

# Diagnosis and management of gastric dysplasia

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Gastric dysplasia is a neoplastic lesion and a precursor of gastric cancer. The Padova, Vienna, and World Health Organization classifications were developed to overcome the discrepancies between Western and Japanese pathologic diagnoses and to provide a universally accepted classification of gastric epithelial neoplasia. At present, the natural history of gastric dysplasia is unclear. Much evidence suggests that patients with high-grade dysplasia are at high risk of progression to carcinoma or synchronous carcinoma. Therefore, endoscopic resection is required. Although patients with low-grade dysplasia have been reported to be at low risk of progression to carcinoma, due to the marked histologic discrepancies between forceps biopsy and endoscopic specimens, endoscopic resection for this lesion is recommended, particularly in the presence of other risk factors (large size; depressed gross type; surface erythema, unevenness, ulcer, or erosion; and tubulovillous or villous histology). *Helicobacter pylori* eradication in patients with dysplasia after endoscopic resection appear to reduce the incidence of metachronous lesions.

**Keywords:** Intraepithelial neoplasia; Dysplasia; Adenoma; Stomach

## INTRODUCTION

Gastric cancer remains one of the most challenging malignant diseases worldwide. Gastric dysplasia is a precancerous lesion and the penultimate stage in gastric carcinogenesis, particularly the intestinal type, as hypothesized by Correa [1]. Therefore, identification, management, and surveillance of such lesions are important for early detection and prevention of gastric cancer. Nevertheless, the accurate diagnosis and management of this lesion remain controversial. Therefore, in this review, current knowledge of this lesion is discussed, together with relevant diagnostic and therapeutic strategies.

## DEFINITION

The World Health Organization (WHO) defines dyspla-

sia in the gastrointestinal system as the presence of histologically unequivocal neoplastic epithelium without evidence of tissue invasion [2]. Some confusion exists regarding the terms adenoma and dysplasia. Originally, adenoma was considered a raised circumscribed lesion, either sessile or pedunculated, in contrast to dysplasia, which was defined as a flat or depressed mucosa [3]. However, use of terms such as “flat adenoma” or “depressed adenoma” by some investigators has resulted in confusion. The WHO defines gastric adenomas as circumscribed, polypoid lesions composed of tubular and/or villous structures, lined by dysplastic epithelium [4]. There has been an effort to standardize the terminology of adenoma and dysplasia; adenoma has been defined as neoplastic circumscribed benign lesions unassociated with underlying inflammation such as atrophic gastritis whether pedunculated, sessile, flat, or depressed. In contrast, dysplasia is defined as benign neoplastic lesions associated with underlying inflammation [5].

Currently, however, adenoma and dysplasia are used indiscriminately by most clinicians.

### CLASSIFICATION SYSTEMS

Several dysplasia classification systems—including the Padova, Vienna, and WHO systems—have been developed to standardize the definition of gastric dysplasia and neoplasia between Western and Japanese pathologists (Table 1). This standardization was necessary because of the marked discrepancies between Western and Japanese pathologic diagnosis of these lesions. Carcinoma is diagnosed in Japan based on cytological and architectural changes irrespective of the presence of invasion, whereas in the Western system it is based on invasion into the lamina propria; this emphasizes invasion as an indicator of metastatic potential [6]. A weakness of the Japanese classification system is the lack of a distinction between noninvasive and invasive mucosal carcinoma; such a distinction seems to have prognostic importance. In contrast, the diagnostic discrepancies between biopsy specimens and corresponding resected specimens are a weakness of the Western classification system [6]. The Japanese Society for Research on Gastric Cancer classification does not include the term dysplasia. Dysplasia is usually classified as low or high grade. Low-grade dysplasia (LGD) and high-grade dysplasia (HGD) correspond to borderline lesions (group III) and strongly suspicious for invasive carcinoma (group IV), respectively, in this system [7]. In contrast, there is no recognition of noninvasive carcinoma and mucosal carcinoma without submucosal invasion in the Western system [7]. The Padova, Vienna, and WHO classification schemes aim to provide a universally accepted classification system for gastric epithelial neoplasia. On this basis, Japanese pathologists accepted use of the terms adenoma and dysplasia and Western pathologists accepted that of noninvasive carcinoma. LGD and HGD are classified as noninvasive, low-grade neoplasia of category 3 and noninvasive, high-grade neoplasia of category 4 in the Vienna and revised Vienna classification systems, respectively [8,9]. In this classification system, the diagnoses “carcinoma *in situ*,” “suspicious for invasive carcinoma,” and “intramucosal carcinoma” were included in category 4 [9]. The WHO classification is similar to the Vienna

**Table 1. Gastric epithelial neoplasia classification systems**

Japanese (JRS GC)	Western: Goldstein et al. [4]	Padova [40]	Vienna [8]	Revised Vienna [9]	WHO [10]
Group I: Normal or benign	Reactive	Category 1: Negative for dysplasia	Category 1: Negative for dysplasia	Category 1: Negative for dysplasia	No intraepithelial neoplasia/dysplasia
Group II: Benign with atypia	Indefinite for dysplasia	Category 2: Indefinite for dysplasia	Category 2: Indefinite for dysplasia	Category 2: Indefinite for dysplasia	Indefinite for intraepithelial neoplasia/dysplasia
Group III: Borderline	Low-grade adenoma/dysplasia	Category 3.1: Noninvasive low-grade neoplasia (low-grade adenoma/dysplasia)	Category 3: Noninvasive low-grade neoplasia (low-grade adenoma/dysplasia)	Category 3: Mucosal low-grade neoplasia (low-grade adenoma/dysplasia)	Low-grade intraepithelial neoplasia/dysplasia
Group IV: Strongly suspicious for invasive carcinoma	High-grade adenoma/dysplasia	Category 3.2: Noninvasive high-grade neoplasia (high-grade adenoma/dysplasia)	Category 4: Noninvasive high-grade neoplasia (high-grade adenoma/dysplasia)	Category 4: Mucosal high-grade neoplasia (high-grade adenoma/dysplasia)	High-grade intraepithelial neoplasia/dysplasia
Group V: Definitive for invasive carcinoma	Invasive carcinoma	Category 4: Suspicious for invasive carcinoma (with lamina propria invasion)	Category 5: Invasive neoplasia (intramucosal carcinoma or beyond)	Category 5: Submucosal invasion by carcinoma	Intramucosal invasive neoplasia (intramucosal invasive carcinoma)
		Category 5: Invasive neoplasia (intramucosal/submucosal carcinoma or beyond)		Category 4: Intramucosal carcinoma	Invasive neoplasia

JRS GC, Japanese Research Society for Gastric Cancer; WHO, World Health Organization; CIS, carcinoma *in situ*.

classification; however, the term “dysplasia” is used synonymously with “intraepithelial neoplasia/dysplasia” [10]. Therefore, categories 3 and 4 in the revised Vienna classification system correspond to low-grade and high-grade intraepithelial neoplasia/dysplasia, respectively, in the WHO classification.

## CLINICAL FEATURES AND NATURAL HISTORY

The prevalence of dysplasia is reported to be 0.5% to 3.75% in Western countries and 9% to 20% in regions with a high incidence of gastric adenocarcinoma, such as Colombia and China [11]. Patients with such lesions are predominantly male and are ~10 years younger than gastric cancer patients (61.35 years for gastric dysplasia vs. 70 years for gastric cancer) [12]. Gastric dysplasia can be found anywhere in the stomach, but most commonly in the antrum [13]. Most gastric dysplasia is discovered incidentally during screening endoscopic examinations.

Both LGD and HGD have the potential to progress to carcinoma. Therefore, predicting the risk of malignant transformation at diagnosis for these lesions is important. However, the real risk of progression to cancer for dysplasia remains unclear. Indeed, well-defined, long-term follow-up studies, well-designed biopsy-sampling protocols, and obtaining informed patient consent can be problematic in clinical trials in terms of clarifying the natural history of gastric dysplasia. The risk of malignant change increases with the histological grade of the dysplasia. Previous studies have consistently demonstrated that patients with HGD are at high risk of progression to carcinoma or synchronous carcinoma. The rate of malignant change of HGD has been reported to be range from 60% to 85% over a median interval of 4 to 48 months [14-20]. A recent nationwide cohort study, which demonstrated that ~25% of patients with HGD received a diagnosis of gastric cancer within 1 year of the initial diagnosis, confirmed the high risk of malignant change in HGD [21]. Compared to HGD, LGD has a lower risk of progression to carcinoma. LGD has been documented to regress in 38% to 75% and persist in 19% to 50% of cases [22]. Of LGD cases, 0% to 23% exhibit malignant change within a mean of 10 to 48 months [15,18,20,23,24]. Recent observational studies have confirmed the low risk of malignant change in patients with

LDG (3% to 9%) [20,23].

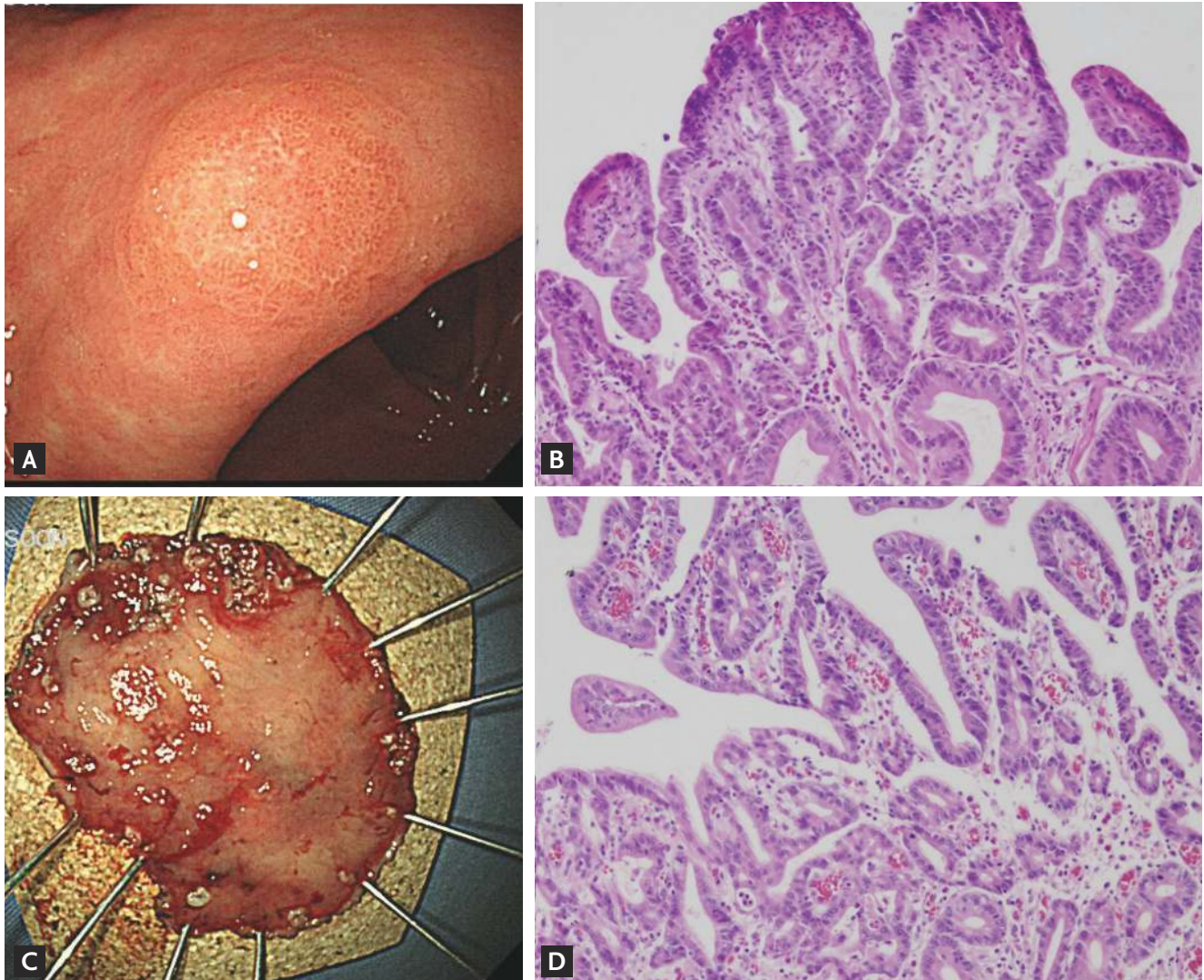
Gastric dysplasia has a high risk of synchronous carcinoma in other areas of the stomach [25]. Synchronous adenocarcinoma has been found in up to 30% of patients with gastric dysplasia [26].

## HISTOLOGIC DISCREPANCY: FORCEPS BIOPSY AND ENDOSCOPIC RESECTION

A concern regarding the accurate diagnosis of gastric dysplasia is that endoscopic forceps biopsy specimens are not representative of the entire lesion; therefore, significant discrepancies can be found between histologic diagnoses based on forceps biopsy and resected specimens (Fig. 1). A series of studies have reported that diagnosis of LGD by forceps biopsy could be upgraded to HGD or carcinoma. A recent meta-analysis [27] of 16 studies involving 3,303 patients with endoscopic forceps biopsy-proven gastric LGD lesions showed that 25% were diagnosed as advanced lesions, including gastric HGD (16.7%) and gastric carcinoma (6.9%) after endoscopic resection. In other words, one out of four forceps biopsy-proven gastric LGDs might be underdiagnosed and should actually be HGD or even gastric carcinoma. This high rate of underdiagnosis indicates that merely a follow-up strategy is insufficient for patients with LGD.

Repeat endoscopic biopsy is a possible solution to this issue. However, this also has limitations, as demonstrated by a 70.4% rate of histological concordance between repeat endoscopic biopsy and postendoscopic resection specimens [28].

Theoretically, obtaining a larger specimen using the large cup of jumbo biopsy forceps (open diameter of 8 mm) can increase diagnostic accuracy. However, a recent study reported that jumbo forceps biopsy specimens do not increase the concordance rate compared to conventional forceps (open diameter of 6.8 mm) specimens [29]. The authors instead recommended obtaining at least four endoscopic biopsy specimens to improve the histologic accuracy. This resulted in an increased concordance rate in LGD from 76.2% for the first endoscopic biopsy to 95.2% [29]. However, increasing the number or size of forceps biopsies can alter the neoplastic lesion and cause submucosal fibrosis, which can make endoscopic resection problematic. Therefore, these strate-



**Figure 1.** A lesion whose diagnosis was upgraded from gastric low-grade dysplasia to early gastric cancer after endoscopic resection. (A) Endoscopic findings before endoscopic resection show a 0.6 × 0.5 cm superficial elevated mass at the lesser curvature of the antrum. (B) Histologic features of low-grade dysplasia in the initial forceps biopsy specimen (H&E, ×200). (C) The endoscopic submucosal dissection specimen (3.7 × 2.7 cm). (D) Histologic features of the resected specimen. Moderately differentiated tubular adenocarcinoma arising from a tubular adenoma is evident. The tumor was 0.5 × 0.4 cm in size (H&E, ×200).

gies to improve diagnostic accuracy have limitations in terms of clinical application.

It is important to determine the type of gastric LGD likely to be underdiagnosed. Various findings have been reported concerning this issue. It is generally accepted that the probability of malignant transformation of dysplasia increases with lesion size. Adenoma 2 cm or more in diameter has been considered potentially malignant [30]. Several studies have confirmed that a lesion size ≥ 2 cm is an independent predictor of upgraded histology in LGD lesions. However, even small LGDs (< 2 cm) may

be upgraded to an HGD or carcinoma. One study indicated that ~20% of lesions with a diameter of less than 1 cm and about 35% of those with a diameter of 1 to 1.9 cm were HGD or carcinoma [31]. Other studies showed that forceps biopsy-proven gastric LGDs of ≥ 1 cm diameter were an independent risk factor for HGD or carcinoma [32,33].

The surface appearance of dysplasia has also been identified as a risk factor for upgrade to a diagnosis of HGD or carcinoma in gastric LGD after endoscopic resection. Features associated with an upgraded diagnosis

include depressed macroscopic type, surface erythema, surface unevenness (nodularity), and erosion or ulceration [31,32,34-39]. The risk of malignancy is also related to the villosity of the growth pattern [33].

In summary, larger size; depressed gross type; a surface appearance with erythema, unevenness, ulcer, or erosion; and tubulovillous or villous histology on forceps biopsy specimens are predictive factors for an up-graded diagnosis in LGD patients following endoscopic resection. Therefore, it is recommended that an endoscopic forceps biopsy-proven gastric LGD lesion with these predictive factors undergo endoscopic resection.

## MANAGEMENT

Generally there is no controversy regarding the appropriate management of HGD. Such lesions require endoscopic resection due to the potential for progression to carcinoma and the coexistence of carcinoma. In contrast, few definite guidelines regarding the management of LGD are available. Given the lower risk of malignant transformation, some investigators recommend annual endoscopic surveillance with rebiopsy for LGD [40,41], while others suggest that active resection is necessary because histological diagnosis based on forceps biopsy can be inaccurate due to sampling error, and the final diagnosis can be upgraded to HGD or even invasive carcinoma after endoscopic resection [42]. Repeated endoscopic examination with biopsies can impose a physical, psychological, and financial burden on the patient, although few studies of these issues have been reported [42]. In contrast, endoscopic resection is less invasive than surgical resection but also has a risk of complications.

In the revised Vienna classification, endoscopic treatment or surgical local treatment was recommended for HGD [43]. In addition, endoscopic treatment or follow-up was recommended for LGD [43]. The choice of treatment is dependent on the size of the lesion; depth of invasion as assessed endoscopically, radiologically, or ultrasonographically; and other general factors (patient age and comorbidities) [43].

Several guidelines recommend endoscopic resection for gastric dysplasia. The most recent American Society for Gastrointestinal Endoscopy (ASGE) guidelines

[44] suggested that adenoma of any size should be removed endoscopically if possible. The British Society of Gastroenterology guidelines [13] also recommended complete removal of adenoma if safe to do so. The European guidelines [45] recommended that if LGD is diagnosed endoscopically, endoscopic resection should be considered to obtain a more accurate histologic diagnosis. Otherwise, endoscopically indefinite lesions should undergo follow-up within 1 year after diagnosis. In addition, they recommended that endoscopic resection should be considered for patients with endoscopically defined HGD. If the lesion is endoscopically indistinct HGD, the guidelines recommend immediate endoscopic reassessment with extensive biopsy sampling and surveillance at 6- to 12-month intervals. Moreover, they highlighted that disappearance of dysplasia or its assumed disappearance as assessed by follow-up endoscopic biopsies does not rule out the possible progression to invasive cancer.

Finally, because there is a risk of synchronous carcinoma in patients with gastric dysplasia, thorough evaluation of the entire stomach should be performed and any abnormalities biopsied. Endoscopic surveillance is also mandatory after resection to screen for metachronous lesions [13,46]. Concerning the surveillance schedule, the ASGE guidelines suggest surveillance endoscopy 1 year following resection of gastric dysplasia [44]. The British Society of Gastroenterology guidelines recommend endoscopic follow-up 6 months after resection in patients with incompletely resected polyps or those with HGD, and 1 year after removal of other polyps [13].

## HELICOBACTER PYLORI ERADICATION FOR PREVENTION OF METACHRONOUS LESIONS AFTER ENDOSCOPIC RESECTION OF GASTRIC DYSPLASIA

Previous studies have evaluated the effect of *Helicobacter pylori* eradication on preneoplastic lesions such as gastric atrophy and intestinal metaplasia. Conflicting results have been reported regarding the reversibility of gastric atrophy and intestinal metaplasia after eradication therapy. *H. pylori* eradication appears to improve atrophy but not intestinal metaplasia [47]. Another issue is whether *H. pylori* eradication reduces the subsequent

development of metachronous cancer after endoscopic resection of early gastric cancer (EGC). Nonrandomized and randomized control studies have demonstrated that *H. pylori* eradication can reduce the development of metachronous gastric cancer after endoscopic resection of EGC [48,49]. Based on these results, several guidelines recommend *H. pylori* eradication in patients with previous EGC after endoscopic resection [50-54].

Few studies have assessed the effect of *H. pylori* eradication on gastric dysplasia. Studies regarding the effect of *H. pylori* eradication on the development of metachronous lesion after endoscopic resection of gastric dysplasia are also limited [55-58]. Correa et al. [55] demonstrated that *H. pylori* eradication and dietary supplementation increased the rate of regression of precancerous lesions, including dysplasia. However, that study had several limitations, such as a small number of patients and issues with diagnosis of dysplasia; that is, the majority of subjects with dysplasia should have been classified as “indefinite for dysplasia” according to international standards. A long-term follow-up (> 12 months) study showed that *H. pylori* eradication significantly altered the natural history of advanced precancerous changes [58]. A significantly lower risk of evolution into high-grade noninvasive neoplasia or into invasive gastric cancer was found in patients with *H. pylori*-eradicated low-grade noninvasive neoplasia compared to those with *H. pylori*-positive low-grade noninvasive neoplasia. To date, the preponderance of evidence suggests that eradication has no effect on dysplasia.

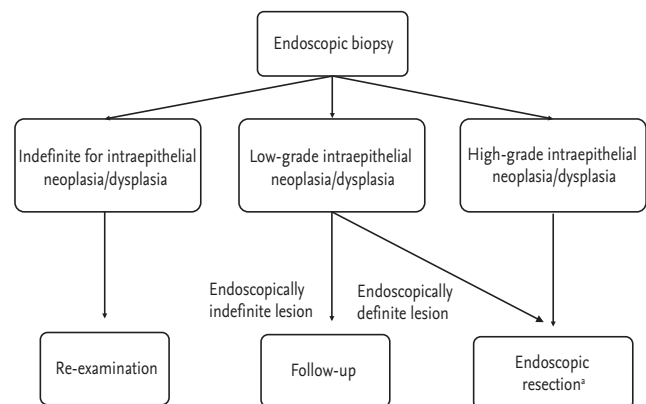
However, some studies have demonstrated that *H. pylori* eradication can prevent the development of metachronous lesions after endoscopic resection of gastric dysplasia. In one retrospective study of 1872 patients with gastric dysplasia who underwent endoscopic resection, the cumulative incidence of metachronous lesions was significantly lower in the *H. pylori*-eradicated group than the *H. pylori*-persistent (noneradicated or failed) group [59]. Another retrospective study analyzed 1,007 patients with EGC who underwent endoscopic resection, and found that *H. pylori* eradication reduced the metachronous recurrence of gastric neoplasm [60]. Furthermore, this outcome remained evident in an analysis that included 480 patients with LGD [60]. Another retrospective study that assessed 129 patients positive for *H. pylori* who underwent endoscopic resection for gastric

dysplasia [61] found that *H. pylori* eradication was an independent risk factor for a reduced incidence of subsequent gastric dysplasia. Therefore, *H. pylori* eradication may be useful for the prevention of metachronous lesions after endoscopic resection in patients with gastric dysplasia.

Currently, the European guidelines recommend *H. pylori* eradication for patients with previous dysplasia after endoscopic or surgical therapy [45]. The ASGE guidelines also recommend *H. pylori* eradication in patients with dysplasia. In addition, they recommend systemic sampling of the surrounding nonpolypoid gastric mucosa to evaluate *H. pylori* and metaplastic atrophic gastritis in the presence of multiple dysplasias [44].

## CONCLUSIONS

Accurate diagnosis, management, and surveillance of gastric dysplasia are critical for early detection and prevention of gastric cancer. Due to the significant diagnostic discrepancies between forceps biopsy and endoscopic resected specimens, endoscopic resection should be considered not only for diagnosis but also treatment of gastric dysplasia. Fig. 2 shows a proposed treatment strategy for gastric intraepithelial dysplasia diagnosed by endoscopic biopsy. Endoscopic surveillance is essential and *H. pylori* eradication may be beneficial for prevention of metachronous lesions after endoscopic resec-



**Figure 2.** Proposal of treatment strategy for gastric intraepithelial neoplasia/dysplasia diagnosed by endoscopic biopsy. <sup>a</sup>*Helicobacter pylori* eradication is recommended if identified after endoscopic resection in patients with dysplasia.

tion in patients with gastric dysplasia.

### Conflict of interest

No potential conflict of interest relevant to this article was reported.

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