

Answering Reviewers

We appreciate reviewers' kind and careful comments on our paper.

COMMENTS TO AUTHORS

The authors present their case series of post procedural pain following endoscopic submucosal dissection of esophagus and try to correlate it with various factors. Though a small sample, yet it sheds light on a common problem after such procedures

Reply:

We appreciate your careful comments on our paper. We believe that the first definition of a clinical syndrome that can be often encountered is the advantage of this study. Thank you again for your thoughtful comments.

COMMENTS TO AUTHORS

This is a retrospective study addressing the analysis of PEECS for esophageal lesions. I have some comments:

1. According to the authors it is the first series describing the PEECS for esophageal lesions. This is an advantage of the study. The authors should stress it in the introduction as it is "new" data.

Reply:

We are very thankful to your thoughtful comment. We agree with your suggestion, and we think it is the advantage of this study that we first described it. Therefore, we would like to enhance this advantage by adding the following to the manuscript, Introduction section. Thank you again for your sincere advice.

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Several previous studies analyzed PEECS after gastric or colonic ESD, but PEECS after esophageal ESD has not been studied yet^[12,13]. Actually, some patients demonstrate clinical signs of PEECS after esophageal ESD associated with fever, chest pain and leukocytosis, despite the absence of perforation. However, the possibility of PEECS in the esophagus has received little attention. **As far as we know, no studies have yet been conducted on PEECS in the esophagus, and we tried to investigate this new study.** Therefore, we aimed to evaluate the incidence and risk factors of PEECS in the esophagus.

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2. It remains unclear what time (how many years) it took to make 55 ESD?

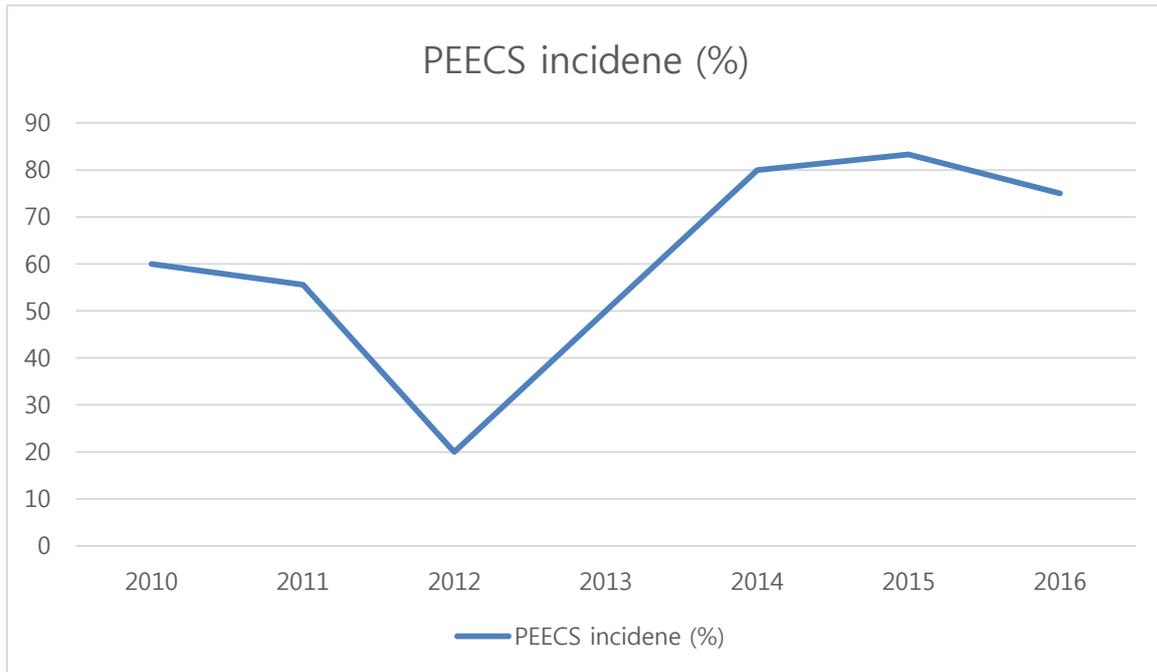
Reply:

We are very thankful for your thoughtful comment. We retrospectively analyzed prospectively collected database of patients who underwent esophageal ESD for superficial esophageal squamous neoplasms between March 2009 and December 2016 at Gangnam Severance Hospital, Seoul, Korea. Therefore, we have collected about 7 years of data and these are explained in the Material and Method section. We hope that it will be a satisfactory answer for you.

3. It would be interesting to analyze if the learning curve is related with PEECS? Was it more in the first period?

Reply:

We appreciate your careful comments on our paper. We think your opinion is very interesting. Therefore, we analyze a relationship between the procedure year and PEECS like below.



Unfortunately, the incidence of PEECS according to the procedure year was not statistically significant. We thank you for your advice once again and add the following to the Result section.

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However, patient-related factors (sex, age, comorbidity) and tumor-related factors (gross appearance, tumor location, tumor histology, tumor invasion depth) were not significantly associated with the development of PEECS (Table 2). **Also, ESD learning curve did not show statistically significant relationship with PEECS.** Multivariate analysis revealed that a resection area larger than 6.0 cm² (odds ratio [OR] 4.995, 95% confidence interval [CI] 1.110 - 22.489, *P* = 0.036) and a present of muscle layer exposure (OR 5.661, 95% CI 1.422 - 22.534, *P* = 0.014) were independent risk factors for PEECS (Table 3).

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4. Was it operator dependent?

Reply:

We appreciate your careful comments on our paper. Two experienced operators (Y.H.Y and J. K) performed esophageal ESD. The difference in PEECS incidence among the operators was not statistically significant (55.8% vs 50%, $P = 0.529$). We revised the Results resection as you mentioned. We thank you for your proper comments.

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However, patient-related factors (sex, age, comorbidity) and tumor-related factors (gross appearance, tumor location, tumor histology, tumor invasion depth) were not significantly associated with the development of PEECS (Table 2). Also, ESD learning curve did not show statistically significant relationship with PEECS. **The difference in PEECS incidence among the operators was not statistically significant (55.8% vs 50%, $P = 0.529$).** Multivariate analysis revealed that a resection area larger than 6.0 cm² (odds ratio [OR] 4.995, 95% confidence interval [CI] 1.110 - 22.489, $P = 0.036$) and a present of muscle layer exposure (OR 5.661, 95% CI 1.422 - 22.534, $P = 0.014$) were independent risk factors for PEECS (Table 3).

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5. The major problem is - retrospective design, which is usually related with some data recording bias? It may lead to biased results and conclusions

Reply:

We are very thankful to your thoughtful comment. Since this study is a retrospective design, it has several limitations like you mentioned. Therefore, we added relevant contents to Discussion section.

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There are several limitations of our study. First, it was a small number and retrospective study that was performed at a single center. Thus, the cut off values we have established need external validation. **Furthermore, there may be a recording**

bias because of retrospective design.

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COMMENTS TO AUTHORS

This is very interesting paper about PEECS. Author concluded that esophageal PEECS is a systemic inflammatory response syndrome caused by electrical burns and transmural penetration of oro-esophageal secretion rather than true infection. I ask some question.

1. Please comment the difference of the criteria of SIRS between PEECS and no PEECS. SIRS: pulse, fever, respiratory rate,leukocyte

Reply:

We are very thankful to your thoughtful comment. In 1992, the American College of Chest Physicians and the Society of Critical Care Medicine defined systemic inflammatory response syndrome as 2 or more of the following variables:

- ✓ Fever of more than 38°C or less than 36°C
- ✓ Heart rate of more than 90 beats per minute
- ✓ Respiratory rate of more than 20 breaths per minute or arterial carbon dioxide tension (PaCO₂) or less than 32 mm Hg
- ✓ Abnormal white blood cell count (>12,000/μL or <4,000/μL or >10% immature [band] forms)

However, the definition of PEECS has not been established, and it has been variously defined in several studies. In our study, we defined PEECS in the esophagus as meeting one of the following criteria without any obvious perforation: fever ($\geq 37.8^{\circ}\text{C}$), leukocytosis (> 10800 cells/ μl), or regional chest pain more than 5/10 points as rated on a numeric pain intensity scale. It is similar to the definition of

SIRS (fever, leukocytosis), but not exactly same. In our data, there were no patients who fit the definition of SIRS regardless of PEECS. Perhaps it was because we excluded patients who had definite complications such as infection or perforation. We therefore believe that PEECS is a different clinical syndrome from SIRS. Having accepted your meticulous advice, we revised the discussion section as follows.

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This is the first study of PEECS for esophageal lesions. PEECS is a common clinical syndrome characterized by chest pain, leukocytosis, or fever after esophageal ESD. **It is another kind of clinical syndrome that is different from systemic inflammatory response syndrome.** However, PEECS can be easily controlled by conservative management without surgical intervention when there is no obvious perforation. We found that the incidence of PEECS was high when the resected tumor area exceeded 6.0 cm² or when the muscle layer exposure was present. If these risk factors are accompanied, careful attention should be paid to the potential occurrence of PEECS after esophageal ESD.

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