Author’s response to reviews

**Title:** A randomized controlled trial of endoscopic steroid injection for prophylaxis of esophageal stenoses after extensive endoscopic submucosal dissection

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**Author’s response to reviews:** see over
Dear Dr. Morawska:

RE: MS: 1354694746131717

A randomized controlled trial of endoscopic steroid injection for prophylaxis of esophageal stenoses after extensive endoscopic submucosal dissection

Thank you for your decision letter of 30 October 2014. We appreciate your supportive response regarding our manuscript. We are resubmitting the enclosed manuscript, A randomized controlled trial of endoscopic steroid injection for prophylaxis of esophageal stenoses after extensive endoscopic submucosal dissection, for reconsideration of publication in BMC Gastroenterology as a Research Article.

In accordance with your suggestions, we have revised our paper. We believe that it now addresses all aspects of the reviewers’ comments. We hope that you will find it suitable for publication.

Thank you for your reconsideration of our paper and we look forward to hearing from you.

Yours sincerely,

Yoshiaki Arimura, M.D.
Authors’ Reply to Reviewers:

Referee 1 Comments:
1. The case number for final analysis was obviously not reached (should have been 16 per group). Please comment on this in the Discussion section, because it weakens the validity of the study.

Response: Thank you for your advice. Original descriptions concerning this (the first paragraph in the Results section and Figure 5) appeared to be misleading. According to your suggestion, we have rewritten and highlighted them in red to make it clearer that the case number for final analysis is 16 per group.

Referee 2 Comments:
1. Pech Oliver et al recently published in Gastroenterology a study with over 1000 patients which proved that endoscopic mucosal resection is a safe procedure with a very high rate of complete remission. Rates of esophageal stenosis are much lower after EMR than after extensive ESD. Moreover this, there was only one perforation in the whole study-population. The question is: why perform ESD with risk for consecutive esophageal stenosis and the need of dilatation, instead of using EMR? Please discuss these facts in your manuscript.

Response: Thank you for your insightful comment. Fundamentally, an expected circumferential mucosal defect involving ≥75% of the circumference of the esophagus could not be treated by EMR. Such patients with an extensive mucosal defect were eligible for this study. Furthermore, we had previously discussed this issue in detail in an earlier manuscript (Ref 1, Takahashi et al. Gastrointest Endosc 2010, 72:255–264, 264.e1–2). Therefore, we would like to discuss this matter briefly here.

EMR has been widely accepted as an effective, minimally invasive treatment for early esophageal cancer. EMR is also accepted as potentially curative in patients with negligible risks of nodal involvement. En bloc curative resection, meaning
resection in a single piece with tumor-free lateral and vertical margins, is considered to be the ideal for both endoscopic and surgical resection because it provides an accurate histological assessment and reduces the risk of recurrence. Because piecemeal EMR, meaning EMR in multiple segments, was previously reported to be a risk factor for postoperative local recurrence, en bloc resection, which depends on technical expertise, is desirable for early esophageal cancer. Furthermore, accurate pathological analysis including risk evaluation of lymph node metastasis may be extremely difficult after piecemeal resection.

In comparison with EMR, en bloc resection and the local recurrence rate were significantly better in the ESD group (P = .0009 and .065, respectively). The frequency of perforation was not significantly different between the two groups (P = .68). Four independent risk factors for local recurrence were identified by the Cox regression model: EMR, deep cancer invasion, upper esophagus location and family history of esophageal cancer. A radical cure is mostly obtained by successful endoscopic retreatment of local recurrence after previous endoscopic resection. Disease free survival was significantly better with ESD. Consequently, we concluded that ESD shows a higher cure rate and is safer than conventional endoscopic resection when applied to early esophageal cancer. If you have any further questions, it may be helpful to refer to our original paper.

2. In table number 2 there are 3 carcinomas with deeper submucosal invasion (sm2). These patients have a relevant risk to develop lymphoid metastasis. Why wasn’t surgery performed? Please comment on this.

**Response:** Thank you for your comment. Three patients with sm2 invasion had relative contraindications for surgical intervention falling under any of the following reasons: age considerations (patients were 76, 79 and 89 years old), serious medical conditions (affecting cerebral vascular disease, multiple primary cancers, and low performance status), and/or decisions to decline surgery. A treatment plan for these patients was carefully chosen under full informed consent. These descriptions are
included in the footnotes in Table 2.

**Editorial Comments:**

1. As part of the process of revising your manuscript we would like to use the WebCONSORT tool which is designed to help you improve the reporting of your randomized trial.

    **Response:** Thank you for your advice. We registered WebCONSORT and received WebCONSORT registration confirmation e-mail.

2. Please include the full name of the ethics committee that approved your study.

    **Response:** Thank you for your advice. The full name, the Ethics Committee of Keiyukai Sapporo Hospital, was included (Page 6, Line 5).

3. Please include the date of trial registration in the abstract.

    **Response:** Thank you for your advice. Information of trial registration was included in the abstract.