Endoscopic Features of Low-grade Gastric Dysplasia on Forceps Biopsy Showing Upgraded Histology after Endoscopic Resection

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Celebrating the last night, December 31, 2009

Written by Chan Sik Won

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Abstracts

Backgrounds: Gastric dysplasia is generally accepted as a precursor lesion for gastric carcinoma. About 25-35% of histological diagnosis from endoscopic forceps biopsy for gastric dysplastic lesion has changed after endoscopic resection (ER). The aims of this study was to determine the predictive endoscopic features of high-grade gastric dysplasia (HGD) or early gastric cancer (EGC) after ER, which was initially diagnosed as low-grade dysplasia (LGD) on forceps biopsy.

Methods: From July 2005 until May 2009, 241 LGD lesions were diagnosed by initial endoscopic forceps biopsy were enrolled and underwent ER. After ER, all lesions were categorized as two groups based on final histological findings; up-graded histology (UH; LGD to HGD or EGC) and concordant to down-graded histology (CDH; LGD to gastritis or LGD). As predictive variables for UH, the size, gross endoscopic appearance, location of the dysplastic lesion, surface nodularity or redness, presence of depressed portion, numbers of forceps biopsy specimens, *Helicobacter pylori* infection and intestinal metaplasia were retrospectively investigated.

Results: Among 241 LGDs diagnosed by initial forceps biopsy, 100 lesions (41.5%) revealed histological discrepancy after ER; HGD in 56 (23.2%), adenocarcinoma in 39 (16.2%), and chronic gastritis in 5 (2.1%) patients. Therefore, 39% of initially diagnosed LGDs on forceps biopsy, was categorized as UH after histological examination of resected specimen. In univariate analysis, the large lesion (> 15 mm, $p < 0.05$), the lesion with depressed portion ($p < 0.05$), and the lesion with surface nodularity ($p < 0.05$) were significantly related to UH group after ER. In the multivariate analysis, the large size (> 15 mm, OR 2.8; 95% CI 1.46-5.43, $P < 0.02$) and depressed portion (OR 2.7; 95% CI 1.44-5.03, $P < 0.02$) were predictive factors for UH after ER.

Conclusion: Our study showed that substantial proportion of forceps biopsy from gastric tumor did not represent the whole lesion and additional endoscopic resection should be preferentially considered for the lesion with a depressed portion or larger than 15 mm in size even though endoscopic biopsy showed LGD.

Key Words: Gastric dysplasia; Endoscopic forceps biopsy; Endoscopic resection; Early gastric cancer

Introduction

Dysplasia refers to an unequivocal neoplastic transformation in the epithelium without penetration into the lamina propria (intramucosal carcinoma) (1, 2). Gastric dysplasia is generally accepted as a precursor lesion for gastric carcinoma (3). The chance of carcinoma developing in a gastric dysplasia may depend on the histological type and grade, size, and surface appearance of the gastric dysplasia (4, 5). Therefore, the lesion diagnosed as high grade dysplasia (HGD, category 4 in the Vienna classification) in endoscopic forceps biopsy specimen should always be followed by complete resection of entire lesion, endoscopically or surgically (6, 7).

Contrary to the HGD, there have been some arguments for the treatment of LGD. Some asserted that endoscopic surveillance with re-biopsy could be scheduled periodically because of low risk of malignant transformation (8, 9), whereas others suggested guiding principle for the management of LGD should be the endoscopic resection of the lesion (5). If the endoscopic forceps biopsy represents the whole lesion, endoscopic follow-up is enough for the management of LGD. However, a finding of low grade dysplasia (LGD, category 3 in the Vienna classification) in forceps biopsy material can not completely exclude the presence of HGD or a focus of carcinoma in the other part of the lesion (4, 10, 11). In particular, even though endoscopic forceps biopsy is the best way of obtaining accurate diagnostic information, histological discrepancy between endoscopic forceps biopsy specimen and the endoscopic resection was ranged from 25% to 35% (12-14). In this study, we investigated the predictive endoscopic features of HGD or early gastric cancer (EGC) after ER, which was initially

diagnosed as LGD on forceps biopsy.

Subjects and methods

1. Study population

From July 2005 to May 2009, LGD lesions from 241 patients diagnosed by initial endoscopic forceps biopsy were retrospectively enrolled and underwent ER at the Yonsei University Wonju Christian Hospital, South Korea. After ER, all lesions were categorized as two groups based on final histological findings; up-graded histology (UH; LGD to HGD or EGC) and concordant or down-graded histology (CDH; LGD to gastritis or LGD).

2. Methods

Endoscopic resection was performed by endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) method. Gastric lesions were first identified and demarcated using white-light endoscopy and chromoendoscopy with indigo–carmine solution (GIF-Q 240, 260; Olympus Optical Co., Ltd., Tokyo, Japan). Marking around the lesions was carried out with spotty cautery using a argon plasma coagulation. Isotonic saline mixed with epinephrine (1:10000) was injected into the submucosal layer to produce a mucosal bleb. A circumferential mucosal incision was made around the lesion and then resection with a snare (EMR or polypectomy) or a hook knife and/or IT (insulated tipped) knife (Olympus Optical, Tokyo, Japan) ESD was performed. All patients were sedated by intravenous injection of 3–4 mg of midazolam and/or 20 mg of propofol. Ten to 20 mg of propofol was additionally given for conscious sedation as needed throughout the procedure.

As a predictive variables for UH, the size, numbers of forceps biopsy specimens,

location of the dysplastic lesion, surface nodularity or redness, presence of depressed portion, *Helicobacter pylori* infection and intestinal metaplasia were investigated as potential factors for histological discrepancy. The location of dysplastic lesion, surface nodularity and redness, depressed portion were investigated by white-light endoscopy and chromoendoscopy using indigo-carmine. A mucosal depressed portion was defined as a lesion with a mucosal defect or scar from a previous ulcer. The size of dysplastic lesion, presence *Helicobacter pylori* infection and coexistence of intestinal metaplasia were investigated by pathology report of resected specimen.

One expert gastrointestinal pathologist reviewed the histopathological findings of both endoscopic forceps biopsy materials and endoscopically resected specimen. The biopsy specimen from the gastric lesion was fixed in formalin and bisected for hematoxylin-eosin (H&E) staining. The resected specimens were also fixed on a flat board and observed macroscopically; they were then fixed in formalin and examined in step sections. The resected specimens were sectioned perpendicularly by 2 mm intervals. All of the lesions were classified as standardized guidelines which is proposed by the Vienna classification of gastrointestinal neoplasia (11).

3. Statistical analysis

All statistical tests were performed by two-sided tests and a p-value < 0.05 was considered statistically significant. Statistical analysis was performed with the SPSS PC window program (Statistical Package for the Social Science, SPSS Ins, Chicago, USA). Associations between the categorical parameters and sub-groups of UH, CDH were assessed by the chi-square test. Multiple logistic regression analysis for the predictive factors for up-

graded histologic discrepancy after ER was performed to examine the effects of the independent variables, and adjustments were made for the effects of each of the variables on the other variables.

Results

1. Clinicopathological characteristics of patients and gastric lesions

Table 1 showed the clinicopathological characteristics of patients and gastric lesions. Total 241 patients (mean age ; 62.6 ± 10 years old, M:F=175:66) and 241 lesions were enrolled in this study. The mean size of the lesion was 12.8 ± 7.9 mm and the numbers of forceps biopsies were 2.5 ± 1.3. When we divided gastric areas into three sections (body including fundus, angle, and antrum), 152 cases were located on antrum. The frequencies of depressed portion, surface nodularity and redness were 46%, 55% and 39%. The frequencies of *Helicobacter pylori* infection and intestinal metaplasia were 48% and 85%.

Table 1. Clinicopathological characteristics of patients and gastric lesions

	Cases (%)
Age (mean ± SD)	62.6 ± 10
Sex	
Male	175 (72.6)
Female	66 (27.4)
Size of lesion (mean ± SD)(mm)	12.8 ± 7.9
Numbers of forceps biopsy	2.5 ± 1.3
Location of lesion	
Antrum	152 (63)
Angle	31 (13)
Body and Fudus	58 (24)
Depressed portion	
Positive	110 (46)
Negative	131 (54)
Surface nodularity	
Positive	133 (55)
Negative	108 (45)
Surface redness	
Positive	93 (39)
Negative	148 (61)
Helicobacter pylori infection	
Positive	116 (48)
Negative	125 (52)
Intestinal metaplasia	
Positive	205 (85)
Negative	36 (15)

2. Histological comparison between forceps biopsies and resected specimens

Among 241 patients with LGD on forceps biopsy, 141 cases (59%) showed concordant histology whereas 100 cases(41%) revealed histological discrepancy; 39 cases of adenocarcinoma, 56 cases of HGD, and 5 cases of chronic gastritis. Therefore final histology was concluded as upgraded histology in 39% (95/241) of initially diagnosed LGD on forceps biopsy (Table 2).

Examples histological discrepancy are given in Figure 1 and 2. Figure 1 shows upgraded histology of LGD to HGD and Figure 2 shows upgraded histology to adenocarcinoma.

Table 2. Histological comparison between forceps biopsies and resected specimens.

		LGD on Forceps Biopsy cases (%)
Endoscopically Resected specimens	Gastritis†	5 (2.1)
	LGD†	141 (58.5)
	HGD‡	56 (23.2)
	Carcinoma‡	39 (16.2)
	Total	241

†: CDH (concordant or down-graded histology) group, ‡: UH(up-graded histology) group

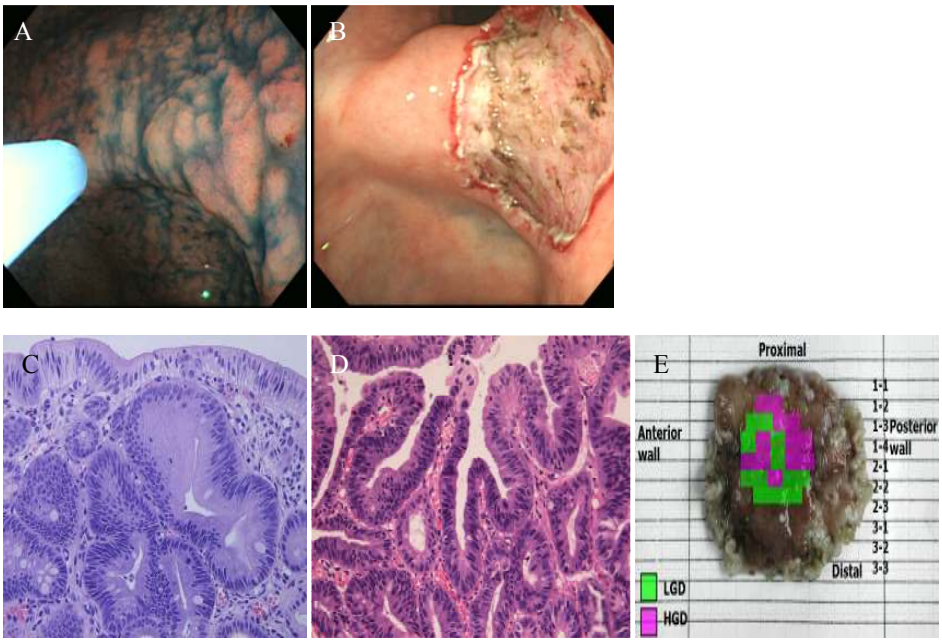

Figure 1. A case showing upgraded histology of LGD to HGD.

A. Endoscopic finding of the lesion with indigocarmine spray. Endoscopy reveals an 15 mm sized elevated mucosal lesion with surface nodularity and redness in the posterior wall of angle.

B. After endoscopic resection, 2 cm sized mucosal defect was observed.

C. Microscopic feature of forceps biopsy. The biopsy specimen reveals mild glandular disarray and increased cellularity with basally located enlarged hyperchromatic nuclei. These findings are consistant with LGD (H&E stain, x400).

D. Microscopic feature of resected specimen. The part of lesions shows marked glandular disarray with vesicular round nuclei and marked increase in mitosis. These findings are suitable for HGD (H&E stain, x400).

E. Mapping of resected specimen. Tumor size is 15 mm, and, LGD is mixed with HGD.

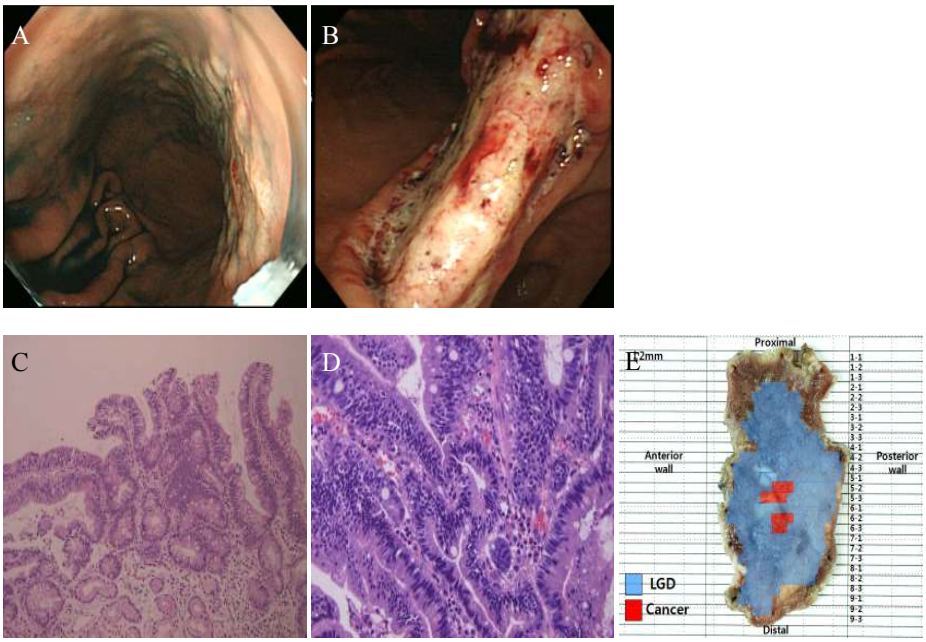

Figure 2. A case showing upgraded histology of LGD to adenocarcinoma.

A. Endoscopic finding of the lesion with indigocarmine spray. Endoscopy reveals a 40 mm sized flat mucosal lesion with surface nodularity in the lesser curvature side of angle to mid body.

B. Large mucosal defect after ESD was noted over gastric angle.

C. Microscopic feature of forceps biopsy. The biopsy specimen reveals increased cellularity and villous appearance in the surface epithelium with elogated cigar shaped nuclei confined to the basal half of epithelial cells. These findings are consistant with LGD (H&E stain, x200).

D. Microscopic feature of resected specimen. The glandular architecture is severely distorted by marked proliferation of disarrayed glands with invasion. This finding is suitable for well differentiated adenocarcinoma confined to the lamina propria (H&E stain, x400).

E. Mapping of resected specimen. Tumor size is 45 mm, and we can see focal cancer lesions mixed with LGD. The Lateral & vertical margins are free.

3. Factors related to the histological discrepancy

Table 3 summarizes the comparison between UH group and CDH group in LGD on forceps biopsy. In 39 of 95 cases (41%) with UH, lesion size was larger than 15 mm. Of 146 cases with CDH, only 34 cases (23.2%) were larger than 15 mm. Fifty two of 95 cases (54.7%) with UH had depressed portion on the lesions, however, 50 of 146 cases (34.2%) with CDH had depressed portion in the lesion. Sixty five of 95 cases (68.4%) with UH had surface nodularity, while 68 of 146 cases (46.6%) with CDH had surface nodularity.

On univariate analysis, the large size of lesion, the lesion with depressed portion and surface nodularity were significantly related to UH (Table 3). On the multivariate analysis for the risk factors of UH, the large size and depressed lesion were significant risk factors for UH after endoscopic resection in LGD on forceps biopsy (odds ratios 2.8 and 2.7) (Table 4). There were no significant associations of UH with age, sex, surface redness, numbers of forceps biopsy specimens, *Helicobacter pylori* infection and intestinal metaplasia (Table 3 and 4).

Table 3. Comparison between UH group and CDH group after endoscopic resection.

	UH group	CDH group	*p* value
Age(mean±SD)	63.9±9.7	61.8±10.1	n.s.
Sex			
Male	68	107	n.s
Female	27	39	
Size of lesion			<0.05
≤15mm	56	112	
>15mm	39	34	
Numbers of forceps biopsy			
1-2	54	86	n.s
≥3	41	60	
Surface redness			n.s
Positive(+)	42	51	
Negative(-)	53	95	
Depressed portion			<0.05
Positive(+)	52	50	
Negative(-)	43	96	
Surface nodularity			
Positive(+)	65	68	<0.05
Negative(-)	30	78	
Helocobacter pylori infection			
Positive(+)	48	68	n.s.
Negative(-)	47	78	
Intestinal metaplasia			
Positive(+)	84	121	n.s.
Negative(-)	11	25	

UH: up-graded histology, CDH: concordant or down-graded histology, n.s: not significant

Table 4. Multivariate analysis for the risk of UH after endoscopic resection.

Factors	OR (95% C.I)	*p* value
Large size (> 15 mm)	2.8 (1.46-5.43)	0.002
Depressed portion (+)	2.7 (1.44-5.03)	0.002
Surface nodularity(+)	1.7 (0.90-3.12)	0.104
Age (> 65 yrs)	1.4 (0.82-2.57)	0.203
Numbers of forceps biopsy	1.1(0.84-1.32)	0.675
Surface redness (+)	1.0 (0.55-1.82)	0.999
Intestinal metaplasia(+)	1.6 (0.72-3.75)	0.239
Helicobacter pylori infection(+)	1.5 (0.82-2.57)	0.203

Discussion

Dysplasia was defined as a benign unequivocal neoplastic epithelial lesion, histologically distinguished from invasive carcinoma and also from reparative changes (3). It is well known that gastric dysplasia is a precursor lesion to gastric carcinoma and classified as “noninvasive neoplasia” by the Padova international classification (2). Gastric dysplasia could be categorized into low grade or high grade by the severity of histological abnormality using a two tier system (11). The characteristics of LGD were multiple small round glandular structures similar to adenomatous polyps in the colon. However, it has been difficult in the discrimination of gastric dysplasia owing to various reasons. The first reason is interobserver variability. Fertitta AM et al. reported that 51% of cases initially diagnosed as moderate dysplasia by general pathologists were confirmed as hyperplasitc or metaplastic lesions (12). But it is reported that the variation is much lower in high grade lesions (8). Second reason is the specimen size. Because the specimen of forceps biopsy was tiny and break into splinters, it could not represent the whole lesion and be misleading the disease severity. Third reason is pathophysiology of gastric carcinogenesis. A series of changes have been identified as precursors to the intestinal type of gastric carcinoma, representing apparently sequential steps in the precancerous process, namely superficial gastritis, chronic atrophic gastritis, intestinal metaplasia, dysplasia and cancer (13). Similarly, the genetic evolution of cancer involves the accumulation of multiple mutations. In gastric cancer, altered loci include p53, APC, K-ras and multiple microsatellites instability in cancers with a replication error (RER) or USM (ubiquitous somatic mutation) phenotype (14). For this reason, various degree dysplasia is able to coexist in same lesion with heterogeneity. In spite of these limitation, clinicians should be determine the therapeutic plans by the endoscopic biopsy result.

In this study, we investigated the risk factors of endoscopic features that showing upgraded histological discrepancy in the lesion which was diagnosed as LGD on forceps biopsy.

We focused LGD histology and there are some important reasons. First, LGD had histologically vague position. Until very recently, there was a substantial lack of agreement on the issue of dysplasia and its grading among pathologists, especially between from Japan and the Western contries. As a result of two consensus conferences held in Padova and Vienna, we now have the Padova International Classification (2) and the Vienna Classification (11). When the pathologists involved in set up the Padova classification participated in a test of variability after the conference, they fulfilled general agreement 77.7% to 86.5% of the time (15). The κ coefficients were a little over 0.6, indicating moderately good agreement. However, interobserver variability in diagnosing dysplasia is inevitable whenever a continuous spectrum is subjectively divided. The difficulty in differentiating reactive from dysplastic changes may account for reports of reversibility of LGD (16). For this reason, interobserver variability could more often in LGD. In our study, only one expert gastrointestinal pathologist reviewed forceps biopsy materials and resected specimen, and this fact could reduce the interobserver variability.

Second, LGD had some argument for the treatment. When the two tier system was used, low grade dysplasia was shown to regress in between 38 and 49%, to persist in 19–28% and to progress to high grade dysplasia in between 0 and 15% of cases. High grade dysplasia was regressed in about 5%, persisted in 14% and progressed in 81–85% of cases (15, 17). For this reason, the lesion diagnosed as high grade dysplasia in endoscopic forceps biopsy material should always be followed by complete resection of entire lesion, endoscopically or surgically (6, 7). Since several long term follow-up studies showed that LGD lesions less progressed to

HGD or carcinoma, some authors recommended scheduled endoscopic surveillance and re-biopsy (9, 18). However, another group suggested to remove the LGD lesions because of histological discrepancy between forceps biopsy and resected specimen (19-21). In our study, most part of histological discrepancy was up-graded histology(39%), whereas down-graded histology was only 5%. Furthermore, scarring change of the lesion due to multiple biopsy could interfere ER. Mindy JH et al. reported that EMR is superior to biopsy for the diagnostic evaluation of large lesions (22). For these reasons, We suggest that endoscopic resection is more suitable for LGD treatment strategy. Consequently, it is better that not only endoscopic forceps biopsy but also endoscopic findings related with risk of discrepancy are considered for therapeutic plans of LGD lesions.

It has been reported that histological discrepancy between endoscopic biopsy and surgical specimen were ranged from 25% to 35% (23-25). In our data, histological discrepancy between forceps biopsy and ER specimens is confirmed in 100/241 (41.5%) of total cases. So, it is considered that we could obtain important information from an endoscopic findings. Recent data revealed that the larger size of lesion (>15mm), redness, nodularity of surface lesions and presence of depressed portion could be markers for malignancy risk (4, 5). Also, adenomatous polyps with a diameter above 2 cm size have been regarded as having a malignant potential (26). In our data, the lesions with larger size than 15 mm, with depressed portion, and with surface nodularity were more often presented in UH than in CDH from LGD lesion of forceps biopsy. In the multivariate analysis, the risk of UH was significantly increased by 2.8 fold in lesions larger than 15 mm and 2.7 fold in lesions with depressed portion. These results suggested that the size of lesion and existence of depressed portion may be a risk factors related with UH.

However, our study had some limitations. First, the possibility of selection bias may be

present because this study was performed retrospectively. Second, the concordance rate of endoscopic findings between observers was not investigated. Third, numbers of forceps biopsy differed from each other. Further prospective study is needed to get over these limitations.

In conclusion, we suggest that additional endoscopic resection should be preferentially considered for the lesion with a depressed portion or larger than 15 mm in size even if endoscopic biopsy showed LGD for the purpose not only proper treatment but also exact diagnosis.

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Abstract (In Korean)

겸자 생검에서 저도 위 이형성증을 보인 병변의 내시경적 절제 후 상향적 불일치를 보일 수 있는 병변에 대한 내시경적 예측인자 분석

(지도교수: 김현수)

원찬식

연세대학교 대학원 의학과

연구배경: 위 이형성증은 위암의 전구 병변으로 알려져 있다. 겸자 생검 조직 소견과 내시경적 점막 절제술 후 조직소견은 25-35%에서 불일치를 보인다. 본 연구는 겸자 생검상 저도 위이형성을 보였으나 내시경적 점막 절제술 후 조직 소견상 고도 위이형성이나 조기 위암을 보인 병변에 대해서 이러한 악화된 조직 소견을 예측할 수 있는 내시경 소견상의 특징에 대해 조사하였다.

방법: 2005 년 7 월부터 2009 년 5 월까지 241 개의 겸자 생검에서 저도이형성증을 보이고 내시경적 점막 절제술을 시행한 병변을 대상으로 조사하였다. 겸자 생검상 저도위이형성증에서 내시경적 점막 절제술 후

고도위이형성증이나 조기위암으로 악화된 조직소견으로 진단된 그룹과 내시경적 점막 절제술 후 저도위이형성증이나 위염으로 진단된 두개의 그룹으로 나누어 악화된 조직소견을 예측할 수 있는 내시경적 특징에 대해 조사하였다. 악화된 조직소견을 예측할 수 있는 인자로는 이형성 병변의 크기, 이형성 병변의 위치, 점막 표면 홍조 유무, 함몰 병변 동반 유무, 겸자 생검의 개수, 병변 점막 표면의 결절 동반 유무, 헬리코박터 균 감염 여부, 장상피화생 동반 여부 등을 조사하였다.

결과: 겸자 생검상 저도위이형성증으로 진단된 241 개의 병변중 내시경적 점막절제술 후 100 개의 병변(41.5%)에서 조직학적 불일치를 보였으며 고도이형성증은 56 개 (23.2 %), 조기위암은 39 개 (16.2 %), 만성 위염은 5 개 (2.1%)로 39%가 악화된 조직소견으로 나왔다. 단변량 분석 결과 병변의 크기 (> 15 mm, $p < 0.05$), 함몰 병변, 병변 점막 표면의 결절 동반이 악화된 조직소견과 상관관계가 있었으며 다변량 분석에서는 병변의 크기와 함몰 병변이 내시경적 절제술 후 악화된 조직소견을 예측 할 수 있는 것으로 나왔다.

결론: 본 연구 결과 겸자 생검만으로는 점막 병변을 감별하는 것이 완전하지 않으며 겸자 생검상 크기가 15 mm 이상이거나 함몰병변일 경우에는 내시경적 점막 절제술을 고려하는 것이 좋을 것으로 사료된다.

중심단어: 위이형성증, 겸자 생검, 내시경적 점막 절제술, 조기 위암