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MINIREVIEWS

Optimal management of biopsy-proven low-grade gastric dysplasia

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Abstract

Gastric adenocarcinoma generally culminates *via* the inflammation-metaplasia-dysplasia-carcinoma sequence progression. The prevalence of gastric adenomas shows marked geographic variation. Recently, the rate of diagnosis of low-grade dysplasia (LGD) has increased due to increased use of upper endoscopy. Many investigators have reported that gastric high-grade dysplasia has high potential for malignancy and should be removed; however, the treatment for gastric LGD remains controversial. Although the risk of LGD progression to invasive carcinoma has been reported to be inconsistent, progression has been observed during follow-up. Additionally, the rate of upgraded diagnosis in biopsy-proven LGD is high. Therefore, endoscopic resection (ER) may be useful in the treatment and diagnosis of LGD, especially if lesions are found to have risk factors for upgraded histology after ER, such as large size, surface erythema or depressed morphology. Fatal complications in endoscopic submucosal dissection (ESD) are extremely low and its therapeutic and diagnostic outcomes are excellent. Therefore, ESD should be applied preferentially instead of endoscopic mucosal resection.

Key words: Intraepithelial neoplasia; Low-grade dysplasia; Adenoma; Endoscopic resection; Endoscopic submucosal dissection

Core tip: According to the guideline, endoscopic resection or follow-up is recommended for noninvasive category 3 low-grade dysplasias (LGDs), while category 4 lesions such as high-grade dysplasia, non-invasive carcinoma and intramucosal carcinoma should be removed by local resection. However, as LGD has a relatively high underdiagnosis rate and rarely contains submucosal cancer, a follow-up strategy might result in the opportunity for endoscopic therapy being missed. Furthermore, repeated endoscopic examinations with biopsies might impose a psychological and financial burden on the patient. Based on its efficacy and safety, the use of endoscopic submucosal dissection as a primary procedure for LGD should be considered.

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INTRODUCTION

Gastric cancer (GC) is the fourth-most common cancer and the second-leading cause of cancer-related deaths worldwide, and is especially prevalent in Asia-Pacific countries, including South Korea[1]. In general, gastric adenocarcinoma culminates *via* the inflammation-metaplasia-dysplasia-carcinoma sequence progression, which is described as the Correa cascade of multi-step gastric carcinogenesis[2]. Gastric atrophy and intestinal metaplasia are lesions that confer a high risk for the development of gastric adenocarcinoma, and gastric epithelial dysplasia (GED) is considered the penultimate stage of gastric carcinogenesis[3,4]. Understanding the clinicopathological characteristics of GC is important for prevention. Along with the increasing number of endoscopies performed, the detection of precancerous lesions has increased in clinical practice[5].

The prevalence of gastric adenomas shows marked geographic variation. The reported prevalence is approximately 0.5%-3.75% in western countries and approximately 9%-20% in Asian countries where the prevalence of GC is high[6-8]. Some precancerous lesions progress to adenocarcinoma, whereas others remain unchanged for an extended period of time[9,10]. Furthermore, irrespective of used classification, several studies have demonstrated inter-observer variation in the histological assessment of GED[11-13]. Therefore, it is difficult to establish coincident international guidelines for the management of such lesions.

This review discusses the current optimal strategies for managing gastric low-grade dysplasia (LGD). In preparation for this review, we searched for epidemiological studies, clinical studies, meta-analyses and published guidelines related to GED in the Medline and PubMed databases. The search was performed using index words related to LGD ("gastric epithelial dysplasia" or "low grade dysplasia" or "gastric adenoma" or "gastric dysplasia") and treatment ("endoscopic resection" or "endoscopic submucosal dissection").

DEFINITION

Dysplasia is defined as an unequivocally neoplastic but non-invasive lesion, distinguished from regenerative changes[14]. Used initially to define inflammatory bowel diseases, the term is currently applied throughout the gastrointestinal tract and other organs. Grundmann[15] first used the term gastric dysplasia, and the World Health Organization (WHO) defined dysplasia as cellular atypia, abnormal differentiation and disorganized architecture[4,6]. Conventionally, dysplasia was a term used to describe flat or depressed lesions, whereas adenoma described raised circumscribed lesions that were either sessile or pedunculated. Therefore, a WHO committee defined adenoma as a circumscribed benign neoplasm composed of tubular and/or villous structures lined by dysplastic epithelium. On the other hand, Lewin[16] defined adenoma as a circumscribed lesion unassociated with underlying inflammation whether pedunculated, sessile, flat or depressed; and dysplasia was defined as a benign neoplastic lesion associated with underlying inflammation. However, most clinicians use these terms widely without distinction between adenoma and dysplasia in clinical practice.

Although the biological potential of GED as a precancerous lesion is clear, the classification of these lesions has been controversial in the diagnostic approach. For example, Japanese studies have referred to these lesions as borderline (Group 3 or 4), while the terms gastric adenoma or dysplasia have been used widely in Western countries (Table 1)[12,17]. Because dysplasia implies carcinoma in Japan, pathologists are reluctant to use the term gastric adenoma with LGD[18]. Furthermore, intraepithelial gastric neoplasias are classified into adenoma or carcinoma with low and high-grade cytological atypia[19]. Therefore, the term adenoma with low-grade atypia has been substituted for dysplasia in Japan. From the Japanese viewpoint, gastric adenoma with LGD diagnosed using western criteria include typical adenomas of the small intestinal type and tubular structures, and are thus diagnosed as carcinoma without invasion in Japan[18]. The Vienna classification for GED was proposed as a consensus between western and Asian countries (Table 1)[11,20]. In this classification, dysplastic lesions without invasion of the lamina propria are placed as category 3 or 4 according to the degree of cytologic atypia or architectural complexity[9,11]. Category 3 is a non-invasive low-grade neoplasia, also known as low-grade adenoma/dysplasia. Currently, the WHO recommends the terminology of non-invasive low-grade and high-grade intraepithelial neoplasia and defines carcinoma as invasion into the lamina propria or beyond[21].

NATURAL HISTORY

Although several studies have addressed the risk of carcinoma in GED[22-24], its natural course remains unclear. A large cohort study from the Netherlands suggested that the risk of progression to cancer within 10 years was 3.9% in individuals with LGD[25]. The differences among previous studies regarding the natural course of LGD are due primarily to the differences in diagnostic criteria including the classification and grading (Table 1). Additional reasons for these differences include sampling error in forceps biopsy, discrepancies between forceps biopsy and endoscopic resection (ER), and variations in the rate of malignant transformation. As mentioned earlier, noninvasive intramucosal neoplastic lesions with high-grade cellular and architectural atypia are termed intramucosal carcinoma in Japan, whereas the same lesions are diagnosed as high-grade dysplasia (HGD) by most pathologists in western countries[26]. Under these definitions, lesions diagnosed as gastric adenomas in

Table 1 Common reporting classifications of gastric epithelial neoplasia

Vienna classification[11,20]	WHO[21]	JGCA[19]
Negative for neoplasia/dysplasia		Group 1; Normal tissue or non-neoplastic lesion
Indefinite for neoplasia/dysplasia		Group 2; Material for which diagnosis of neoplastic or non-neoplastic lesion is difficult
Noninvasive neoplasia, low grade (low-grade adenoma/dysplasia)	Low-grade intraepithelial neoplasia	Group 3; Adenoma
Noninvasive neoplasia, high grade	High-grade intraepithelial neoplasia	
High grade adenoma/dysplasia		Group 4; Neoplastic lesion that is suspected to be carcinoma
Noninvasive carcinoma		Group 5; Carcinoma
Suspicious of invasive carcinoma		
Invasive carcinoma	Carcinoma	

WHO: World Health Organization; JGCA: Japanese Gastric Cancer Association.

Japan rarely progress to cancer[18]. Yamada *et al*[27] reported follow-up data for 48 gastric adenomas (38 LGD and 10 HGD) with a median of 4.7 years. During the follow-up period, 37 (97%) LGD lesions showed no histological change, while the remaining lesions progressed to HGD. However, this description of an indolent natural course may have been influenced by selection bias and the use of different LGD classifications in Japan. LGD lesions with invasive carcinoma were more likely to be excluded at the time of the first biopsy. Additionally, a substantial number of patients were excluded since they underwent ER or surgery due to a larger lesion or greater malignant potential. Therefore, half of the patients (19/38) in the study had lesions < 0.5 cm, with most lesions (76.3%, 29/38) measuring < 1 cm. This selection bias may influence a favorable LGD prognosis[28]. In contrast, Rugge *et al*[29] performed a prospective long-term follow-up study to evaluate the clinicopathological behavior of GED. A total of 118 gastric non-invasive neoplasias, including 90 LGDs, were followed for a mean of 52 mo. Among 90 LGDs, 48 (53.3%) were no longer detectable and 28 (31.1%) were unchanged; however, 14 (15.5%) LGDs evolved into HGD and GC.

To date, few studies have determined the predictors for malignant transformation of GEDs[30-32]. Gastric inflammation is a well-known risk factor for gastric carcinoma[33,34]. Correa[2] postulated that chronic gastritis may lead to intestinal metaplasia and atrophy, and that these lesions should be considered a GC risk factor as they are frequently found to be closely related to cancer. In a study that evaluated the endoscopic, pathological and immunophenotypic differences in LGD and HGD lesions according to the revised Vienna classification, Jung *et al*[32] determined that the size, color change and ulceration of the lesion, as well as gastritis score of the surrounding mucosa and positive expression of MUC6, were risk factors for malignant transformation. Because of the use of different diagnostic criteria and ethical reason, it is difficult to confirm a consistent natural history of LGD at present. Recent observational studies have indicated that the cancer progression risk of LGD is relatively low[27,29]. Nonetheless, it is possible that LGD can progress to invasive carcinoma[24,29,35]. Therefore, further studies are needed to understand the natural course of LGD to determine the most effective management option for follow-up treatment.

DISCREPANCIES BETWEEN BIOPSY AND ER

The endoscopic forceps biopsy (EFB) is crucial for grading pre-neoplastic gastric lesions and determining an appropriate treatment strategy. Because EFB specimens are not representative of the entire lesion, significant histologic discrepancies have been found between diagnoses based on EFB and subsequent ER (Figure 1). Recent advances in technology such as image-enhanced endoscopy with narrow-band imaging have led to improvements in the diagnostic accuracy of gastric lesions. However, the discrepancy between pre-endoscopic and post-ER diagnoses remains a concern[36]. Several studies have indicated that pretreatment EFB is inadequate for obtaining a correct diagnosis. We retrospectively reviewed 285 lesions that were initially diagnosed as LGD by EFB[37]. After ER, 46 LGDs (16.1%) showed an upgraded histology: 22 HGD (7.7%) and 24 differentiated adenocarcinoma (8.4%)[37]. In another study from South Korea, Kim *et al*[38] reported that the histologic discrepancy rate was 18.7% (51/273) in LGDs detected using forceps biopsy. Among 51 upgraded lesions, 24 lesions (8.8%) were upgraded to a diagnosis of adenocarcinoma.

Discrepancies in EFB and ER diagnoses contribute to the suboptimal treatment of biopsy-proven LGDs. Therefore, it is essential to identify the risk factors affecting these discrepancies for the proper management of LGD. We found that a lesion size ⩾ 2 cm, surface erythema and a depressed-type lesion were significant predictors of upgraded LGDs. Several studies have reported similar results regarding the endoscopic risk factors for histologic discrepancies in patients with LGD (Figure 2). Kim *et al*[38] reported that lesion size and the presence of spontaneous bleeding were significant factors predicting an upgraded histology after ER; in contrast, the presence of whitish discoloration was a significant negative factor. In a different retrospective

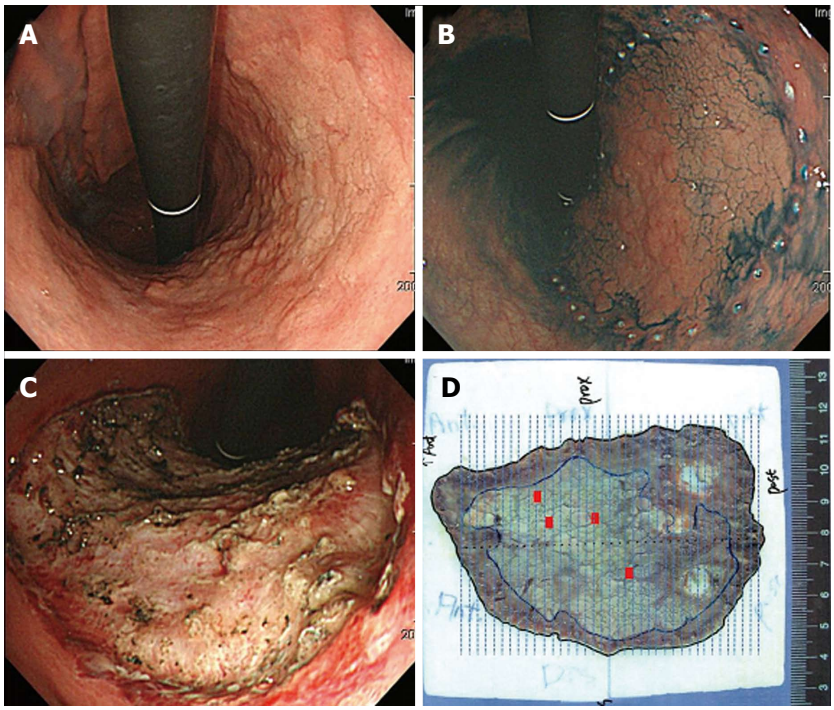

Figure 1 A lesion with a histologic upgraded from extended low-grade dysplasia to adenocarcinoma following endoscopic submucosal dissection. A: White light endoscopy reveals a large elevated mucosal lesion with nodularity in the lesser curvature side of the body. This lesion was diagnosed as LGD by the endoscopic forceps biopsy; B: This lesion is removed by ESD; C: A large mucosal defect is noted over the gastric body after ESD; D: Mapping of the resected specimen. The tumor size is 75 mm, focal cancer lesions (red bar) mixed with LGD are evident. The lateral and vertical margins are free from tumor. LGD: Low-grade dysplasia; ESD: Endoscopic submucosal dissection.

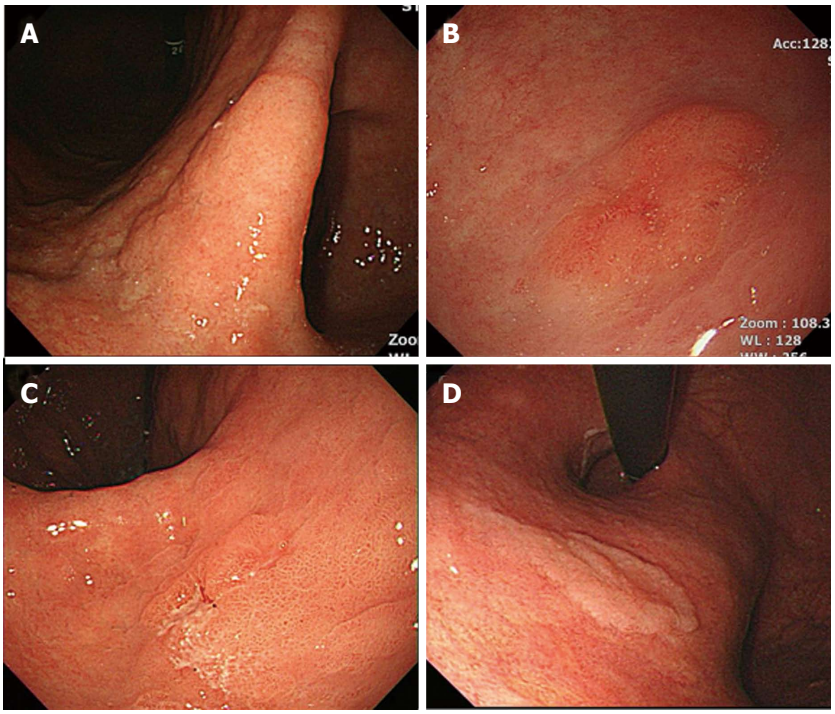

Figure 2 Endoscopic images of biopsy-proven low-grade dysplasia. A-C: lesion size > 2 cm (A), surface erythema (B), and depressed appearance (C) are endoscopic risk factors for an upgraded histology after endoscopic resection; D: In contrast, the presence of whitish discoloration was a negative factor.

study, Cho *et al*[28] demonstrated that a lesion size ⩾ 1 cm, depressed morphology, and erythema were significantly associated with HGD and carcinoma. In a study from Japan[39], a lesion size > 2 cm and depressed appearance were significant independent factors suggesting cancer. To summarize, lesions of larger size and morphology with surface erythema and depression in biopsy-proven LGDs were predictive of an upgraded histology after ER. Therefore, when selecting treatment methods for these lesions, the collection method of the suspected malignant foci should be taken into consideration. ER should be considered for diagnostic and therapeutic purposes in lesions with these risk factors.

MANAGEMENT

In developing a therapeutic plan for LGD management, it is important to identify LGDs that have histological and classical risk factors for GC progression. In South Korea, ERs-including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD)-are performed widely for the treatment of gastric adenoma, in which early GC and gastric adenoma

are prevalent. According to the revised Vienna classification, ER or follow-up is recommended for noninvasive category 3 LGD lesions, while category 4 lesions such as HGD, non-invasive carcinoma and intramucosal carcinoma should be removed by endoscopic or surgical resection[20]. Some investigators have suggested regular endoscopic surveillance with repetitive biopsy, while others have proposed ER for accurate diagnosis and treatment of LGDs. As mentioned earlier, various factors account for these discrepancies, including differences in diagnostic criteria, inconsistent results among studies of the natural course in LGD, and histologic discrepancies in EFB and ER.

Recent advances in endoscopic techniques have enabled the removal and histological diagnosis of most intra-mucosal lesions regardless of size, shape and location in the stomach[40]. However, performing resections in all patients with LGDs with relatively low malignant potential may lead to significant increases in cost, procedure time, risk of complication, and requirement for advanced technical skills. Although EMR is an easily and rapidly applicable method for therapeutic and diagnostic modalities, it has some limitations. Conventional EMR techniques are unreliable for lesion > 2 cm in diameter due to high rates of positive lateral and/or deep resection margins[41,42]. Even in lesions < 2 cm, the complete resection rate with EMR was 33%-76%[43,44]. Lesion factors, such as tumor size and location, contribute to the difficulty of en bloc resection. To overcome these problems, the development of ESD has allowed complete resection regardless of tumor size and location. In a meta-analysis[45], ESD was significantly more effective than EMR for en bloc resection, complete resection, curative resection and local recurrence. Whereas intra-operative bleeding, perforation risk, and operation time were significantly greater for ESD, overall bleeding risk and all-cause mortality did not differ significantly between ESD and EMR. One meta-analysis[46] showed that procedure-related bleeding (OR = 2.2, 95%CI: 1.58-30.7) and perforation rates (OR = 4.09, 95%CI: 2.47-6.80) during ESD were much higher compared with those for EMR. However, these were not statistically significant in another meta-analysis including 12 studies[45]. Both studies[45,46] showed that ESD was more time-consuming.

Several studies have evaluated endoscopic techniques as a treatment for LGD. Kim *et al*[47] compared the therapeutic outcomes of ESD and EMR in histologically confirmed LGD cases. The en bloc resection rate was significantly lower in the EMR groups (31.1%) compared with the ESD group (75.0%) (P < 0.001). However, no significant difference was observed in the prevalence of remnant lesion or recurrence rate (P = 0.911). On the other hand, Choi *et al*[48] reported a 96.1% complete resection rate using ESD, and the local recurrence rate was 1.4% in patients with biopsy-proven LGD. In this study, no patient had perforation and four (1.4%) patients had significant post-ESD bleeding that was treatable by endoscopic intervention. A multicenter study by the Osaka University ESD study group[49] analyzed a total of 468 subjects with GED. The results showed that the complete en bloc resection rate was 97%, and the incidences of post-ESD bleeding, perforation and serious complication were 5.5%, 4.7% and 0.43%, respectively. Miyamoto *et al*[50] reported that tumor size and location of the lesion are important factors that affect the success rate of en bloc resection. Because not all lesions can be resected en bloc for technical difficulty, another treatment option such as ablation therapy should be considered for the treatment of LGDs[51].

As LGD has a relatively high underdiagnosis rate and rarely contains submucosal cancer, a follow-up strategy might result in the opportunity for endoscopic therapy being missed[49]. Furthermore, repeated endoscopic examinations with biopsies might impose a psychological and financial burden on the patient. Based on its efficacy and safety, the use of ESD as a primary procedure for LGD should be considered.

CONCLUSION

The increased use of upper endoscopy has resulted in increased diagnosis of gastric adenoma. Although many investigators have suggested that gastric HGD should be removed due to its high potential for malignancy[20], the treatment of gastric LGD remains controversial. Although previous studies have reported inconsistent results regarding the risk of LGD progression to invasive carcinoma, such progression can occur during follow-up. Additionally, the rate of upgraded diagnosis in biopsy-proven LGDs is high. Considering these results, the use of ER might enhance treatment and diagnosis, especially of lesions with risk factors such as large size, surface erythema or depressed morphology. Furthermore, the incidence of fatal complications of ESD has been extremely low, with excellent therapeutic and diagnostic outcomes. Therefore, ESD should be applied in preference to EMR.

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