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EDITORIAL

Diagnosis and therapies for gastric non-invasive neoplasia

Motohiko Kato

Motohiko Kato, Department of Gastroenterology, National Hospital Organization Tokyo Medical Center, Tokyo 152-8902, Japan

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Correspondence to: Motohiko Kato, MD, PhD, Department of Gastroenterology, National Hospital Organization Tokyo Medical Center, 2-5-1 Higashigaoka, Meguro-ku, Tokyo 152-8902, Japan. moto2hiko@icloud.com
Telephone: +81-3-34110111
Fax: +81-3-34129811

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Abstract

There has been a great discrepancy of pathological diagnosis for gastric non-invasive neoplasia/dysplasia between Japanese and western pathologists. In Japan, lesions that most western pathologists diagnose as dysplasia are often considered adenocarcinoma based on nuclear and structural atypia regardless of the presence of invasion. In the Vienna classification, gastric non-invasive intraepithelial neoplasia (NIN) were divided into low grade and high grade (including intramucosal cancer of Japanese criteria). The diagnosis by both endoscopy and pathology of biopsy specimen is difficult. Recent advances of diagnostic modality such as magnified endoscopy and imaged enhanced endoscopy is expected to improve the diagnostic yield for NIN. There are two treatment strategies for NIN, observation and diagnostic therapy by endoscopic resection (ER). ER is acceptable because of its less invasiveness and high local control rate, on the other hand, cancer-developing rate of low-grade NIN is reported to be low. Therefore there is controversy for the treatment of gastric NIN. Prospective study based on unified pathological definition is required in the future.

Key words: Gastric; Non invasive intraepithelial neoplasia; Gastric; Adenoma; Adenocarcinoma; Diagnosis

Core tip: The discrepancy of pathological diagnosis for gastric non-invasive neoplasia/dysplasia between Japanese and western pathologists was solved by Vienna classification. Although recent advances of diagnostic modality such as magnified endoscopy and imaged enhanced endoscopy is expected to improve the diagnostic yield for non-invasive intraepithelial neoplasia (NIN), precise prediction of histology is not easy by the findings of conventional white light endoscopy and pathologic findings of forceps biopsy. There is still a controversy regarding the treatment of NIN, observation and diagnostic therapy by endoscopic resection. Prospective study based on unified pathological definition is required in the future.

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INTRODUCTION

Gastric cancer is one of the most common neoplasms worldwide, accounting for over 870000 new cases and more than 650000 deaths annually[1]. Early gastric cancer (EGC), which is defined as cancer of which the invasion depth remains mucosa or submucosa is known to have a good prognosis[2] and endoscopic resection (ER) is widely accepted as a local treatment for these lesions[3-7]. There is a benign non-invasive intraepithelial neoplasia (NIN), also called as gastric adenoma or dysplasia. On the contrary to colorectal adenoma, "adenoma-carcinoma sequence" in the stomach has not been proven, NIN is generally considered to be a premalignant lesion[8-10].

The diagnosis of NIN according to both endoscopic and histopathological findings is not always easy. Moreover there are some controversies concerning how to treat NIN[11]. In this editorial, we discuss clinical problems concerning diagnosis and treating NIN.

CHANGES IN CLASSIFICATION FOR GASTRIC INTRAEPITHELIAL NEOPLASIA

Vienna classification

It is known that there is a considerable difference in pathological diagnosis of gastric epithelial neoplasia by between western and Japanese pathologists. Western pathologists have used "dysplasia" for unequivocal neoplastic epithelium. Dysplasia was divided into high- and low-grade based on structural atypia and they seldom diagnosed as "adenocarcinoma" unless invasion was confirmed[12-14]. In Japan, lesions that most western pathologists diagnose as dysplasia are often considered adenocarcinoma based on nuclear and structural atypia regardless of the presence of invasion (Table 1).

To resolve some confusions caused by these diagnostic discrepancies between western and Japanese pathologists, in September 1998 approximately 30 pathologists from 12 countries met in Vienna and made a consensus on the terminology for gastrointestinal epithelial neoplasia, named the Vienna classification[11]. In this classification, gastric non-invasive neoplasia/dysplasia was divided into low grade (category 3) and high-grade (category 4). Category 4 includes high-grade adenoma/dysplasia", "non-invasive carcinoma (carcinoma *in situ*)" and "suspected invasive carcinoma" were clustered into a single category (category 4), termed "noninvasive high-grade neoplasia". In the Vienna classification revised in 2000[15], intra-mucosal carcinoma was added into category 4. The agreement on the diagnosis for category 4 among Japanese and western pathologists improved to 80% for gastric lesions[16].

Table 1 Vienna classification and Japanese classification of gastric cancer for diagnosis of gastric intraepithelial neoplasia

Vienna classification		Japanese	Western
Category 3	Low grade adenoma/ dysplasia (LGA)	Adenoma	Adenoma
Category 4.1	High grade adenoma/ dysplasia (HGA)	Adenoma/ cancer	Adenoma
Category 4.2	Non-invasive carcinoma (carcinoma *in situ*)	Cancer	Adenoma/cancer
Category 4.3	Suspicion of invasive carcinoma	Cancer	Adenoma/cancer
Category 5.1	Intramucosal carcinoma	Cancer	Adenoma/cancer
Category 5.2	Submucosal carcinoma or beyond	Cancer	Cancer

Difficulties of pathological diagnosis of specimen obtained by endoscopic forceps biopsy

Although pathological diagnosis established by endoscopic biopsy specimen is the gold standard for gastric epithelial neoplasia, discrepancy between final diagnoses established by endoscopically or surgically resected specimen would sometimes occur. The frequency of the discrepant diagnoses ranges widely in published reports. Recently we report that the diagnosis was changed in 44% of patients who were diagnosed as NIN proven by biopsy (95%CI: 39%-49%). Moreover, in that study, there were 2 lesions (0.42%) of adenocarcinoma with submucosal invasion of more than 500 μm, one of which involved the lymphatic duct[17]. The reasons for the difficulty in making an accurate diagnosis based on a biopsy specimen are as follows: (1) the structural atypia of both adenoma and well-differentiated adenocarcinoma is too subtle to detect in small biopsy specimens; and (2) cancer sometimes exists focally in the lesion and a sampling error might occur (Figure 1). Thus, pathologist might change the diagnosis from adenoma to carcinoma when they determine larger specimen.

ENDOSCOPIC DIAGNOSIS OF GASTRIC INTRAEPITHELIAL NEOPLASIA

Conventional white light endoscopy

Endoscopy has an advantage on the diagnosis of NIN because it is possible to assess the lesion as a whole. Some endoscopic findings have been reported to predict high-risk lesions for malignancy, lesion size, macroscopic type, color of the lesion, and surface pattern (Figure 2). Typical gastric low grade NIN reveals to have slightly elevated (Paris classification type 0-Ⅱa[18]) and whitish color with smooth surface. On the contrary, depressed macroscopic type, redness, and nodular surface are reported to reflect malignant histology. These endoscopic findings are

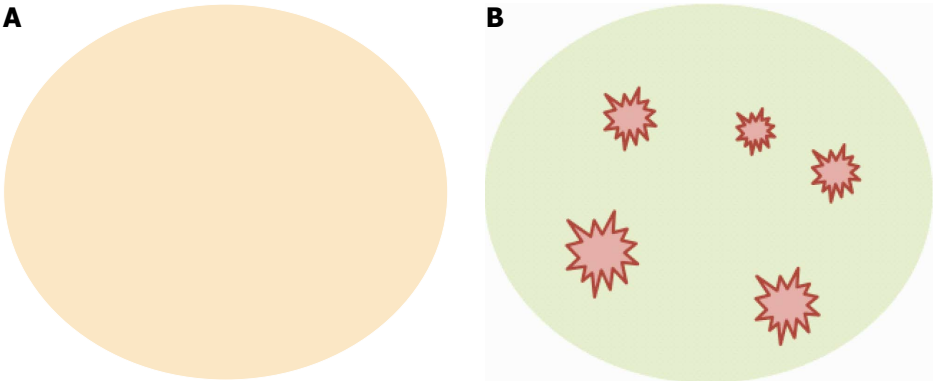

Figure 1 Pathological features of non-invasive neoplasia. A: If the structural atypia was weak, pathological diagnosis is difficult by small specimen obtained by endoscopic forceps biopsy; B: If cancer foci exist focally, sampling error may occur by endoscopic forceps biopsy.

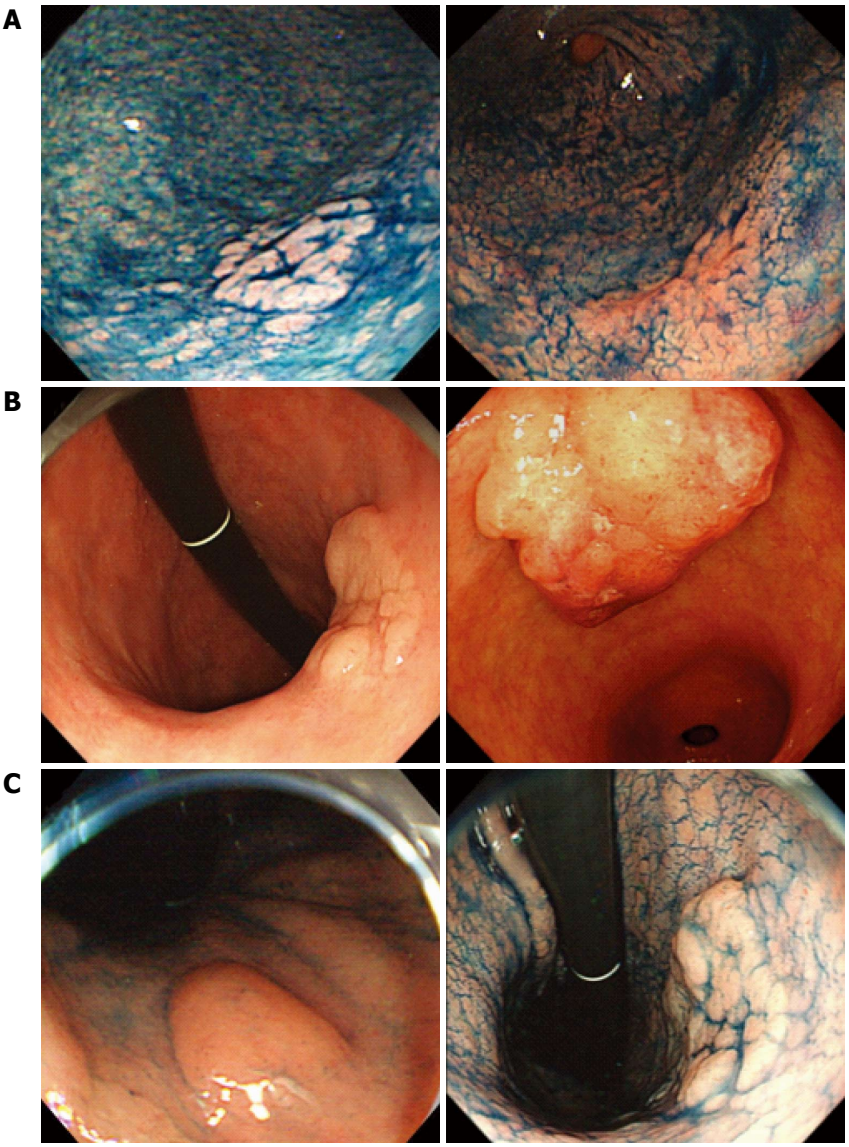

Figure 2 Endoscopic findings of non-invasive neoplasia. A: Macroscopic type:elevated (left), and depressed (right); B: Color:reddish (left), and discolored (right); C: Surface pattern: smooth (left) and nodular (right). List of abbreviations: ER: Endoscopic resection; QOL: Quality of life; EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

Table 2 Diagnosis yields for gastric non-invasive intraepithelial neoplasia of various endoscopic modality

Ref.	Modality	Sensitivity	Specificity	Accuracy
Cho *et al*[21], 2011	WLE	7.5%	99.4%	68.2%
Kato *et al*[17], 2011	WLE	42.0%	59.0%	56.0%
Kanesaka *et al*[28], 2014	NBI-ME	90.0%	87.8%	88.2%
Miwa *et al*[22], 2012	NBI-ME	82.4%	97.3%	NA
Yao *et al*[27], 2008	NBI-ME	94.0%	96.0%	98.7%
Wang *et al*[29], 2012	CLE	66.7%	92.3%	86.8%
Li *et al*[30], 2011	CLE	88.1%	98.6%	96.2%

WLE: White light endoscopy; CLE: Confocal laser endomicroscopy.

Table 3 Long-term follow-up outcomes of gastric non-invasive intraepithelial neoplasia

Ref.	Incrusion criteria	Duration	Regression	Accuracy
Suzuki *et al*[31], 2015	Vienna C3 and C4	NA	26.0%	0.0%
Yamada *et al*[32], 2004	Vienna C3	4.7Y	0.0%	2.7%
	Vienna C4	4.7Y	0.0%	10.0%
Saito *et al*[33], 2000	Adenoma	2Y	NA	6.3%
Kokkola *et al*[34], 1996	Mild dysplasia	NA	NA	0.0% (4% to moderate)
Bearzi *et al*[35], 1994	LGD	NA	49.4%	32.1%
Fertitta *et al*[36], 1993	Moderate and severe dysplasia	13M	NA	33.0%
Di Gregorio *et al*[37], 1993	Mild dysplasia	NA	74.0%	7.0%
Saraga *et al*[38], 1987	Mild and moderate dysplasia	42M	NA	1.6%
	Severe dysplasia	42M	NA	86.0%

NA: Not available.

useful because of convenience, however they are not satisfactory because the negative predictive value is not so high. We analysed the association between endoscopic findings[19-22] and final pathological findings in 468 NIN cases and lesion diameter larger than 20 mm and depressed macroscopic type were significantly more frequently seen cases who were diagnosed as adenocarcinoma after ER. However, the lesions were diagnosed as NIN based on smaller lesion size and elevated macroscopic type, the under-diagnosis rate was over 30%[17]. Therefore only conventional endoscopic diagnosis is not sufficient to make a precise pre- operative diagnosis.

Magnified endoscopy

Magnified endoscopy is reported to be useful for differentiation of gastric NIN. Tanaka analysed the diagnostic yield of magnified endoscopy with acetic acid spraying and they reported the diagnostic accuracy was over 95%. Moreover, Ohnita *et al*[23] reported the findings of magnified endoscopy with crystal violet dye correlates with the histological types of gastric epithelial neoplasia.

Recently novel diagnostic modalities, image enhanced endoscopy (IEE), are widely used. Narrow band imaging is a kind of IEE of which the usefulness have been reported for differential diagnosis or estimation of invasion depth for epithelial neoplasia arising from gastrointestinal tract[24-26]. Yao *et al*[27] reported that finding a white opaque substance on magnified endoscope with NBI could predict the final pathology of gastric NIN with a sensitivity of 94% and a specificity of 96%. Kanesaka *et al*[28] focused on crypt opening on magnified endoscopy with NBI and dense crypt opening pattern could predict malignant histology with a sensitivity of 90% and specificity of 87.8%.

Although the diagnostic yields of magnified endoscopy especially combined with IEE were excellent and seemed to be superior to conventional white light imaging (Table 2), most of the reports are single-centered retrospective study from high volume center, therefore expert bias is not negligible and the results should be confirmed by future prospective study (ideally randomized trial) to generalize the results.

Other modalities

There are a few reports concerning the diagnostic capability of confocal laser endomicroscopy (CLE) for identification of gastric superficial cancer/HGIN lesions[29,30]. Although these studies included only relatively small sample size of gastric NIN, the diagnostic yield of CLE is good and it might improve preoperative diagnosis (Table 2).

TREETMENT FOR GASTRIC NIN

There are two treatment strategies for gastric NIN, observation and aggressive endoscopic treatment as a diagnostic therapy.

Observation (including Helicobacter pylori eradication)

According to the studies focused on the long-term follow up outcomes for gastric NIN, the incidence of progression of histology widely ranged 0% to 86%[31-38] (Table 3). Histological grade is considered to caused this difference, in low grade NIN (Vienna category 3) the incidence rate of histological progression to high grade NIN or carcinoma remained less than 10%[31,32], moreover, some cases spontaneously regress during follow-up[31,35,37]. It is also reported that eradication therapy of *Helicobacter pylori* might reduce gastric cancer development[33] or it might accomplish regression of NIN from comparatively small studies[31,39]. These facts suggest that the malignant potential of low grade NIN is low and observation would be acceptable, whereas high grade NIN should be resected.

Endoscopic resection

The other strategy is diagnostic therapy. As mentioned

above, it is difficult to make an accurate pathological diagnosis with small biopsy specimens, ER might be used for the purpose of "total biopsy". It is reported that pathological diagnosis changes in 10% to 50% of the patients after ER[17,40-42]. ER is a less invasive treatment, however, complications such as perforation or bleeding sometimes occurs. In our comparatively large-scale retrospective study in which 468 NIN cases underwent ESD, R0 resection was accomplished in 97% of the patients and ESD-related bleeding and perforation rate was 5.4% and 4.7%. Most of the complications were managed conservatively and serious complication rate was 0.43%. These outcomes seem to be acceptable considering the high under-diagnosis rate of forceps biopsy[17]. The advantage of ER is to release the patients from physiological, psychological, and financial strains caused by repeated endoscopic examination with biopsies.

CONCLUSION

The discrepancy of pathological diagnosis for gastric non-invasive neoplasia/dysplasia between Japanese and western pathologists was solved by Vienna classification. Although recent advances of diagnostic modality such as magnified endoscopy and imaged enhanced endoscopy is expected to improve the diagnostic yield for NIN, precise prediction of histology is not easy by the findings of conventional white light endoscopy and pathologic findings of forceps biopsy. There is still a controversy regarding the treatment of NIN, observation and diagnostic therapy by ER. Prospective study based on unified pathological definition is required in the future.

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