

## Endoscopic management of gastric dysplasia: Cutting edge technology needs a new paradigm

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### Abstract

There has been tremendous progress in endoscopic techniques for the management of premalignant or malignant gastric lesions. Gastric cancer remains the second most common cause of cancer related mortality worldwide. This means that there is a need for early detection and diagnosis of premalignant lesions or early cancer in clinical practice. Despite substantial development of endoscopic resection techniques, the management of gastric premalignant lesions is controversial because of the lack of consensus and accurate risk stratification. Future study of various aspects would clarify these issues but in the meantime we should reconsider the current algorithm approach for the management of gastric low grade dysplasia.

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**Key words:** Grade dysplasia; Endoscopic resection; Submucosal dissection

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### INTRODUCTION

Gastric epithelial dysplasia (GED) is defined as noninvasive, neoplastic gastric epithelium. However, the term GED has become progressively complex and confusing because of differences in definitions and nomenclature that have been based on cytological, microscopic, endoscopic or gross features<sup>[1]</sup>. When the dysplastic lesion is flat or depressed the term dysplasia is used; if protruding from the mucosa, adenoma is used. These terms have been used for indicating the morphological type of the lesion and are considered as having same histology in clinical practice<sup>[2,3]</sup>.

There have been debates about the histological diagnostic criteria for gastric dysplasia or adenoma, especially between pathologists in Japan and the West<sup>[4]</sup>. The Vienna classification for gastric dysplasia was produced as a consensus for reducing the gap of the discrepancies between Western and Asian pathologists<sup>[5]</sup>. Ramification of the category according to the diagnostic criteria enabled us to reduce the gap in category 4 (high grade intraepithelial neoplasia, HGD) and 5 (carcinoma). However, discrepancy still exists in category 3 (low grade intraepithelial neoplasia, LGD). Although a designation of low-grade means a comparatively reduced risk of malignant transformation compared to high-grade, it should be kept in mind that a background intestinal metaplasia accompanying low grade dysplasia might be associated with an increased risk of malignancy<sup>[6]</sup>.

Endoscopic resection techniques have developed and there are almost no limits in endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) for the management of gastric neoplasia. The technical improvement in EMR/ESD procedures has enabled en bloc resection of the entire mucosal lesion regardless of its size and location in stomach<sup>[7]</sup>. The endoscopic management of HGD or carcinoma was well established with no controversy. However, EMR/ESD of gastric low grade adenoma may be controversial and resection of all these lesions demands costs and time. There are also patients

who are not candidates for ESD or EMR due to economic problems or physical limitations.

New techniques in therapeutic endoscopy demand an upgraded approach paradigm. So, taking into account all of this, the best management will be discussed.

## EPIDEMIOLOGY OF GASTRIC LGD

The prevalence of GED ranges widely according to region. In the region with the high risk of gastric cancer such as Korea and Japan, prevalence ranges from 9%-20% in contrast to the lower risk regions of up to 3.75%<sup>[8,9]</sup>. This difference can be explained by several factors such as genetics, incidence of helicobacter pylori infection and environmental factors<sup>[10]</sup>. Most of these gastric tumors are incidentally found during screening endoscopy in prevalent areas. GED has various morphologies on endoscopic findings: protruding or depressed; whitish or reddish; lobular or granular; and combining ulcer or not. These lesions might not be evident during endoscopy and repeat biopsy or EMR/ESD may be needed to confirm.

## NATURAL HISTORY OF GASTRIC EPITHELIAL DYSPLASIA

Proper management for GED needs the understanding of the natural course of this entity. GED (LGD or HGD) are regarded as precancerous lesions and the endoscopic management of HGD is uniform. However, the clinical course of LGD is variable and the transformation rate ranges from 0% to 23% (Table 1).

A recent study by Rugge *et al*<sup>[11]</sup> revealed that the risk of invasive gastric cancer increases with the histological grade of the non-invasive neoplasia. They included a total of 90 consecutive cases with LGD prospectively followed up. They excluded the patients in whom gastric cancer was detected within 12 mo from the initial diagnosis to rule out the chance of missed diagnosis at the initial endoscopy procedure. Of these cases, 78% of cases were no longer detected or unchanged; however, 17% (20/90) of cases evolved into gastric cancer. Evolution to invasive carcinoma was documented in 8 of 90 cases (8.9%) of LGD. This study is a prospective long-term follow up study of LGD, focusing on cancer risk. These results mean that although most of LGDs in stomach remain stable, during follow up they can progress in significant proportion.

However, this is not the case in a recent Japanese study<sup>[12]</sup>. This study included 48 lesions diagnosed as LGD or HGD on first biopsies. These lesions were followed for a median of 4.7 years. They reclassified the lesions according to the Vienna classification. Of the 38 cases of LGD, only 1 case showed progression to noninvasive carcinoma with the remaining cases unchanged. Even the HGD showed a stable course with only 1 case of intramucosal carcinoma. They insisted that LGD lesions have quite a low risk of progressing to HGD or noninvasive carcinoma and were never observed to progress to invasive

**Table 1** Natural courses studies of low and high grade dysplasia progressing to carcinoma

	Low grade dysplasia	Mean interval to carcinoma	High grade dysplasia	Mean interval to carcinoma
Saraga <i>et al</i> <sup>[19]</sup>	2% (1/64)	4 yr	81% (7/21)	4 mo
Lansdown <i>et al</i> <sup>[20]</sup>	0% (0/7)	-	85% (11/13)	5 mo
Di Gregorio <i>et al</i> <sup>[21]</sup>	7% (4/73)	2 yr	60% (6/10)	11 mo
Kokkola <i>et al</i> <sup>[22]</sup>	0% (0/84)	-	67% (2/3)	1.5 yr
Rugge <i>et al</i> <sup>[11]</sup>	8.9% (8/90)	48 mo	69% (11/16)	30 mo
Yamada <i>et al</i> <sup>[12]</sup>	0% (0/38)	-	10% (1/10)	4.6 yr
Park <i>et al</i> <sup>[13]</sup>	11.5% (3/26)	3.7 yr	100% (1/1)	5.6 yr

carcinoma. Although this study is a long-term follow up study for gastric dysplasia, the diagnostic criteria should be considered and conclusions accepted with caution. As mentioned earlier, despite the efforts to overcome the gap between Western and Asian pathologists regarding the discrepancies in the concept of GED, there is still a lack of diagnostic pathological criteria. Overestimation of the pathological diagnosis could lead to the benign course of the lesion, especially in LGD.

Another Asian study revealed contrary results<sup>[13]</sup>. Twenty-six cases of gastric LGD were followed up for a median of 66 mo. Three cases out of 26 LGD progressed to invasive carcinoma. Four cases out of 26 LGD progressed to HGD. The author concluded that gastric intraepithelial neoplasia should be treated actively using recently advanced therapeutic endoscopic techniques, regardless of the degrees of dysplasia. Although this study is a small retrospective one, the proportion of progression to invasive carcinoma is similar to the study by Rugge *et al*<sup>[11]</sup>.

Although it requires years for a gastric LGD to progress into an invasive form and not all cases of LGD transform to advanced carcinoma, the recent advances in endoscopic resection can reduce the risk and cost of procedure and should be reconsidered as a first option for the management of gastric LGD. It may be sufficient to follow up the gastric neoplasia at a 1 year interval in cases of unavoidable observation.

## DISCREPANCY OF THE INITIAL BIOPSY WITH FINAL PATHOLOGY

When we consider EMR/ESD for gastric LGD or HGD, the concept of inaccuracy in a forceps biopsy should be kept in mind. Actually, the reactive changes may mimic the morphological appearance of GED and are well recognized as a pitfall in diagnosis<sup>[10]</sup>. Likewise, the pathological diagnosis of the gastric HGD by forceps biopsy probably means invasive carcinoma after EMR/ESD.

There are several studies regarding the discrepancy between forceps biopsy and final pathological diagnosis<sup>[7,14-18]</sup>. Park *et al* researched the possible risk factors of predicting malignant transformation of the gastric LGD. Eight of the 118 adenomas proved to have malignant foci. Univariate analysis revealed that location, histological

type, surface redness and degree of dysplasia of the lesion were significant predictors for malignant potential. In multivariate analysis, only the degree of dysplasia had significance. The author concluded that gastric HGD should be resected for possible malignancy.

Another large prospective study in a German group revealed that the size of tumor is important. They prospectively included 194 patients with 222 endoscopically removable gastric polyps ( $\geq 5$  mm) who underwent forceps biopsy and complete polypectomy. They excluded cases of fundic gland polyps and polyposis syndrome. Of the 222 polyps, histological examination of the polypectomy specimens revealed neoplasia in 19% (6% adenocarcinoma). The complete agreement was found in 124 cases (55.8%) and clinically important differentiation between tumor like lesions and neoplasia was possible in 90.5%. They insisted on complete removal by an experienced endoscopist of all epithelial gastric polyps larger than 5mm after thorough individualized risk benefit analysis. Most of the patients had no symptoms in this population. These results can be explained in two other aspects. The meticulous examination of the forceps biopsy samples by an experienced pathologist would be sufficient for a correct histological diagnosis without polypectomy. The other aspect is the problem of coexistence of malignant foci, as in 3.1% of the hyperplastic polyps in this study.

The recent study by Jung *et al* also mentioned the risk factors of malignant transformation in gastric LGD. This study included 114 patients with gastric LGD which was diagnosed at initial forceps biopsies. They divided these patients into two groups according to the post-EMR/ESD pathological diagnosis. The carcinoma group (63 cases) had distinct phenotypes such as depressed gross appearance, combined HGD, reddish surface and mucosal ulceration. In multivariate analysis, combined HGD was a significant independent predictor of carcinomas. Although all the gastric LGD could not be resected because of the patient's medical condition or equipment availability, these characteristics should be considered as an indication for endoscopic resection or be followed closely by available screening methods.

Contrary to the up-staging of the post-EMR/ESD diagnosis, one study mentioned down-staging after EMR/ESD<sup>[18]</sup>. Out of 633 patients treated with EMR or ESD, 20 patients (3.2%) were included in this study. The mean size of tumor was 6.4 mm. Sixty-five percent were LGD; the remainder was HGD or intramucosal carcinoma. Following endoscopic resection, no neoplasia was evident although only macroscopic lesions and no random biopsy cases were included in this study. The authors concluded that the tumors might have been small enough to be removed by the previous forceps biopsy.

All these studies regarding the discrepancy between the forceps biopsy and final pathological diagnosis are important in managing patients with gastric LGDs. When a forceps biopsy is performed on the lesion, more pieces mean more accuracy in diagnosis. However, it could hamper a procedure like ESD because of excessive scar formation resulting in the fibrosis. A few samples for for-

ceps biopsy diagnosis could not rule out sampling errors, like the hidden part of the iceberg. More validated studies using recently introduced instruments such as magnifying endoscopy, autofluorescence imaging and confocal endomicroscopy are needed to identify the high risk groups of hidden malignancy in lesions.

## CONCLUSION

EMR/ESD is gaining in popularity and substituted surgical policy on the management of early gastric cancer. More patients will benefit from screening programs for the early detection of gastric cancer and EMR/ESD is the leading technique at this point. Premalignant lesions would also be detected more during screening endoscopy. Assuming the progression of gastric LGDs to HGDs or carcinoma is not rare, close follow up strategies without informing the patients about endoscopic resection should be reconsidered. Given the availability of endoscopic management techniques and the problems of hidden malignancy in gastric LGDs, endoscopic management instead of an annual follow up strategy should be considered first in clinical practice. Future studies of molecular, genetic and morphological characteristics of gastric LGDs could be helpful in deciding management and stratifying the risk of progression.

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