Surg Endosc
DOI 10.1007/s00464-017-5971-5

Predictors of upstage diagnosis after endoscopic resection of gastric low-grade dysplasia

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Received: 18 January 2017 / Accepted: 29 October 2017

Abstract

Background The optimal management of precursor lesions such as gastric low-grade dysplasia is crucial in order to improve gastric cancer-related mortality. However, there are no universally accepted management guidelines regarding which lesions should be resected or should be monitored by follow-up visits.

Patients and methods We retrospectively analyzed data from 1006 gastric low-grade dysplasia lesions that had been resected via endoscopic submucosal dissection. We also evaluated the endoscopic risk factors associated with upstage diagnosis from low-grade dysplasia to high-grade dysplasia or gastric cancer.

Results The mean age of our patients was 63.7 ± 9.1 years and 70.3% of our study population included men. The predominant location and gross type of lesions was the lower third of the stomach (78.6%) and the elevated type (57.8%), respectively. The rates of pathological concordance, upstage, and downstage diagnosis were 85.3, 12.1, and 2.6%, respectively. Multivariate analysis, after adjusting for age and sex, showed that a lesion size ≥ 10 mm (Odds ratio [OR] 2.231; $p = 0.003$), erythema (OR 7.315; $p < 0.001$), nodularity (OR 5.589; $p < 0.001$), depression (OR 3.024; $p = 0.002$), and erosion (OR 7.680; $p < 0.001$) were all factors significantly associated with upstage diagnosis. Furthermore, an increasing number of risk factors was associated with an increasing frequency of upstage diagnosis; if there were no risk factors, then there was no upstage diagnosis.

Conclusions This study identified several risk factors that were significantly associated with the upstage diagnosis of gastric low-grade dysplasia: lesion size ≥ 10 mm and a variety of surface changes (erythema, nodularity, depression, and erosion). Our data indicate that if there is no evidence of these endoscopic risk factors, then regular follow-up may be considered, according to the patient's combined comorbid conditions.

Keywords Dysplasia · Endoscopic submucosal dissection · Gastric cancer

Although the incidence of gastric cancer has been decreasing, it remains the second leading cause of cancer-related death [1]. The early detection and management of gastric cancer and precursor lesions, such as gastric dysplasia, is crucial in our efforts to improve gastric cancer-related mortality. For high-grade dysplasia, endoscopic or surgical resection is strongly recommended due to the high risk of developing adenocarcinoma and the likelihood of malignant lesions inside the gastric dysplasia [2]. Although low-grade dysplasia is a well-known precursor for lesions of gastric cancer [2–4], there are no universally accepted management guidelines regarding which lesions should be resected or which patients can be managed through a watch-and-wait approach. According to the revised Vienna classification, a gastric low-grade dysplasia is classified as category 3 (low-grade neoplasia), and endoscopic resection, or a regular

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Published online: 06 December 2017

follow-up examination, is recommended, depending on the overall size, invasion depth, and combined comorbid conditions [5].

The correct diagnosis and management of gastric low-grade dysplasia is important. Although endoscopic forceps biopsy is an essential diagnostic tool for gastric superficial neoplasm, the specimens obtained using this technique may not be representative of the entire lesion [6]. A focal higher-grade lesion, or minute cancer, may be hidden in the low-grade dysplasia lesion or a sampling error may occur [6]. To reduce diagnostic discrepancy, and to determine an appropriate treatment plan, it is important that the malignant features are ascertained during endoscopic examination. Recently, endoscopic submucosal dissection (ESD) had become a useful procedure for the treatment of gastric superficial neoplasm, including gastric dysplasia and early gastric cancer. ESD increases the en bloc resection rate for lesions larger than 10 mm, compared with conventional endoscopic mucosal resection using an electrosurgical snare [6]. However, repeated endoscopic examination in biopsies without endoscopic resection may increase physical or psychological stress for patients with gastric low-grade dysplasia and the appropriate treatment time may be missed.

In the present study, we aimed to evaluate the endoscopic risk factors associated with the upstaged diagnosis of gastric low-grade dysplasia to high-grade dysplasia and gastric cancer by endoscopic forceps biopsy. In addition, information was collated to determine which lesions require only regular follow-up without endoscopic resection, and whether such cases can be identified based on the presence of certain risk factors.

Patients and methods

Patients

The medical records of patients who underwent ESD at the Pusan National University Yangsan Hospital in South Korea between November 2008 and May 2016 were reviewed retrospectively. During this study period, a total of 1006 gastric low-grade dysplasia lesions were identified via endoscopic forceps biopsy and ESD was performed. Written informed consent was obtained from all patients prior to the procedure. The study was approved by the ethics committee of the institutional review board.

Procedures

We performed ESD in accordance with a previously published method [6, 7]. The ESD procedure can be summarized in three steps: first, a mixture of normal saline with epinephrine and indigo carmine was injected into the submucosal layer to elevate the lesion from the muscularis propria after marking around the lesion; second, the mucosa surrounding the lesion was pre-cut with an electrosurgical generator (ERBE VIO 300D, Endocut I mode, Effect 3, duration 2; Erbe Co, Tubingen, Germany) and a needle, or insulation-tipped electrosurgical knife; finally, the connective tissue of the submucosa beneath the lesion was dissected with an electrosurgical knife with coagulation current (Swift coagulation 60W, ERBE VIO 300D).

Clinicopathological factors and definitions

For each subject, baseline characteristics and endoscopic findings were re-assessed. Each endoscopic report was reviewed to determine the macroscopic appearance of the lesions involved (Fig. 1). The Paris classification [8] was used to define the gross type of superficial lesions: elevated, flat, or depressed. Lesion size was ascertained from the pathological examination report. Surface erythema was defined as red discoloration on the mucosal surface of the lesion compared to the surrounding mucosa. Surface nodularity was defined as the presence of irregularly raised or nodular mucosa. Lesions with ulcerations or scarring secondary to previous ulceration (converging folds or deformity of the muscularis propria) were regarded as ulcerations. If the lesion could not be elevated by submucosal injection, or if visible fibrosis was identified during submucosal dissection, we recorded the presence of submucosal fibrosis. Lesion location was described using the Japanese Classification of Gastric Cancer [9]: upper, middle, and lower third of the stomach. The resected specimens were then stretched, pinned, and fixed with formalin. Specimens which were resected in a piece-meal fashion were reconstructed as accurately as possible. Fixed specimens were then sectioned at 2

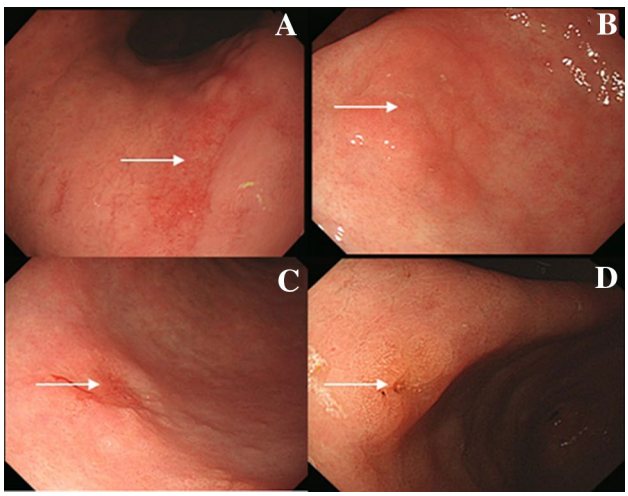

Fig. 1 Typical endoscopic features of upstage diagnosis. **A** Surface erythema, **B** surface nodularity, **C** depression, **D** surface erosion

mm intervals. An "upstage diagnosis'" was defined as when lesions were diagnosed as high-grade dysplasia or adenocarcinoma after ESD.

Statistical analysis

Categorical variables were tested by univariate analysis with the Chi-square test or Fisher's exact test while continuous variables were tested with the Student's *t* test. Variables for which $p < 0.05$ in the univariate analysis were subsequently included in a forward stepwise multiple logistic regression model to identify independent associated risk factors for upstage diagnosis after ESD. A value of $p < 0.05$ indicated statistical significance and all statistical calculations were performed with SPSS version 21.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

During the study period, 1006 ESD procedures were performed for gastric low-grade dysplasia and diagnosed via endoscopic forceps biopsies. Mean patient age was 63.7 ± 9.1 years, and 707/1006 (70.3%) of the patient cohort was male. The predominant location of lesions was the lower third of the stomach (791/1006; 78.6%) and the most common gross type of lesion was the elevated type (581/1106; 57.8%). The pathological concordance rate from endoscopic forceps biopsy and resected specimens was 85.3% (858/1106). The upstage and downstage diagnostic rate was 12.1% (122/1106) and 2.6% (26/1106), respectively. Overall, the rates of en bloc resection, and complete resection, were 97.8 and 97.1%, respectively (Tables 1, 2; Fig. 2).

Comparative analysis between the resected specimens and endoscopic forceps biopsy (concordance or downstage diagnosis group *versus* upstage diagnosis group) by univariate analysis showed that lesion size, gross type, and surface configuration (erythema, nodularity, depression, erosion, and ulceration) were significant risk factors (Table 3). Multivariate analysis, after adjusting for age and sex, showed that a lesion size ≥ 10 mm (OR 2.231; 95% CI 1.302–3.821; $p = 0.003$), erythema (OR 7.315, 95% CI 4.227–12.657; $p < 0.001$), nodularity (OR 5.589; 95% CI 3.478–8.983; $p < 0.001$), depression (OR 3.024; 95% CI 1.485–6.160; $p = 0.002$), and erosion (OR 7.680; 95% CI 3.203–18.412; $p < 0.001$) were significant predictive factors for upstage diagnosis (Table 4).

The number of risk factors was determined, and a high number of risk factors were associated with an increased frequency of upstage diagnosis. When the number of risk factors was zero, there was no incidence of upstage diagnosis. When the number of risk factors was more than 4, the incidence of upstage diagnosis was higher than 81.8% (Fig. 3).

Table 1 Baseline characteristics

	Low-grade dysplasia from endoscopic biopsy ($n = 1006$)
Age, years, mean (SD)	63.7 (9.1)
Male gender, *n* (%)	707 (70.3)
Tumor location, longitudinal, *n* (%)	
Lower third	791 (78.6)
Middle third	132 (13.1)
Upper third	83 (8.3)
Lesion size, mm, mean (SD)	12.8 (8.3)
Gross type, *n* (%)	
Elevated	581 (57.8)
Flat	325 (32.3)
Depressed	100 (9.9)
Surface configuration, *n* (%)	
Erythema	116 (11.5)
Nodularity	234 (23.3)
Depression	77 (7.7)
Erosion	36 (3.6)
Ulceration	47 (4.7)
Submucosal fibrosis, *n* (%)	96 (9.5)
Pathologic concordance, *n* (%)	858 (85.3)
Upstage diagnosis rate, *n* (%)	122 (12.1)
Downstage diagnosis, *n* (%)	26 (2.6)
En bloc resection, (*n*, %)	985 (97.9)
Complete resection, (*n*, %)	977 (97.1)

SD standard deviation

Discussion

Because gastric low-grade dysplasia is a precancerous lesion, it is necessary to develop an optimized management plan for these lesions. The risk of developing cancer from low-grade dysplasia has been reported to be 25 times higher compared with the general population, and 10 times higher than in patients with intestinal metaplasia [2]. Therefore, close endoscopic surveillance, or endoscopic resection, if possible, should be performed for gastric low-grade dysplasia [5]. However, there are no consensus guidelines for which lesions should be resected or monitored by follow-up when the result of endoscopic forceps biopsy is low-grade dysplasia. Many studies have reported diagnostic discrepancy between tissues obtained by endoscopic forceps biopsy and that obtained by endoscopic resection. The diagnostic discrepancy rate of gastric low-grade dysplasia from endoscopic forceps biopsy has been reported to be 16–37% [6, 10, 11]. In the present study, upstage diagnosis was observed

Table 2 Comparison according to the results of the resected specimens

	Concordance or downstage diagnostic group ($n=884$)	Upstage diagnostic group ($n=122$)	Total ($n=1006$)	p value
Age, years, mean (SD)	63.7 (9.1)	63.7 (9.2)	63.7 (9.1)	0.994
Male gender, *n* (%)	612 (69.2)	95 (77.9)	707 (70.3)	0.050
Tumor location, longitudinal, *n* (%)				0.069
Lower third	693 (78.4)	98 (80.3)	791 (78.6)	
Middle third	112 (12.7)	20 (16.4)	132 (13.1)	
Upper third	79 (8.9)	4 (3.3)	83 (8.3)	
Lesion size, mm, mean (SD)	12.3 (7.8)	15.8 (9.9)	12.83 (8.278)	< 0.001
Lesion size (Maximal diameter), *n* (%)				< 0.001
< 10 mm	382 (43.2)	27 (22.1)	409 (40.7)	
10–19 mm	348 (39.4)	63 (51.6)	411 (40.9)	
20–29 mm	121 (13.7)	23 (18.9)	144 (14.3)	
≥ 30 mm	33 (3.7)	9 (7.4)	42 (4.2)	
Lesion size (Maximal diameter), *n* (%)				< 0.001
< 10 mm	382 (43.2)	27 (22.1)	409 (40.7)	
≥ 10 mm	502 (56.8)	95 (77.9)	597 (59.3)	
Gross type, *n* (%)				0.028
Elevated	522 (59.0)	59 (48.4)	581 (57.8)	
Flat	281 (31.8)	44 (36.1)	325 (32.3)	
Depressed	81 (9.2)	19 (15.6)	100 (9.9)	
Surface configuration, *n* (%)				
Erythema	64 (7.2)	52 (41.8)	116 (11.5)	< 0.001
Nodularity	165 (18.7)	69 (56.6)	234 (23.3)	< 0.001
Depression	47 (5.3)	30 (24.6)	77 (7.7)	< 0.001
Erosion	14 (1.6)	22 (18.0)	36 (3.6)	< 0.001
Ulceration	32 (3.6)	15 (12.3)	47 (4.7)	< 0.001
Submucosal fibrosis, *n* (%)	81 (9.2)	15 (12.3)	96 (9.5)	0.270
En bloc resection, (*n*, %)	864 (97.7)	121 (99.2)	985 (97.9)	0.296
Complete resection, (*n*, %)	857 (96.9)	120 (98.4)	977 (97.1)	0.381

SD standard deviation

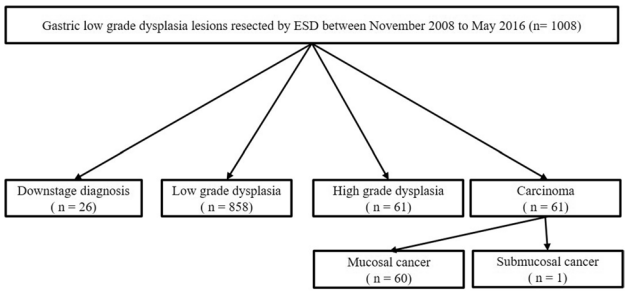

Fig. 2 Study flow and results

in 12.1% of patients, and lesions larger than 10 mm and surface changes (erythema, nodularity, depression, and erosion) were shown to be factors which were significantly associated with upstage diagnosis. When low-grade dysplasia patients were diagnosed via endoscopic forceps biopsy, and had no

Table 3 Logistic regression analysis of risk factors for the presence of high-grade dysplasia and/or invasive carcinoma in the low-grade dysplastic lesions removed by endoscopic resection

Characteristic	Adjusted OR (95% CI)	p value
Male	1.190 (0.710–1.995)	0.509
Lesion size ≥ 10 mm	2.231 (1.302–3.821)	0.003
Gross type		0.655
Elevated	1	
Flat	1.085 (0.482–2.443)	
Depressed	1.332 (0.586–3.026)	
Erythema	7.315 (4.227–12.657)	< 0.001
Nodularity	5.589 (3.478–8.983)	< 0.001
Depression	3.024 (1.485–6.160)	0.002
Erosion	7.680 (3.203–18.412)	< 0.001
Ulceration	1.521 (0.619–3.736)	0.361

CI confidence interval

Table 4 Effect of the presence of 0–5 risk factors for the upstage diagnosis of gastric low-grade dysplasia (risk factors were lesion size ≥ 10 mm, surface erythema, nodularity, depressed morphology , and surface erosion) (univariate analysis, $p < 0.001$)

No. of risk factors	Concordance or downstage diagnostic group ($n = 884$)	Upstage diagnostic group ($n = 122$)	Total ($n = 1006$)
0	311 (35.2)	0 (0)	311 (30.9)
1	388 (43.6)	24 (19.7)	412 (41.0)
2	152 (17.2)	63 (51.6)	215 (21.4)
3	31 (3.5)	23 (18.9)	54 (5.4)
4	2 (0.2)	9 (7.4)	11 (1.1)
5	0 (0)	3 (2.5)	3 (0.3)

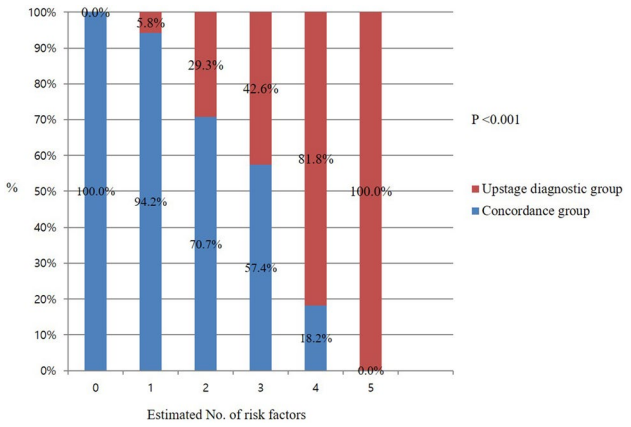

Fig. 3 The effect of the presence of 0–5 risk factors upon upstage diagnosis in patients with gastric low-grade dysplasia (risk factors: lesion size ≥ 10 mm; surface erythema; nodularity; depressed morphology ;and surface erosion)

other endoscopic risk factors, there was incidence of upstage diagnosis to high-grade dysplasia and carcinoma.

The diagnostic discrepancy between endoscopic forceps biopsy and completely resected specimens remains a common clinical concern. Such diagnostic discrepancy may be related to an incorrect target biopsy, a biopsy specimen too small to interpret properly, or the focal existence of high-grade dysplasia or a cancerous lesion in the background of low-grade dysplasia. Increasing the number of biopsies may improve the diagnostic accuracy of gastric dysplasia. A reported concordance rate of up to 79.1–83.1% was previously reported for when more than two biopsy specimens were obtained [12]. In our institute, although 1–2 endoscopic forceps biopsies are performed for suspicious intraepithelial neoplasm when preparing ESD, and in accordance with the size of the lesion and the endoscopist's decision, the diagnostic accuracy was similar or more severe (diagnostic concordance rate was 85.3% in the present study). For an advanced lesion, more than 4 endoscopic biopsies could provide higher diagnostic accuracy (diagnostic rate up to 95% or more) [13]. Although multiple biopsy samples can reveal an accurate diagnosis, most gastric low-grade dysplasia lesions are small and are located superficially (81.6% of the lesions were < 20 mm in the present study). When preparing endoscopic resection such as ESD, the submucosa fibrosis induced by endoscopic multiple forceps biopsy may represent an obstacle for complete endoscopic resection. Although larger biopsy specimens may represent another option with which to reduce the incidence of diagnostic discrepancy, previous studies comparing conventional endoscopic forceps and jumbo forceps showed no significant difference [12]. A meticulous first biopsy of suspicious lesions is crucial for the diagnosis of minute gastric cancers because bleeding during the first biopsy may prevent the subsequent biopsy [14].

Although endoscopic forceps biopsy is the most important diagnostic tool for malignant or premalignant lesions, this technique may not provide a tissue sample that is representative of the entire lesion. Therefore, knowing the associated malignant endoscopic features to suspect higher-grade lesions is important. Previous studies have reported that the important endoscopic features when suspecting malignant changes are lesion size and changes in surface appearance compared to the surrounding normal gastric mucosa [6, 10, 11, 15, 16]. During endoscopy, lesion size is one of the most important risk factors to consider. In the present study, a lesion size of ≥ 10 mm was shown to be a significant risk factor. A previous study reported that lesions larger than 20 mm [15] were a significant risk factor. However, it is important to note that malignant lesions may be found which are < 10 or 10–20 mm in size [10]. After examining lesion size, the next step is to evaluate the surface appearance of the lesion. In the present study, surface changes (erythema, nodularity, depression, and erosion) were important factors to consider in our endoscopic findings. In the present study, we evaluated the association between the total number of risk factors and the incidence of upstage diagnosis. If a gastric dysplasia lesion had no risk factors, then upstage diagnosis did not occur. If the number of risk factors increased, then the rate of upstage diagnosis also increased. The growth rate of gastric dysplasia may represent another important factor to consider during follow-up examination [15]. Therefore, during regular follow-up examinations, the changes of size and surface appearance are important for creating a proper treatment plan.

In contrast to upstage diagnosis after ESD, 2.6% of cases were downstaged in the present study. Endoscopic forceps biopsy represents a simple diagnostic method with which to diagnose gastric superficial neoplasm. However, the pathological discrepant results between the resected specimen and endoscopic forceps biopsy specimen are common. Previous studies reported that the incidence of downstaging, or negative pathological results, after endoscopic resection was 2.0–4.4% [17–19]. The reason for pathological downstaging after endoscopic resection might be the complete removal of the initial lesions by endoscopic forceps biopsy, over-estimation of the biopsy specimen, and/or a different ESD site. Small lesions might be completely removed through tissue acquisition by endoscopic forceps biopsy, or might not even be included in the histological slide prepared from resected specimens during mapping. Frequently, pathologists find it ambiguous to confirm whether lesions are true neoplastic lesions since atypical or borderline epithelial lesions are difficult to diagnose because of their regenerative or neoplastic nature [5].

There are several limitations in the present study. First, this study was a retrospective study at a single academic referral center. Therefore, selection bias may be present. Second, we were unable to evaluate the extent of gastric atrophy and intestinal metaplasia which were associated with gastric cancer and dysplasia. Third, we were unable to evaluate the presence of *H. pylori* because many patients underwent only one type of *H. pylori* evaluation (such as biopsy or the rapid urease test). We could not include the presence and eradication of *H. pylori* as risk variables. Fourth, the biopsy protocol was not standardized in terms of biopsy numbers and sites of target biopsy; this may have resulted in diagnostic errors of pre-ESD diagnosis in patients with gastric dysplasia.

In summary, the optimal management of gastric low-grade dysplasia may be essential in preventing the occurrence of gastric cancer and improving the mortality associated with gastric cancer long term. This study identified several endoscopic findings associated with the upstaged diagnosis of gastric low-grade dysplasia, such as a lesion size ≥ 10 mm and a variety of surface changes (erythema, nodularity, depression, and erosion). The risk of upstage diagnosis increased with a higher number of risk factors. If there is no evidence of risk factors, then regular follow-up may be considered, in accordance with the patient's combined comorbid conditions.

Compliance with ethical standards

Disclosures Cheol Woong Choi, Dae Hwan Kang, Hyung Wook Kim, Su Bum Park, Su Jin Kim, Hyeong Seok Nam, and Dae Gon Ryu have no conflicts of interest or financial ties to disclose.

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