Please discuss the association between the procedure time and aspiration pneumonia.**

--> We are very thankful to your thoughtful comment. The aspiration pneumonia occurred in 15 (0.9%) patients. The procedure time was longer in patients with aspiration pneumonia (83.3 vs. 55.1 min,  $P = 0.125$ ). However, the difference was not statistically significant. As your comments, we added sentences into the discussion like below.

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aspiration pneumonia was treated with antibiotics and conservative care. **The aspiration pneumonia occurred in 15 (0.9%) patients. The procedure time was longer in patients with aspiration pneumonia than others (83.3 vs 55.1 min,  $P = 0.125$ ). However, the difference was not statistically significant.** Although many endoscopists worry that submucosal fibrosis might cause perforation, in this study, there were no perforations reported in the secondary ESD group.  
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**#4 Were there any patients treated by except ESD? Please mention it.**

--> We think that your comment is very important. However, we enrolled 1623 consecutive patients underwent gastric ESD for gastric neoplasms at Gangnam Severance Hospital in Seoul. Therefore, there were no patients treated by except ESD.

**#5 You mentioned “secondary ESD should be performed by an experienced endoscopist...” Please mention the detail of endoscopists in this study. If possible, the technical outcomes should be compared between experts and trainees.**

--> We are very thankful for your kind comments on our paper. Primary ESD procedures in this study were performed by one of 5 ESD endoscopists. Two of them were fully skilled experts (YYH, far more than a thousand cases of ESD experience; KJH, more than five hundreds cases of ESD experience) and another three were less-skilled ESD endoscopist

whose ESD experience is less than a hundred cases. However, secondary ESD in this study was exclusively performed by only two fully skilled ESD experts (YYH and KJH). That might be a reason why the outcomes of secondary ESD group were relatively good despite of technical difficulty. As your comments, we added sentences into the discussion like below.

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Therefore, this observation may explain the rarity of perforation. **And, primary ESD procedures in this study were performed by one of 5 ESD endoscopists. Two of them were fully skilled experts (YYH, far more than a thousand cases of ESD experience; KJH, more than five hundreds cases of ESD experience) and another three were less-skilled ESD endoscopists whose ESD experience is less than a hundred cases. However, secondary ESD in this study was exclusively performed by only two fully skilled ESD experts (YYH and KJH). That might be a reason why the outcomes of secondary ESD group were relatively good despite of technical difficulty.**

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**#6 There might be an institutional learning curve during the study period. The difference of study period (initial phase vs late phase) might affect the outcomes. Please discuss this point.**

--> We are very thankful to your thoughtful comment. As your comments, we evaluated the outcomes according to an institutional learning curve during the difference of study period (initial phase vs late phase). The en-bloc resection rate was not significantly different (initial phase vs late phase, 98.4 % vs 98.8,  $P = 0.533$ ). And, curative resection rate was significantly lower in initial phase than late phase (84.6% vs 88.8%,  $P = 0.013$ ). When we evaluated the outcomes in secondary ESD group during the difference of study period, the en-bloc and curative resection rates were not statistically different (initial phase vs late phase, 100 % vs 88.2,  $P = 0.505$  and 90.9 % vs 88.2,  $P = 1.000$ ). As your comments, we added sentences into the discussion like below.

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Therefore, this observation may explain the rarity of perforation. **And, primary ESD procedures in this study were performed by one of 5 ESD endoscopists. Two of them were fully skilled experts (YYH, far more than a thousand cases of ESD experience; KJH, more than five hundreds cases of ESD experience) and another three were less-skilled ESD endoscopists whose ESD experience is less than a hundred cases. However, secondary ESD in this study was exclusively performed by only two fully skilled ESD experts (YYH and KJH). That might be a reason why the outcomes of secondary ESD group were relatively good despite of technical difficulty. And, we evaluated the outcomes according to an institutional learning curve during the difference of study period (initial phase vs late phase). The en-bloc resection rate was not significantly different (initial phase vs late phase, 98.4 % vs 98.8,  $P = 0.533$ ). And, curative resection rate was significantly lower in initial phase than late phase (84.6% vs 88.8%,  $P = 0.013$ ). When we evaluated the outcomes in secondary ESD group during the difference of study period, the en-bloc and curative resection rates were not statistically different (initial phase vs late phase, 100 % vs 88.2,  $P = 0.505$  and 90.9 % vs 88.2,  $P = 1.000$ ).**

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**#7 Were there any cases of secondary ESD with no residual tumor was found? Even though horizontal margin is positive or unknown, there is a possibility of no residual tumor because of burning effect. Please mention this point.**

--> We think that your comment is very important. Two patients in the early salvage ESD group have no residual tumor. Because early and late salvage ESD were performed after histological confirmation of positive lateral margins of the initial ESD specimen, as your comments, there is a possibility of no residual tumor because of burning effect. We added sentences into the discussion like below.

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In this study, the en-bloc and curative resection rates of secondary ESD were 92.9% and 89.3%, respectively, which were comparable with those reported previously for secondary

ESD. **And, two patients in the early salvage ESD group had no residual tumor. Although, they showed histological confirmation of positive lateral margins of the initial ESD specimen, no residual lesion might be detected due to burning effects on tissue by electrosurgical unit.**

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**For reviewer 2:**

I appreciate your kind and careful comments on our paper.

**This entitles “Secondary Endoscopic Submucosal Dissection for Locally Recurrent or Incompletely Resected Gastric Neoplasms” is well-written but there are some comments. I have following comments –**

**1. The authors should replace “non-curative resection” with “positive lateral margins or local recurrence after curative primary ESD. Because no-curative section includes a lot of situations.**

--> We think that your comment is very important. As your comments, non-curative resection includes many situations. Therefore, we defined curative resection as expanded indications according to the Japanese gastric cancer treatment guidelines. According to the Japanese gastric cancer treatment guidelines, the expanded indications for curative ER (endoscopic resection) were en bloc resection, negative lateral and vertical margins, no lymphovascular invasion (LVI) and one of the following: (a) tumor size > 2 cm, differentiated type, mucosa, and ulcer (-); (b) tumor size ≤ 3 cm, differentiated type, mucosa, and ulcer (+); (c) tumor size ≤ 2 cm, undifferentiated type, mucosa, and ulcer (-); or (d) tumor size ≤ 3 cm, differentiated type, and submucosal (SM1, < 500 μm from the muscularis mucosa). ER that does not satisfy these criteria is considered non-curative resection, and additive surgical treatment should be performed in such cases because of the risk of LNM. Therefore, we used non-curative resection as mentioned above. As your comments, we added sentences into the method like below.

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Curative resection was defined as expanded indications according to the Japanese gastric cancer treatment guidelines <sup>[5]</sup>. **According to the Japanese gastric cancer treatment guidelines, the expanded indications for curative ER (endoscopic resection) were en bloc resection, negative lateral and vertical margins, no lymphovascular invasion (LVI) and one of the following: (a) tumor size > 2 cm, differentiated type, mucosa, and ulcer (-); (b) tumor size ≤ 3 cm, differentiated type, mucosa, and ulcer (+); (c) tumor size ≤ 2 cm, undifferentiated type, mucosa, and ulcer (-); or (d) tumor size ≤ 3 cm, differentiated type, and submucosa1 (SM1, < 500 μm from the muscularis mucosa).**

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**2. I was wondering what depended on the treatment strategy, early salvage ESD or late salvage ESD. I feel there was a selection bias.**

--> We are very thankful for your kind comments on our paper. Because this is the retrospective study, there was a selection bias. We could not evaluate the reasons for choice of treatment strategy why physician selected early salvage or late salvage ESD.

**3. The authors should the detail of initial lesion corresponding to secondary ESD.**

--> We are very thankful to your thoughtful comment. As your comments, we investigate the initial lesion corresponding to secondary ESD. Five patients received primary ESD at outside the hospital. And, other patients received primary ESD at Gangnam Severance Hospital. The initial lesions corresponding to secondary ESD were dysplasia in 13 patients, and carcinoma in 15 patients. A total of 15 patients with carcinoma had mucosal cancer without lymphovascular invasion. As your comments, we added sentences into the result like below.

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There were significantly more depressed macroscopic lesions in the secondary ESD group and there were no significant differences in lesion location or size between the two groups. **And, we investigated the initial lesion corresponding to secondary ESD. The initial lesions corresponding to secondary ESD were dysplasia in 13 patients, and carcinoma**

**in 15 patients. A total of 15 patients with carcinoma had mucosal cancer without lymphovascular invasion.**

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**4. I think it is difficult to conclude that this paper is the first study to report the feasibility and safety of secondary ESD according to the timing of ESD because of above selection bias or retrospective study.**

--> We think that your comment is very important. Although this is the retrospective study, there is no consensus on the timing of salvage ESD. Until now, there were few reports about the feasibility and effectiveness of early salvage ESD. To the best of our knowledge, this is the first study to report the feasibility and safety of secondary ESD according to the timing of ESD.