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Original article

# Occurrence of metachronous or synchronous lesions after endoscopic treatment of gastric epithelia dysplasia- impact of histologic features of background mucosa

Won-Young Park[a,1], So-Jeong Lee[a,1], Young-Keum Kim[a], Ahrong Kim[a], Do Youn Park[a,*], Bong-Eun Lee[b], Geun-Am Song[b], Gwang Ha Kim[b]

[a] Department of Pathology, Pusan National University Hospital and Pusan National University School of Medicine, and BioMedical Research Institute, Pusan National University Hospital, Busan, South Korea
[b] Department of Gastroenterology, Pusan National University Hospital and Pusan National University School of Medicine, and BioMedical Research Institute, Pusan National University Hospital, Busan, South Korea

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ABSTRACT

*Aims:* Endoscopic resection is a safe and effective method to treat gastric epithelia dysplasia (GED). However, the development of metachronous and synchronous lesions after treatment has become a major concern. In this study, we investigated clinicopathologic features of 105 GED lesions from endoscopic resections between January 2008 and December 2009. Our goal is to find histologic factors that predict synchronous and metachronous lesions after ESD treatment. We assessed the degree of intestinal metaplasia (IM) and atrophy, type of IM, presence of gastritis cystica profunda, and crypt dysplasia in the adjacent mucosa.

*Methods and results:* We divided 105 GED lesions into three groups: a single group without metachronous or synchronous GED or adenocarcinoma (n = 35); a multiple synchronous group (n = 30, group with synchronous occurrence of GED or adenocarcinoma after treatment); and a multiple metachronous group (n = 40, group with metachronous occurrence of GED or adenocarcinoma after treatment). The multiple metachronous and synchronous groups showed larger sizes (p = 0.003) and higher grades (p = 0.021) as compared with the single group. Furthermore, marked IM and atrophy in adjacent mucosa were more easily seen in the multiple metachronous and synchronous groups as compared with the single group (p < 0.0001). Interestingly, the presence of incomplete type of IM (p = 0.025) and crypt dysplasia (p < 0.0001) in background mucosa was associated with occurrence of metachronous and synchronous lesions following endoscopic resection of GED.

*Conclusions:* The histological features of background mucosa, such as intestinal metaplasia, atrophy, and crypt dysplasia could be used as indicators of occurrence of metachronous and synchronous lesions after endoscopic treatment of GED.

## 1. Introduction

Gastric epithelial dysplasia (GED) is universally accepted as a precursor lesion of intestinal type gastric adenocarcinoma [1,2]. With the recent development of endoscopic treatment modalities, endoscopic resection has become increasingly recommended as the standard treatment of GED. However, the occurrence of secondary GED and adenocarcinoma after endoscopic resection, either metachronous or synchronous, remains one of the serious concerns of endoscopic treatment of GED [3–8]. Therefore, it is important to predict occurrence of secondary synchronous or metachronous lesions after endoscopic resection of GED. Regarding risk factors to predict the occurrence of secondary synchronous or metachronous lesions after endoscopic resection of GED, most studies have focused on clinical risk factors, including endoscopic features. There are several studies that Helicobacter pylori eradication can reduce the risk of metachronous lesion after endoscopic resection of GED [9–11]. However, there are a few studies that have observed detailed histopathological features of GED and background mucosa influencing occurrence of secondary synchronous or metachronous lesions after endoscopic treatment of GED.

Classically, GED is broadly categorized into adenomatous (or intestinal), foveolar (or gastric), and hybrid types, based on morphologic

* Corresponding author at: Department of Pathology, Pusan National University Hospital and Pusan National University School of Medicine, 1–10 Ami-Dong, Seo-Gu, Busan, 602–739, South Korea.
*E-mail address:* pdy220@pusan.ac.kr (D.Y. Park).
[1] WYP and SJL contributed equally to this study.

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and immunophenotypic characteristics [13]. These types of GED are further characterized by specific types of background mucosa, revealing for example that adenomatous GED shows a complete type of intestinal metaplasia and foveolar type shows an incomplete type of intestinal metaplasia [12,13]. Moreover, there are several studies on specific histologic features, including crypt dysplasia and immature intestinal metaplasia, which were seen as background mucosa of gastric adenocarcinoma [14–17]. Collectively, these reports reinforce the hypothesis that various morphologic alternations of background mucosa could represent a source for multifocal occurrence of gastric epithelial neoplasm (GED, adenocarcinoma), and could be predictors of occurrence of secondary synchronous or metachronous lesions after endoscopic resection of GED. With this background information, we aimed to evaluate whether any histological features of background mucosa of GED lesions could influence the occurrence of secondary synchronous or metachronous lesions after endoscopic resection of GED, by retrospectively reviewing a series of 105 endoscopic resections of GED and background mucosa and collecting information including histologic type and grade of GED, degree of inflammation and/or atrophy, intestinal metaplasia type of intestinal metaplasia, and presence of crypt dysplasia of background mucosa.

## 2. Material and methods

### 2.1. Study group and clinical characteristics

This study included a cohort of patients who were diagnosed with GED and who underwent endoscopic dissection for diagnostic or therapeutic purposes at Pusan National University Hospital (PNUH) between 2008 and 2009 comprised of individuals from the same cohorts of our previously reported study [18].

Either endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) was used for resection of GED. A snare was used in EMR and a hook knife (Olympus Medical Systems Co Ltd, Tokyo, Japan) was used in ESD. All procedures were performed by expert endoscopist with 5 years or more of experience. We selected ER specimens having enough length of adjacent mucosa (at least 2 mm) of endoscopic resection specimen without cautery artefacts. The group consisted of 105 patients, with 85 men and 20 women with a mean of 66.5 years of age (38–85 years). This study was approved by the institutional review board. The following clinicopathological features were accrued for each of the cases: tumour location (upper, middle, and lower stomach), macroscopic gross type, and tumour size (in mm), as well as the histologic classification and grade. Helicobacter pylori infection was diagnosed based on either positive results on a rapid urease test (CLO test; Ballard Medical Products, Draper, Utah) or histological examination by routine hematoxylin and eosin staining with or without Warthin-starry silver staining at the time of first endoscopic resection of GED.

Patient follow-up was based only on endoscopy. The starting date of the follow-up was defined as the date of endoscopic resection, and the end of the follow-up was the last date of follow-up endoscopy. Follow-up endoscopy was performed initially at a point six months after endoscopic resection, and annually thereafter. Biopsy was performed at sites suspicious of harbouring synchronous or metachronous lesions; any elevated, depressed or discoloured lesions. A synchronous lesion, including GED and adenocarcinoma, was defined as either a concomitant lesion at the time of endoscopic resection, or a lesion detected within a 12-month period after endoscopic resection [8]. A metachronous lesion, including GED and adenocarcinoma, was defined as a lesion diagnosed 12 months after endoscopic resection for the primary lesion, and located in a different part of the stomach, so as to differentiate from recurrence [8]. The mean follow-up period of 105 GED lesions was 37.3 months (range, 12–70 months).

### 2.2. Histopathological evaluation

GED was classified histologically as either adenomatous, foveolar, or hybrid, based on published criteria [12,13]. Adenomatous GED resembled colonic adenoma and was comprised of large tubules lined with basophilic columnar cells with a dense eosinophilic cytoplasm and hyperchromatic, pencillate nuclei showing pseudostratification. Foveolar GED was composed of cuboidal to columnar cells with a pale, clear cytoplasm and hyperchromatic round to oval nuclei. Cases of GED in which at least 10% of the cells showed a second phenotype were classified as hybrid.

We evaluated adjacent mucosa near to GED lesion of the endoscopic resection specimens. The background gastric mucosa was evaluated, with a focus on examining the intensity of inflammation (mononuclear infiltration), degree of atrophy, and grade of intestinal metaplasia, based on the updated Sydney system [19]. Especially, gastric mucosal atrophy was defined as “the loss of appropriate glands, both metaplastic and non-metaplastic atrophy” and graded as previously described [20]. Intestinal metaplasia was further divided into complete and incomplete, as previously described [12]. That is, complete intestinal metaplasia showed small intestinal-typed absorptive enterocytes with brush borders and goblet cells, whereas incomplete intestinal type showed large intestinal non-absorptive columnar cells with goblet cells. In case of mixed complete and incomplete intestinal metaplasia, it was classified according to the prevailing quantity. Crypt dysplasia was defined by the presence of cytologic atypia in the gastric crypts and increased mitosis without the involvement of the surface epithelium, as previously described [12]. Cytologic atypia in here includs nuclear pleomorphism and stratification, increased nuclear/cytoplasmic ratio, enlarged nuclear size and irregularity, hyperchromasia. It is also found in the absence of significant active inflammation, regenerative changes or ulcer detritus. We evaluated the significance of gastritis cystica profunda. Gastritis cystica profunda is a hyperplastic benign lesion, characterized by hyperplastic and cystically dilated glands in submucosa or muscularis propria. It is not usually regarded as premalignant lesion but there have been some reports of cases about gastritis cystica profunda accompanied by gastric carcinoma or adenoma [21].

### 2.3. Statistical analysis

The data was analysed with student’s *t*-test, Fisher’s exact test, or $\chi^2$ test for differences between groups. Independent variables were then analysed by binary logistic regression analysis (backward, stepwise). A value of $p < 0.05$ was considered statistically significant. Statistical calculations were performed with SPSS version 10.0 for Windows software (IBM, Armonk, NY, USA).

## 3. Results

We divided 105 GED lesions into three groups: a single group without metachronous or synchronous GED or adenocarcinoma (n = 35); a multiple synchronous group (n = 27, group with synchronous occurrence of GED (22) or adenocarcinoma (5) after endoscopic resection); and a multiple metachronous group (n = 43, group with metachronous occurrence of GED (22) or adenocarcinoma (21) after endoscopic resection). As shown in Table 1, the single GED group without metachronous or synchronous GED or adenocarcinoma showed small lesion size (1.11 ± 0.08), as compared with the multiple GED group with metachronous or synchronous GED or adenocarcinoma (metachronous: 1.90 ± 0.19, synchronous: 1.38 ± 0.13) ($p = 0.003$). The multiple GED group with metachronous or synchronous GED or adenocarcinoma showed a higher histologic grade compared with the single GED group without metachronous or synchronous GED or adenocarcinoma ($p = 0.021$). Other clinicopathologic features, including age, gender, location, and gross type and histology subtypes of GED lesions, active Helicobacter pylori infection were not associated