

Format for ANSWERING REVIEWERS



April 20, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 10012-review.doc).

Title: Endoscopic features suggesting gastric cancer in biopsy-proven gastric adenoma with high-grade neoplasia

Author: Jung Ho Kim, Yoon Jae Kim, Jungsuk An, Jong Joon Lee, Jae Hee Cho, Kyoung Oh Kim, Jun-Won Chung, Kwang An Kwon, Dong Kyun Park, Ju Hyun Kim

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 10012

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

1 Format has been updated

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

THE REVISIONS

⇒ We have modified the manuscript based on the review and added the requested data and discussion. This is denoted by sky blue-highlighted text.

REVIEWER 1

This is a retrospective study of patients with gastric lesions where biopsies showed gastric adenoma with high-grade dysplasia. Half of these patients turned out to have cancer and endoscopic features in this group were compared with those who didn't have cancer.

Major comments:

1. It has already been shown that, as the authors indicate, lesions greater than 1 cm, a depressed lesion and mucosal erythema are predictive for cancer. How does this study add to what is already known?

⇒ Previous studies have been conducted to identify predictive factors in adenomas for high-grade neoplasia (HGN) or carcinoma because these require different therapeutic plans. No previous studies have identified a predictive factor for cancer upon the diagnosis of HGN from endoscopic forceps biopsies (EFB). So, we had to perform this study, the aim of this study was to identify endoscopic features predicting cancer after endoscopic submucosal dissection (ESD) in patients with an initial diagnosis of gastric adenoma with HGN. In our study, the multivariate analysis showed that only a red color change and mucosal ulceration were independent risk factors for cancer in HGN. Based on the previous literature and our results, we hypothesize that morphological changes occur in a sequential order while low-grade neoplasia (LGN) progresses to HGN and then cancer. If the size of a depressed lesion increases, and surface erythema or surface ulceration develops within LGN, this indicates a high potential for malignant transformation into HGN or cancer. We suggested that red color change and mucosal ulceration are the two most reliable predictive factors for cancer in adenoma with HGN.

2. The authors claim that size, nodularity and macroscopic type are not predictive factors for cancer. Is it possible that these observations are due to a type 2 error due to the sample size? Even if the endoscopic features of ulceration and red colour change are found, how will this change management, as the lesion needs to be excised anyway?

⇒ In patients with early gastric cancer (EGC), the method of resection is determined depending on whether or not lymph node metastasis is present. In the present study, 53.6% of patients with gastric HGN were shown to have gastric cancer after ESD. Therefore, we suggested that the need to evaluate potential lymph node metastasis should be considered before endoscopic resection for predicted EGC. In patients with HGN by EFB, there is no standard pre-resection diagnostic, and pre-resection evaluation for invasion and metastasis in patients with HGN is not recommended. In present study, HGN in lesions with red color change and mucosal ulceration is correlated with the presence of gastric cancer. Therefore, if these findings exist, re-biopsy or staging work up for EGC is considered to avoid the meaningless ESD or endoscopic mucosal resection.

The Discussion has been modified and limitation of this study included to improve clarity.

3. What types of endoscopies and processors were used? Were they magnifying endoscopes? High definition?

⇒ The Method (endoscopic procedures) has been modified and additional information included to improve clarity.

4. A photo of a red colour change would be very helpful.

⇒ Thank you very much for your comments.

5. Although the authors describe the Paris classification in their Methods, it is not presented in their results.

⇒ As described in the Method section, the Paris classification was used for distinguishing detailed patterns of lesions, after which the results were classified into three categories - elevated, flat or depression lesion.

Minor comments:

1. The abstract needs to have a brief background to the rationale of the study.

⇒ The manuscript was prepared in accordance with the author guideline.

⇒ [Structured abstract: AIM (no more than 20 words): Only the purpose should be included. Please write in the form of "To investigate/study/...".]

2. Abstract and methods: the two comparative groups need to be defined.

⇒ We have modified the manuscript accordingly and added the requested data.

The definitions of the two comparative groups had been provided in the Histologic procedure in the Methods section but were moved to the Study population to help readers understand them better.

3. Methods, study population: what does it mean by informed consent was "waived"?

⇒ We have modified the manuscript to eliminate this confusion.

4. The authors themselves indicate that biopsies can result in submucosal lesion fibrosis making endoscopic resection difficult. Can a case be made for not biopsying but relying on endoscopic features alone for diagnostic purposes?

⇒ As described in the Discussion and Comment section, a detailed endoscopic morphological evaluation could provide useful information for selection of the optimal subsequent evaluation methods and treatment strategy prior to endoscopic resection. However, conventional endoscopic findings should be applied complementary with other techniques.

Also, a histologic diagnosis from EFB samples provides the most reliable information for the diagnosis of gastric neoplasia prior to complete resection. Endoscopic findings should be used as additional information.

5. Figure 1: what is the difference between A and B?

⇒ A is a white light endoscopic view and B is a chromoendoscopic view. The latter will be helpful for readers in understanding the gross shape of the lesion.

REVIEWER 2

This is a retrospective study trying to demonstrate the high rate of carcinomas which have been characterized as high grade neoplasms on forceps biopsies. The pathological diagnoses of these lesions are very difficult. There are some of the comments described as follows

1. The authors did not clarify who made pathological diagnoses. All the histopathological findings (of both biopsies and resected specimens) need to be reviewed by one or two experienced pathologists who are blind to both initial diagnosis and the clinical findings when the authors conduct such studies.

⇒ We have modified the manuscript accordingly and added the requested data. (in method section [histologic procedure] and discussion section [limitation])

2. It is very difficult to distinguish among category 4-1 high grade dysplasia, 4-2 non-invasive carcinoma and 4-4 intramucosal carcinoma according to the revised Vienna classification. The authors should show a case upgraded to cancer or downgraded to low grade adenoma with pathological findings of both forceps biopsies and resected specimens.

⇒ We have modified the manuscript accordingly and added the requested data. (Figure 1 and 2).

⇒ Figures of the cases whose final diagnosis was LGN are added.

3. The reference (number; 13, Min BH et al.) that the authors cited also determined the category of gastric epithelial neoplasia according to the revised Vienna classification. It should be presented in "Histologic procedure".

⇒ Thank you very much for your comments. However, we provided a full explanation on the Vienna classification category 3 and 4 in the Introduction and details of pathologic diagnosis in the Histologic procedure. It seems unnecessary to repeat the explanation on the category of gastric epithelial neoplasia in the Histologic procedure again.

4. Mucosal high grade neoplasia according to Vienna classification is recommended for endoscopic or surgical resection. And previous reports showed that HGN on forceps biopsies was one of the predictors of carcinomas. What HGN on forceps biopsies is a candidate for not resection and follow up. If this point was clear, endoscopic findings might help to guide treatment in patients with HGD on forceps biopsies. 5. This study demonstrated that only 14% of high grade neoplasms by initial diagnosis was downgraded to low grade neoplasms after endoscopic resection. More than 85% of them were classified to category 4 before and after total biopsy. Although the authors mentioned that endoscopic findings might help to guide treatment in patients with HGD, I do not think that endoscopic findings would change treatment strategies for these lesions in this study because of this high rate of category 4 after resection.

⇒ In patients with early gastric cancer (EGC), the method of resection is determined depending on whether or not lymph node metastasis is present. In the present study, 53.6% of patients with gastric HGN were shown to have gastric cancer after ESD. Therefore, we suggested that the need to evaluate potential lymph node metastasis should be considered before endoscopic resection for predicted EGC. In patients with HGN by EFB, generally there is no need to evaluate the invasion or metastasis before resection in patients with HGN is not recommended. In present study, HGN in lesions with red color change and mucosal

ulceration is correlated with the presence of gastric cancer. Therefore, these findings suggesting gastric cancer may help to determine the diagnosis and guide treatment in patients with HGN.

6. The study from Min Kyu Jung et al (Surg Endosc (2008) 22:2705–2711) and Akiyoshi Kasuga et al (Digestive Endoscopy (2012) 24, 331–338) should be added in the references and discussed.

⇒ Several references were updated and two references [Min Kyu Jung et al (Surg Endosc (2008) 22:2705–2711) and Akiyoshi Kasuga et al (Digestive Endoscopy (2012) 24, 331–338)] were added. Also, We have modified the manuscript based on the review and added the requested data and discussion.

3 References and typesetting were corrected

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

Yoon Jae Kim, MD.

Sincerely yours,



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