

Jan. 1st, 2016

Dear prof.

**RE: Risk factors for local recurrence after en bloc endoscopic submucosal
dissection for early gastric cancer**

Ju Yup Lee, Kwang Bum Cho, Eun Soo Kim, Kyung Sik Park, Yoo Jin Lee,
Yoon Suk Lee, Byoung Kuk Jang, Woo Jin Chung, and Jae Seok Hwang

Thank you very much for giving us an opportunity for revision. Accurate and kind comments by the reviewer have been addressed. We also believe that these comments improved our manuscript. Changes have been made by changing the font to [Blue](#) in the main manuscript body or red colored letters in case of table in the revised manuscript to avoid any confusion.

I anticipate good response.

Thank you!

Sincerely,

Kwang Bum Cho, M.D., Ph.D.

Reply to Reviewer's comments

Reviewer A:

Comments to the author:

This study is fine. It touches on interesting and important topics. Following points should be considered.

1. Please use not more than two significant digits for all p values. Eg, 0.82, 0.082, 0.0082. Not 0.821, 0.0821.

Answer: Thank you for the kind and accurate advice. Following the reviewer's comment, we correct all p values in manuscript and tables.

2. Please discuss that lack of tumor molecular data is a weakness. Please discuss recent "molecular pathological epidemiology (MPE)" approach (there are several papers on this concept, eg, Gut 2011; Mod Pathol 2013; Cancer Causes Cont 2015), which analyzes tumor molecular pathology of resected tumors. For instance, R Nishihara et al. NEJM 2013 showed that post-colonoscopy cancers are more likely microsatellite instability-high (MSI-high) subtype. In gastric cancer, MSI-high tumor may be difficult to be completely removed. This can help identify people with high risk for recurrence or subsequent cancer.

Answer: Thank you for the kind advice. Following the reviewer's comment, we discussed tumor molecular pathology in discussion section as follow;

A molecular pathological epidemiology approach, which analyzes tumor

molecular pathology of resected tumors, can predict recurrence after ESD. Semba et al.^[27] reported that EGC demonstrating intestinal claudin-positive phenotype has a high risk of synchronous and metachronous gastric neoplasia. Hasuo et al.^[28] investigated the correlation between microsatellite instability (MSI) status and the incidence of metachronous recurrence after initial ESD. They demonstrated that patients with the MSI-type tumors showed a high incidence of metachronous recurrence within a 3-year observation period after initial ESD. These molecular approaches are expected to be of value for decisions regarding therapy and surveillance after ESD.

And also added references are as follow;

27 **Semba S**, Hasuo T, Satake S, Nakayama F, Yokozaki H. Prognostic significance of intestinal claudins in high-risk synchronous and metachronous multiple gastric epithelial neoplasias after initial endoscopic submucosal dissection. *Pathology international* 2008; **58**(6): 371-377 [PMID: 18477216 DOI: 10.1111/j.1440-1827.2008.02238.x]

28 **Hasuo T**, Semba S, Li D, Omori Y, Shirasaka D, Aoyama N, Yokozaki H. Assessment of microsatellite instability status for the prediction of metachronous recurrence after initial endoscopic submucosal dissection for early gastric cancer. *Br J Cancer* 2007; **96**(1): 89-94 [PMID: 17179982 PMCID: PMC2360225 DOI: 10.1038/sj.bjc.6603532]

Reply to Reviewer's comments

Reviewer B:

Comments to the author:

This is a large retrospective study on risk factor for local recurrence after endoscopic submucosal dissection (ESD) of early gastric cancer. The topic is important and interesting, but some points require discussion:

1. the method of exclusion from the study is not clear, particularly the deep and lateral invasion of the tumor.

Answer: Thank you for the kind advice. Following the reviewer's comment, we described more details about deep and lateral margins as follow;

Because we aimed to evaluate the risk factors for local recurrence after en bloc resection only and to analyze the risk factors depending on the safety resection margin,

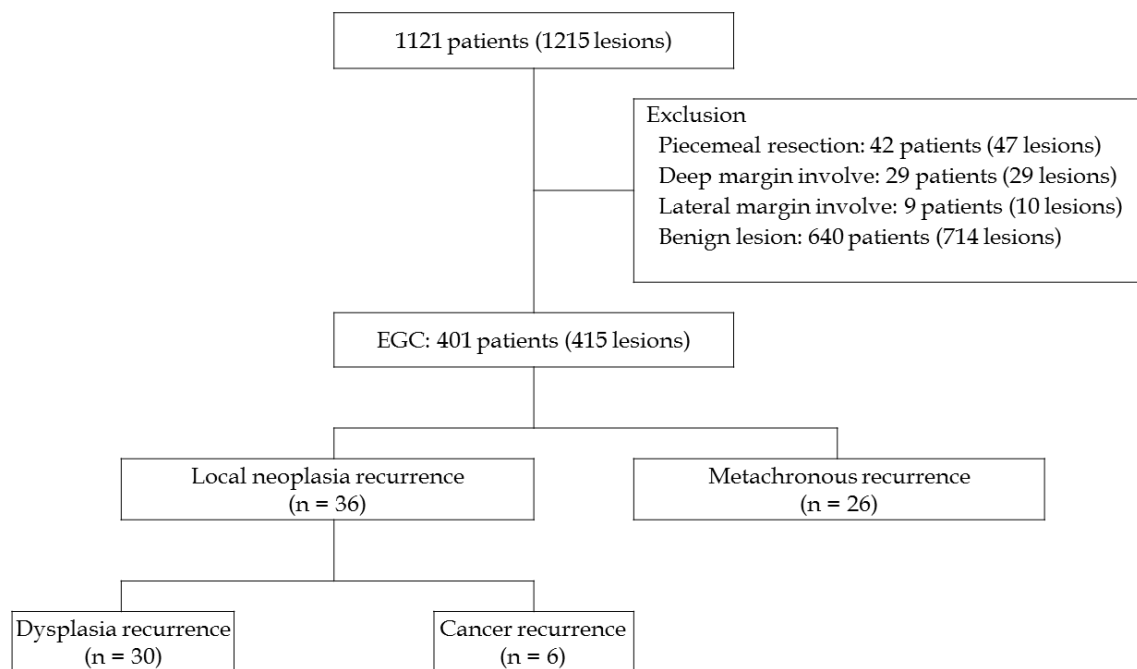
2. Risk of recurrence after ESD for lesions located in the upper third may suggest other therapeutic options?

Answer: Thank you for the kind advice. It did not suggest other therapeutic options, however, in order to reduce post-ESD local recurrences, it would be better to implement the procedures after having more careful assessment when the tumor is located upper third more.

3. Fig 1 from 1121 total patients after exclusio 401 patients were included in the study. What about the remaining patients?.

Answer: Thank you for the kind and accurate advice. A number of 640 patients (710 lesions) that diagnosed with benign lesion also excluded in this study. Following the reviewer's comment, we described it in method and revised figure as follow;

patients who underwent partial resection, with deep resection margin invasion or lateral margin infiltration, and diagnosed with benign lesions were excluded. Finally, data from 401 patients (415 lesions) were analyzed (Figure. 1).



Reply to Reviewer's comments

Reviewer C:

Comments to the author:

At present endoscopic submucosal dissection (EMR) for early gastric cancer is an important technique in advanced endoscopy. The assessment of deep invasion and complete resection of the tumor are the main questions in this field. For this reason accurate analysis of risk factors for local recurrence is a very interesting subject. The authors present a large retrospective series of patients submitted to EMR with a large number of exclusions. Although the analysis is useful for the readers that use this endoscopic technique some remarks should be taken into account.

1. In Methods deep lesion exclusion, which is another important factor related complete resection of the lesions, is not considered. Some comment on this aspect should also be included in the Discussion. What was the method for excluding lesions considered as having deep invasion from the analysis? Some comparison between the total series and the cases included should be made since the conclusions include this concept.

Answer: Thank you for the kind and accurate advice. Because we aimed to evaluate the risk factors for local recurrence after en bloc resection only and to analyze the risk factors depending on the safety resection margin, patients who underwent partial resection, with deep resection margin invasion or lateral margin infiltration, and diagnosed with benign lesions were excluded. Finally,

data from 401 patients (415 lesions) were analyzed.

2. Related to location, are there any bias comparing the lesions included and excluded?

Answer: Thank you for the kind and accurate advice. In this article, the EGC location was classified into upper third, middle third and lower third according to the location of center point. Upper third include cardia, fundus, and proximal body and middle third include low to mid body and lower third include antrum. I agree with the reviewer's opinion and there is some subjective point of view in determining location of tumor and it can act as a bias. However, I'm confident our expert endoscopists can make the bias minimum.

3. The statement of recurrence is confusing and should be rewritten, mainly for clarifying the terms and the definition of "local cancer recurrence" and "cancer recurrence" which were considered two different groups of patients in the paper (Page 7).

Answer: Thank you for the kind and accurate advice. We unify it as local cancer recurrence.

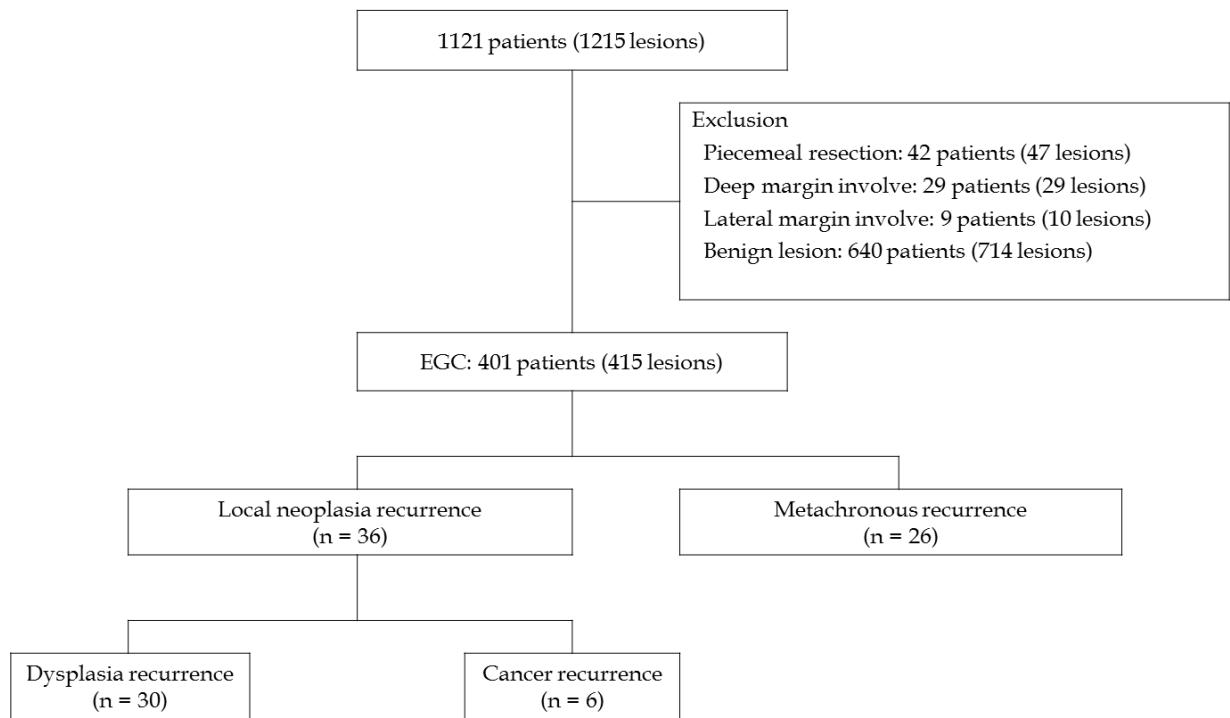
4. Long procedures and those performed in the upper third of the stomach are probably associated variables, which means that they are dependent inducing inadequate statistical interpretation.

Answer: Thank you for the kind and accurate advice. In multivariate analysis, the variable “long procedure time” did not reach a statistical significance (OR = 1.006, $P > 0.005$). Long procedure time was strongly correlated with tumor size and tumor location, so it acts as a confounding factor.

5. In figure 1 the numbers are difficult to interpret because 1121 patients with 80 exclusions do not correlate with the total of 401 patients included. These figures should be (arranged) recalculated for better interpretation.

Answer: Thank you for the kind and accurate advice. A number of 640 patients (710 lesions) that diagnosed with benign lesion also excluded in this study. Following the reviewer’s comment, we described it in method and revised figure as follow;

Patients who underwent partial resection, with deep resection margin invasion or lateral margin infiltration, and diagnosed with benign lesions were excluded. Finally, data from 401 patients (415 lesions) were analyzed (Figure. 1).



6. The English should be improved.

Answer: Thank you for the kind advice. Following the reviewer's comment, English was corrected by native English speaker.

The authors really appreciate the reviewer's kind and accurate comments. The revision based on these comments made this manuscript more accurate and the quality improved. Thank you again.

Kwang Bum Cho, M.D., Ph.D.