

Format for ANSWERING REVIEWERS



October 21, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: KGH-PNUH_2.doc).

Title: Is endoscopic submucosal dissection safe for papillary adenocarcinoma of the stomach?

Author: Hyun Jeong Lee, Gwang Ha Kim, Do Youn Park, Bong Eun Lee, Hye Kyung Jeon, Joon Hyung Jhi, Geun Am Song

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 13837

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated, and we attached a PPT file for Figure 1 and 2.

2 Revision has been made according to the suggestions of the reviewer

(1) Answers to Reviewer 1

- ✓ Before definite treatment, such as ESD or surgery, all patients underwent abdominal CT to determine the presence of lymph node or distant metastases. In most EGC cases, EUS was performed to rule out submucosal invasion; therefore, we typically selected the treatment modality based on the EUS findings. However, although their lesions could have been treated by ESD, several patients initially visited the Department of Surgery and underwent surgery (rather than ESD), particularly in the early part of this study. Therefore, we have added the following sentences to the Methods section to more accurately describe how we selected the treatment modality.

“All patients underwent abdominal computed tomography (CT) to determine the presence of LN or distant metastases before ESD. Furthermore, endoscopic ultrasonography was performed as needed to rule out submucosal invasion.”

- ✓ We have revised the incorrect words.
- ✓ We have added the range for the curative resection rates and long-term outcomes as follows:
“Many recent studies have reported a high curative resection rate (84–95%) and excellent long-term outcomes (a 5-year survival rate of 92–100%) for ESD in EGC based on the absolute and expanded indications [1–4, 11].”
- ✓ We have added Table 5 to describe the characteristics of the ESD patients.
- ✓ We have already stated in the Results section that all patients who underwent additional surgery after ESD were included in Group 1.
“Forty patients underwent primary surgical operation, and the other 9 patients underwent an additional surgical operation for non-curative resection after ESD.”
- ✓ In addition, we have already described this topic (9 patients underwent additional

gastrectomy after ESD) using a footnote with an asterisk (*). In addition, we believe that it will unnecessarily complicate the figure if we insert an arrow between Groups 1 and 2. Therefore, if the present explanation is sufficient, we would prefer to retain this figure in its present form.

(3) Answers to Reviewer 2

- ✓ In our study, all patients underwent abdominal CT to determine the presence of lymph node or distant metastases before definite treatment with ESD or surgery. In most EGC cases, EUS was performed to rule out submucosal invasion. Therefore, if the EUS results suggested that the lesion was submucosal cancer, the patient would undergo surgery, although the final pathology results might still indicate mucosal cancer (after the surgery had been performed). Unfortunately, this is an inherent limitation of EUS. In our experience, the accuracy of EUS for papillary adenocarcinoma is somewhat lower than that for other differentiated-type cancers. In addition, although their lesions could be treated by ESD, several patients initially visited the Department of Surgery and underwent surgery (rather than ESD), particularly in the early part of this study. Interestingly, if a lesion is included in the expanded indication, several surgeons recommend using laparoscopic gastrectomy instead of ESD. This is why several patients with a mucosal cancer underwent surgery, despite the final pathology report indicating their eligibility for ESD.
- ✓ We have added the information regarding D1 and D2 lymphadenectomy to the Results section as follows:

Laparoscopy-assisted gastrectomy with D1 lymphadenectomy was performed in 9 patients, laparoscopy-assisted gastrectomy with D2 lymphadenectomy in 17 patients, and open gastrectomy with D2 lymphadenectomy in 23 patients.
- ✓ First, we reviewed the pre-ESD biopsy results, many of which were obtained at other institutions. Papillary adenocarcinoma was only diagnosed in 8 cases, and other diagnoses included well differentiated tubular adenocarcinoma, moderately differentiated tubular adenocarcinoma, or poorly differentiated adenocarcinoma. We then discussed with an expert pathologist whether it was possible to diagnose papillary adenocarcinoma only on the basis of endoscopic biopsies. This pathologist (Do Youn Park) is an expert pathologist at our hospital, and is interested in the field of EGC. As you know, it is impossible for a small amount of tissue (e.g., a biopsy specimen) to accurately represent the complete pathology of the whole specimen. In addition, other components, such as tubular adenocarcinoma or poorly differentiated adenocarcinoma, can mix with the papillary adenocarcinoma, further complicating the diagnosis. Therefore, we believe that it would be very difficult to diagnose papillary adenocarcinoma using only the pre-ESD biopsy results. In the near future, we plan to study the endoscopic characteristics of papillary adenocarcinoma, including those obtained using magnifying endoscopy, to overcome these challenges.
- ✓ The following sentence in the Discussion section is correct: "The overall incidence of LN metastasis in EGC is known to exceed 10% (2-5% for mucosal cancer vs. >20% for submucosal cancer; 0.4% for differentiated-type intramucosal cancer vs. 4.2-7.3% for undifferentiated-type intramucosal cancer)". We have stated that the incidence of LN metastasis in EGC, including mucosal and submucosal cancers (i.e., T1 lesions), is >10%. According to the previous reports, the incidence of submucosal cancer was 23.6%; therefore, we stated >20% for submucosal cancer. The following sentences are taken from previously published reports.

Many studies have clarified the status of LN metastasis in EGC. The overall incidence of LN

metastases in T1 EGC is 10 to 20%. The characteristics of the tumor such as the size, cancer depth, histologic type, and the presence of lymphovascular invasion are important determinants of the likelihood of spread. For example, the Roviello *et al.* study evaluating 652 cases of resected EGC showed that the incidence of LN metastasis to be 14.1% overall: 4.8% *versus* 23.6% for mucosal *versus* submucosal cancer.

Even in early gastric cancer (EGC), the incidence of lymph node (LN) metastasis exceeds 10%; it was reported to be 14.1% overall and was 4.8 to 23.6% depending on cancer depth.

Akagi T, Shiraishi N, Kitano S. Lymph node metastasis of gastric cancer. *Cancers* 2011; **3**(2): 2141-2159

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'G. Kim', with a stylized flourish at the end.

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