

Comparative analysis of differences between preoperative endoscopic biopsy and postoperative pathological examination for diagnosis of gastric intraepithelial neoplasia

Yangqing Wu , Jianzhong Sang, Jianbo Zhou and Ying Fang

Abstract

Objective: This study was performed to compare the differences between preoperative endoscopic biopsy (PEB) and postoperative pathological examination (PPE) for diagnosis of gastric intraepithelial neoplasia (GIN).

Methods: From September 2016 to July 2019, 188 consecutive patients with GIN at Yuyao People's Hospital were retrospectively analyzed. The 188 patients had 218 GIN lesions. All patients underwent PEB and either endoscopic submucosal dissection or surgical treatment. PPE was performed on pathological tissues that had been surgically removed.

Results: Among 138 cases of low-grade dysplasia (LGD) diagnosed by PEB, 46 were upgraded to high-grade dysplasia (HGD), 20 were upgraded to early gastric cancer (EGC), and 2 were downgraded to inflammation after PPE. Among 42 cases of HGD, 23 were upgraded to EGC, 2 were downgraded to LGD, and 2 were downgraded to inflammation after PPE. Among 38 cases of EGC, 1 was downgraded to HGD and 2 were downgraded to LGD after PPE. The original diagnosis was maintained after the operation in 120 cases of GIN.

Conclusion: Biopsy did not fully reflect the lesions of GIN. Biopsy review should be actively performed, and the lesions should be clarified by endoscopic submucosal dissection or surgery.

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Keywords

Preoperative endoscopic biopsy, postoperative pathological examination, gastric intraepithelial neoplasia, endoscopic submucosal dissection, surgical treatment, dysplasia

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Introduction

Gastric cancer (GC) is one of the most common cancers worldwide, especially in East Asia. Gastric intraepithelial neoplasia (GIN) is one of the more common precancerous lesions, suggesting that GIN may coexist with GC and that GIN may be predictive of future GC.¹ GIN is an area of focus in the prevention and treatment of GC worldwide. In 2010, the 4th Edition of the World Health Organization Classification of Tumours of the Digestive System suggested that GIN can be divided into low-grade dysplasia (LGD) and high-grade dysplasia (HGD). LGD includes mild to moderate dysplasia, while HGD includes severe dysplasia and carcinoma in situ.

The diagnostic methods for GIN include imaging techniques (hypotonic double-contrast radiography and computed tomography (CT)), molecular biology techniques (measurement of carcinoembryonic antigen, alpha fetoprotein, and other parameters), confocal laser endoscopy, and other endoscopic techniques (general endoscopy, electronic ultrasound endoscopy, chromoendoscopy, and magnifying endoscopy). The diagnosis of GIN mainly depends on preoperative endoscopic biopsy (PEB) and endoscopic submucosal dissection (ESD) or postoperative pathological examination (PPE).² The tumors are heterogeneous, and areas of HGD, canceration, and LGD often exhibit a mixed distribution. In clinical practice, we often find that the pathological tumor classification and degree of gastric mucosal invasion are higher after

ESD than after biopsy, and further surgical treatment is sometimes needed after ESD. Underestimation of GIN will delay treatment and directly affect the prognosis.³ The present study was performed to explore the risk factors for postoperative pathological upgradation and the value of biopsy, ESD, and surgery for GIN by comparing the differences between PEB and PPE for diagnosis of GIN.

Methods

Patients

This study was approved by the ethics committee of Yuyao People's Hospital (approval number: 2016015), and all patients provided written informed consent. We retrospectively analyzed 188 consecutive patients with 218 GIN lesions at Yuyao People's Hospital from September 2016 to July 2019. The following data were evaluated: patients' sex and age; lesion location, size, and shape; whether redness was present on the surface; whether white opaque substance (WOS) was present; whether erosion or ulceration was present on the surface; number of biopsies; and the results of PEB and PPE. The preoperative and postoperative pathological results were reviewed by experienced pathologists in our hospital. The study inclusion criteria were (1) preoperative biopsy and diagnosis of LGD or HGD as confirmed by an experienced pathologist after rereading the film, (2) no systemic or lymph node metastasis as

confirmed by preoperative CT, and (3) a ≤ 1 -month interval between biopsy and endoscopic treatment after a diagnosis of HGD or LGD. The exclusion criteria were cognitive impairment and psychosis, lactating women, the presence of other malignant tumors, and a history of allergy. The criteria for lesion resection were as follows. Patients with suspected neoplastic lesions under endoscopy and patients with LGD, HGD, or early GC (EGC) by biopsy underwent resection. Moreover because *Helicobacter pylori* infection or severe inflammation had the potential to interfere with the biopsy results, not all patients with LGD underwent endoscopic resection. Furthermore, each patient underwent narrow-band imaging (NBI) to check for the presence of WOS.

PEB

An Olympus GIF-XQ260 electronic gastroscope (Olympus, Tokyo, Japan) was used for PEB as previously described.⁴ After routine fixation, dehydration, embedding, sectioning, and hematoxylin–eosin (HE) staining, the biopsy specimens were observed under the microscope. The diagnostic criteria for PEB in this study were in reference to the Vienna classification standard formulated by the World Health Organization in 2002 (Table 1). The diagnosis of lesion shape was based on the standards of the Japanese Society of Gastric Cancer and the Paris classification standard.^{5,6}

ESD or surgical treatment

GIN lesions confirmed by PEB were marked with a peripheral ring under endoscopy. Submucosal injection of normal saline, indigo carmine, and epinephrine was performed. After lifting the lesion, an endoscopic knife (YFD-4; Guangzhou Yifudi Medical Device Co., Ltd., Guangzhou, China) was used to cut the lesion around the ring until the whole lesion was peeled off. For patients whose ESD pathologic examination revealed a positive vertical resection margin, further subtotal gastrectomy was performed.

PPE

PPE was performed as described in a previous study.⁷ The specimens obtained after ESD or surgery underwent external fixation. The oral side, anal side, anterior wall, and posterior wall were marked on the specimen. The specimens were then immersed in formalin, fixed for 24 to 48 hours, and dehydrated, embedded, sectioned, and pathologically diagnosed under the microscope. The HE-stained slides from the forceps biopsy and resected specimens were reviewed by the same pathologist to reduce interexaminer differences.

Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA).

Table 1. Vienna classification of gastrointestinal epithelial tumors (2002).

Classification	Definition
Category 1	No dysplasia
Category 2	Uncertain dysplasia
Category 3	Noninvasive low-grade tumor (low-grade adenoma/dysplasia)
Category 4	Noninvasive high-grade tumor (high-grade adenoma/dysplasia; Noninvasive carcinoma (carcinoma in situ, suspected invasive cancer, intraductal carcinoma)
Category 5	Submucosal invasive carcinoma

Measurement data are expressed as mean \pm standard deviation. The chi square test was used to analyze count data between groups. A receiver operating characteristic (ROC) curve was used to compare the disease recognition ability between PEB and PPE. Differences were considered statistically significant at $P < 0.05$.

Results

General clinical data

The 188 patients with GIN comprised 135 men and 53 women aged 43 to 85 years (mean age, 64.0 ± 8.5 years). The mean diameter of the 218 GIN lesions was 14.2 ± 13.2 mm. There were 92 (42.2%) lesions with a diameter of >10 mm and 126 (57.8%) with a diameter of <10 mm. Among the 281 lesions, 8 (3.7%) were located in the cardia, 33 (15.1%) were located in the gastric body, 42 (19.3%) were located in the gastric angle, 134 (61.5%) were located in the gastric antrum, and 1 (0.4%) was located in the gastric fundus.

Results of PEB and PPE

Representative images depicting the PEB and PPE results are shown in Figure 1. Under NBI+magnification, irregular blood vessels and surface structures were seen in the lesion area of the gastric antrum curvature by PEB (Figure 1(b)). In this patient, HE staining of the PEB specimen showed that the lesion in the gastric antrum was LGD (Figure 1(c)). However, according to the PPE findings, the lesion was upgraded to HGD by HE staining (Figure 1(f)).

Comparison of diagnostic results between PEB and PPE

The results of PEB and PPE are shown in Table 2. Of the 218 lesions diagnosed as

GIN before surgery, 138 were LGD, 42 were HGD, and 38 were EGC. In the LGD group, 46 cases were upgraded to HGD, 20 were upgraded to EGC (18 cases of intramucosal cancer and 2 cases of submucosal cancer), and 2 cases were downgraded to inflammation by PPE. In the HGD group, 23 cases were upgraded to EGC (20 cases of intramucosal cancer and 3 cases of submucosal cancer), 2 cases were downgraded to LGD, and 2 cases were downgraded to inflammation. In the EGC group, 1 case was downgraded to HGD and 2 cases were downgraded to LGD. The upgradation rate of PPE diagnosis was 40.8% (89/218), and the degradation rate was 4.1% (9/218). The coincidence rate between PEB and PPE diagnosis was 55.1% (120/218).

Analysis of difference in diagnostic results between PEB and PPE

The lesions were divided into two groups (pathological upgraded group and pathological non-upgraded group), and the reasons for the differences between the two groups were then explored. Lesions with pathological consistency and degradation before and after surgery were also included. As shown in Table 3, a lesion diameter of >10 mm diagnosed by PEB had a significant impact on pathological upgrading in the comparison between the two groups ($P < 0.01$). The detailed data of nine patients with postoperative pathological degradation are shown in Table 4. The ROC curve analysis (Figure 2) showed that the size of the lesion was correlated with pathological escalation (area under the curve = 0.637, $P = 0.001$), with a maximum Youden's index of 0.282 and a corresponding cut-off point of 11.5 mm. When the cut-off value was 11.5 mm, the sensitivity of pathological escalation was 58%, the specificity was 70%, the positive predictive value was 66%, and the negative predictive

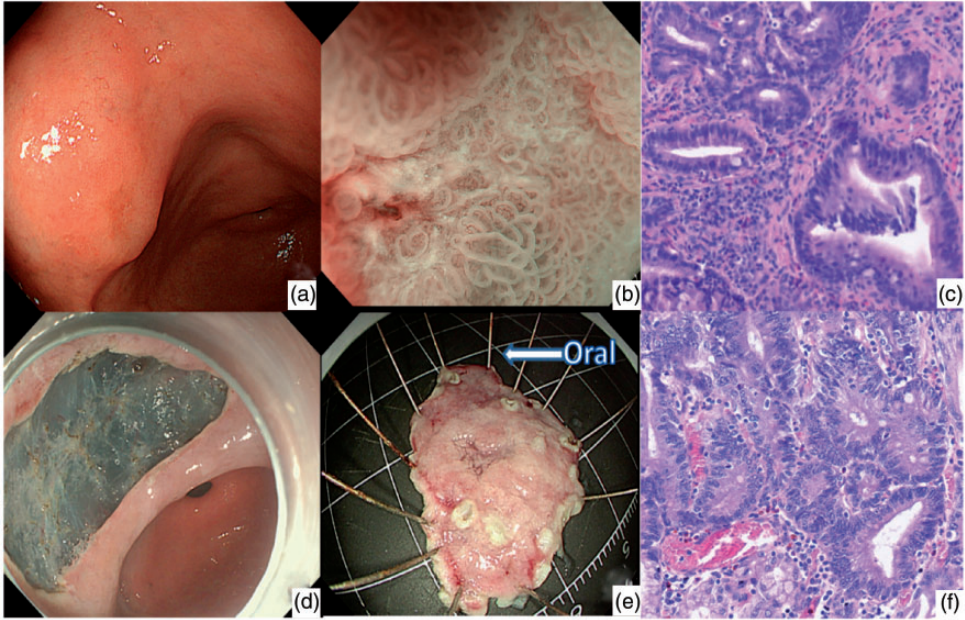


Figure 1. Representative images of preoperative endoscopic biopsy and postoperative pathologic examination of patients with GIN. (a) Pathological changes of GIN type IIa in the gastric antrum observed under white light endoscopy. (b) Pathological changes of GIN type IIa in the gastric antrum observed under narrow-band imaging + magnifying endoscopy (200× magnification). (c) Hematoxylin–eosin staining of preoperative endoscopic biopsy (200× magnification). (d) The surface of the wound after endoscopic ESD. (e) In vitro image of ESD specimen. (f) Hematoxylin–eosin staining of postoperative pathology (200× magnification). GIN, gastric intraepithelial neoplasia; ESD, endoscopic submucosal dissection.

Table 2. Comparison of endoscopic biopsy and postoperative pathology.

Endoscopic biopsy	Postoperative pathology					
	Inflammation	LGIN	HGIN	EGC		Total
				IMC	SMC	
LGIN	2	70	46	18	2	138
HGIN	2	2	15	20	3	42
EGC	0	2	1	30	5	38
Total	4	74	62	68	10	218

LGIN, low-grade intraepithelial neoplasia; HGIN, high-grade intraepithelial neoplasia; EGC, early gastric cancer; IMC, intramucosal cancer; SMC, submucosal cancer.

value was 63%. Therefore, GIN with a lesion diameter of >11.5 mm before surgery should be given particular attention because of the possibility of pathological upgrade.

Discussion

Several studies have shown that 60% to 85% of patients with HGD progress to GC during a follow-up of several months

Table 3. Comparison of postoperative pathological non-upgraded and upgraded groups.

Characteristics	Non-upgraded group (n = 129)	Upgraded group (n = 89)	χ^2 values	P values
Lesion site	–	–	6.443	0.168
Cardia	2	6	–	–
Gastric body	20	13	–	–
Gastric angle	29	13	–	–
Gastric antrum	77	57	–	–
Gastric fundus	1	0	–	–
Lesion size	–	–	16.233	<0.001
≤10 mm	89	37	–	–
>10 mm	40	52	–	–
Lesion morphology	–	–	7.865	0.248
I	5	4	–	–
IIa	27	11	–	–
IIb	7	1	–	–
IIc	66	59	–	–
IIc + IIa	20	12	–	–
IIc + IIb	3	2	–	–
III	1	0	–	–
Lesion color	–	–	1.102	0.294
Redness	81	62	–	–
Non-redness	48	27	–	–
White opaque substance	–	–	0.345	0.557
Present	18	15	–	–
Absent	111	74	–	–
Erosion or ulceration on surface	–	–	1.808	0.179
Present	34	31	–	–
Absent	95	58	–	–
Number of biopsy blocks	–	–	1.129	0.288
I	110	71	–	–
≥2	19	18	–	–

to 3 years, and most cases of GIN can be reversed (proportion of pathological progression, 0%–15%).^{8–11} Therefore, we have more reason to actively implement ESD for patients with endoscopic biopsy suggesting HGD. In contrast, it is easy to overlook the impact of LGD on the patient's disease progression.

Preoperative endoscopy allows for a rough judgment of the tumor depth according to the shape of the tumor combined with CT examination findings, and these data are then combined with the biopsy results for ESD treatment. We recommend

surgery for advanced tumors with deep infiltration. For patients with submucosal infiltration of >500 μ m but a negative vertical margin after ESD, we recommend further surgery or follow-up observation according to patient's age and general condition.

CT is used to exclude tumor growth into the muscularis serosa and even lymph node metastasis, helping to avoid overtreatment under endoscopy. The conventional methods of judging the depth of EGC are white light endoscopy and endoscopic ultrasonography. A recent study suggested that

Table 4. Detailed data of nine patients with postoperative pathological degradation.

Patient no.	Sex	Age (years)	Biopsy pathology	Postoperative pathology	Size (mm)	Site	Morphology	Color	Erosion or ulceration	Number of biopsy blocks
1	Male	69	HGIN	Inflammation	25	Antrum	Ila	Redness	Absent	4
2	Female	56	EGC	LGIN	5	Antrum	Ilb	Non-redness	Absent	1
3	Female	66	LGIN	Inflammation	5	Antrum	Ilb	Redness	Present	1
4	Male	56	HGIN	Inflammation	5	Antrum	Ilc	Redness	Present	1
5	Female	69	HGIN	LGIN	8	Gastric body	Ila	Redness	Absent	1
6	Female	70	LGIN	Inflammation	10	Gastric body	Ilc	Non-redness	Present	2
7	Male	73	HGIN	LGIN	10	Gastric angle	Ilc	Non-redness	Absent	1
8	Male	84	EGC	HGIN	6	Antrum	Ilc	Redness	Present	2
9	Male	56	EGC	LGIN	5	Gastric angle	Ilb	Non-redness	Absent	1

HGIN, high-grade intraepithelial neoplasia; LGIN, low-grade intraepithelial neoplasia; EGC, early gastric cancer.

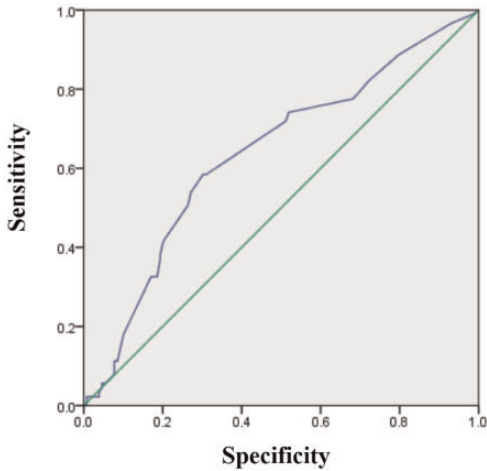


Figure 2. Receiver operating characteristic curve

magnifying endoscopy is associated with postoperative pathological upgrading, which may be due to the influence of magnifying endoscopy on the selection of biopsy sites with severe lesions.¹² Target tissue biopsy is often performed using white light endoscopy, chromoendoscopy, and even combined magnifying endoscopy. First, white light endoscopy is used to observe the location, shape, color, and size of the lesion. The lesion boundaries are determined by chromoendoscopy. Irregular surface structures and blood

vessels are then observed with magnifying endoscopy. The presence of spiral blood vessels or parts with missing surface structures indicates that the lesions may be severe. Improvement of the consistency of biopsy and postoperative pathology would be helpful. However, because of the use of subjective judgment, selection of the biopsy site still has certain limitations.

China does not have clear guidelines and standards for the management of LGD. The latest expert consensus indicates that for patients with LGD showing obvious endoscopically visible lesions and clear boundaries, the diagnosis of biopsy alone is insufficient, and diagnostic ESD resection is recommended.^{13,14} Of course, if the risk factors for LGD upgrading are clarified, the management of LGD will be more accurate. Our study showed that the postoperative pathological upgradation rate of LGD lesions was as high as 47.8% (66/138) and that the postoperative pathological upgradation rate of HGD lesions was 54.8% (23/42). These rates higher than the rates of 33.6% and 42.7% reported in a Japanese study.¹⁵ The difference may be due to the most severe lesions not being found in the biopsy site before the operation. For patients with LGD, because accurate biopsy cannot be performed in the clinical

setting and because of the high rate of postoperative upgrading, more active endoscopic diagnostic ESD may be able to improve the long-term prognosis of these patients.¹⁶ Therefore, we should actively implement endoscopic ESD treatment for patients with LGD. Some scholars in South Korea found that the overall postoperative pathological upgradation rate of patients with GIN was 33.3% and that the degradation rate was 16.7%.¹⁷ The overall rate of postoperative pathological upgradation in the present study (40.8%) was higher than that in the above-mentioned Korean study, and the rate of degradation (4.1%) was lower than that in the Korean study. This suggests that the diagnostic rate of endoscopic biopsy is higher in Japan and South Korea and that the postoperative pathological difference is smaller. For patients with postoperative pathological degradation of LGD, we ask another pathologist to review the preoperative and postoperative pathologic diagnosis to eliminate human error. The reason for postoperative pathological degradation may be that the area containing severe lesions is not large, and the most serious lesions are removed by preoperative biopsy. This suggests the need to strengthen our understanding and observation of GIN. Before endoscopic biopsy, we can use magnifying endoscopy, chromoendoscopy, and NBI for targeted biopsy and thus improve the accuracy of biopsy.

With respect to the reason for degradation, endoscopic biopsy can only show the whole lesion or the most severely affected part of the lesion. In the present study, all patients with GIN in the LGD group, HGD group, and EGC group had submucosal carcinoma, and submucosal infiltration of $>500\ \mu\text{m}$ exceeded the indication for ESD treatment. This result suggests that if ESD is selected to remove a GIN lesion, doctors must carefully evaluate the postoperative

specimens and add surgical treatment if necessary.

A previous study suggested that there are various reasons for postoperative pathological upgradation of patients with GIN, including the shape, location, size, surface color, surface erosion or ulceration, and number of biopsies.¹⁸ In the present study, the gastric antrum was the most common lesion site, accounting for 61.5% (134/218) of lesions, whereas the gastric fundus was the least common, accounting for 0.5% (1/218). In addition, type IIC was the most common lesion, accounting for 57.3% (125/218) of lesions. Acquisition of a single biopsy specimen was the most common, accounting for 83.0% (181/218) of lesion biopsies. Our results showed no significant relationships between pathological upgrading and the location, shape, color, WOS, erosion or ulceration of the lesion surface, or number of biopsies; however, there was a significant correlation between pathological upgradation and a lesion diameter of $>10\ \text{mm}$. Furthermore, an ROC curve was used to analyze the relationship between the lesion diameter and the postoperative pathological upgradation. Our cut-off point was lower than the 18-mm cut-off point at which the lesion diameter in another relevant study had a significant effect on pathological progression.^{17,19-21} However, relevant studies in Japan and China have also suggested that the difference between endoscopic biopsy and postoperative pathology is related to a lesion diameter of $>2\ \text{cm}$.²²⁻²⁴ Previous studies have also shown that a lesion diameter of $<2\ \text{cm}$ may lead to significant differences between the results of biopsies and endoscopic postoperative pathology.²⁵⁻²⁷ The sample size of the present study was limited; larger samples from multiple centers are needed to verify the factors that influence pathological upgradation of GIN.

This study has several limitations. The size and depth of the biopsies differed

among the patients. Too-small or too-shallow biopsies tend to underestimate the nature of GIN.²⁸ The goal of endoscopic biopsy is high accuracy and attainment of tissue from the most severe lesions. During the actual biopsy process, endoscopists select the best biopsy site according to the degree of irregular blood vessels and irregular surface structures under NBI and magnifying endoscopy. However, this is often subjective, and there is no unified standard for the biopsy site and depth. Therefore, the choice of biopsy site and depth is an important factor affecting postoperative pathological upgrading and degradation and is thus worthy of further study. Another limitation is that different biopsy techniques were used. Some of the biopsies were performed under white light endoscopy, and others were performed followed by acetic acid staining, indigo carmine staining, or electronic gastroscopy. Different biopsy techniques affect the subjective judgment of the most prominent part of the GIN lesion, and selection of the biopsy site will consequently differ. Several studies to date have shown that NBI combined with magnifying endoscopy has high diagnostic value for treatment of differentiated EGC.^{29,30}

In conclusion, our results suggest that when the diameter of GIN lesions exceeds 11.5 mm, we should pay attention to the possibility of pathological upgradation. Biopsy cannot fully reflect the nature of GIN. Patients should undergo biopsy re-examination or even ESD or surgery to determine the nature of the lesions.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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