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ORIGINAL ARTICLE

Clinical study of autofluorescence imaging combined with narrow band imaging in diagnosing early gastric cancer and precancerous lesions

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Summary

Purpose: *To evaluate the diagnostic values of autofluorescence imaging (AFI) combined with narrow band imaging (NBI) in diagnosing early gastric cancer and precancerous lesions.*

Methods: *140 patients were investigated for lesions such as gastric mucosal roughness, erosion, plaque, abnormal color, bump or pitting by conventional endoscopy. AFI endoscope was used for the observation, and the endoscopic diagnosis was performed according to the fluorescence forms under the endoscopic AFI mode, as well as the changes of gastric mucosal capillaries and gastric pits under the NBI mode. The corresponding lesions were also biopsied for pathological examination.*

Results: *78 patients were diagnosed as gastritis (including superficial and atrophic gastritis), 45 as intestinal metaplasia, 6 as dysplasia, and 11 as early gastric cancer. The sensitivity and specificity of AFI-NBI combination were 88.89 and 91.58% in the diagnosis of intestinal metaplasia; 83.33 and 98.51% for dysplasia; and 90.91 and 99.22% for early gastric cancer. All of them were significantly higher than the simple fluorescence endoscopy.*

Conclusions: *The AFI-NBI combination could improve the detection rate of early gastric cancer and precancerous lesions.*

Key words: *autofluorescence imaging, diagnosis, early gastric cancer, narrow-band imaging, precancerous lesions*

Introduction

Conventional electronic endoscopy mainly relies on the naked eyes to perform observations under white light, which can only find lesions with significant changes of shape or color (e.g. protruded lumps, depressed ulcers, etc.), while it is difficult to diagnose tiny and flat early cancerization and dysplasia or even to lead to misdiagnosis. Many authors have reported that AFI could help distinguish the normal gastrointestinal mucosa from abdormal tissues, thus improving the detection rate of dysplasia and early cancer [1-4], while the combination of NBI and magnifying endoscopy could make morphological observation of the gastrointestinal mucosal microvessels and gastric pits much more clear and intuitive [5-9].

In this study, the diagnostic value of AFI-NBI combination for early gastric cancer diagnosis and precancerous lesions was investigated, and the results are reported below.

Methods

Patients

From outpatients and inpatients, admitted at the Department of Digestion, Shanghai Pudong Hospital

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Table 1. The relationship between endoscopic and histological diagnosis

Group	*AFI* *N (%)*	*AFI+NBI* *N (%)*	*Biopsy* *N (%)*
Gastritis	82 (58.57)	72 (51.43)	78 (55.71)
Intestinal metaplasia	41 (29.29)	48 (34.29)	45 (32.14)
Dysplasia	8 (5.71)	8 (5.71)	6 (4.28)
Early gastric cancer	9 (6.43)	11 (7.86)	11 (7.86)

and Affiliated Xinhua Hospital of Shanghai Jiaotong University, from February 2012 to October 2013, 140 cases with gastric mucosal roughness, erosion, plaque, abnormal color, bump or pitting under conventional endoscopy were further investigated with AFI-NBI observation (Olympus GIF FQ260Z, Olympus EVIS LUCERA CV-260SL and CLV-260SL, Olympus Medical Corporation, Tokyo, Japan). Sixty-two of the patients were male and 78 female, aged 29 to 81 years, with an average age of 41.42 years. This study was conducted in accordance with the declaration of Helsinki and after approval from the Ethics Committee of Shanghai Jiaotong University. Written informed consent was obtained from all participants.

Specific operations

After the patient was positioned under the scope, the conventional white light imaging (WLI) was firstly performed for observation. The suspicious lesions found were then rinsed with saline and subsequently AFI followed. The color changes of suspicious lesions were observed and the plane depth was adjusted to make the endoscopic observation clear. The AFI images were then acquired and preserved for the AFI diagnosis. Then, NBI and zooming were performed to observe the shapes and structures of focal gastric mucosal microvessels and pits to make a diagnosis. All the examined mucosal sites were biopsied and the biopsied tissues were formalin-fixed, paraffin-embedded, cut in 4 μm-thick sections and stained with hematoxylin/eosin (H&E) for pathological examination.

Classification of gastric pits shapes

According to the classification criteria of Sunjin et al. the gastric pits were divided into the following 6 basic types: A type: dot-like; B type: short rod-like: the pits are deep, might have branches and bending, although significantly less than C type; C type: the pits are prolonged, tortuous, with significantly increased bending and branches, which might be connected to each other and dendritic; D type: plaque-like, grid-like, with cobblestone-like changes; E type: the pits appear villous-like and finger-like protrusions, with intestinal villi-like changes; F type: disordered or no structure [10].

Classification of mucosal microvascular changes

According to Nakayoshi et al. classification method, the changes of mucosal capillaries were divided into 4 types: type I: no mucosal capillary; type II: starfish-like; type III: fine mesh or spiral-like; type IV: irregular or coarse newborn vessels [11].

Statistics

Statistical analyses were performed using SPSS 11.0 software. Data were usually described as arithemtic means with standard deviation (SD). Statistically significant differences were determined using x^2 test and Student's t-test. $P<0.05$ was considered as statistically significant.

Results

Pathological diagnosis

Pathologically, there were 11 (7.86%) cases with early gastric cancer (6 males and 5 females, aged 48 to 74 years, mean 60), 45 (32.14%) cases with intestinal metaplasia, 6 (4.29%) cases with dysplasia and 78 (55.71) cases with gastritis (Table 1).

AFI-NBI sensitivity, specificity, positive and negative predictive values

The diagnostic sensitivity and specificity were 88.89 and 91.58% for intestinal metaplasia, with the Youden index (it evaluates the authenticity of a screening test) being 0.80 (>AFI 0.62); 83.33 and 98.51% for dysplasia, with the Youden index 0.82 (>AFI 0.64); 90.91 and 99.22% for early gastric cancer, with the Youden index 0.90 (>AFI 0.62), which were all significantly higher than the simple fluorescence endoscopy ($p<0.05$). The positive predictive value of AFI-NBI in the diagnosis of early gastric cancer was 90.91%, with negative predictive value 99.22%. The missed diagnosis rate was 9.1% and the misdiagnosis rate 0.78% (Table 2).

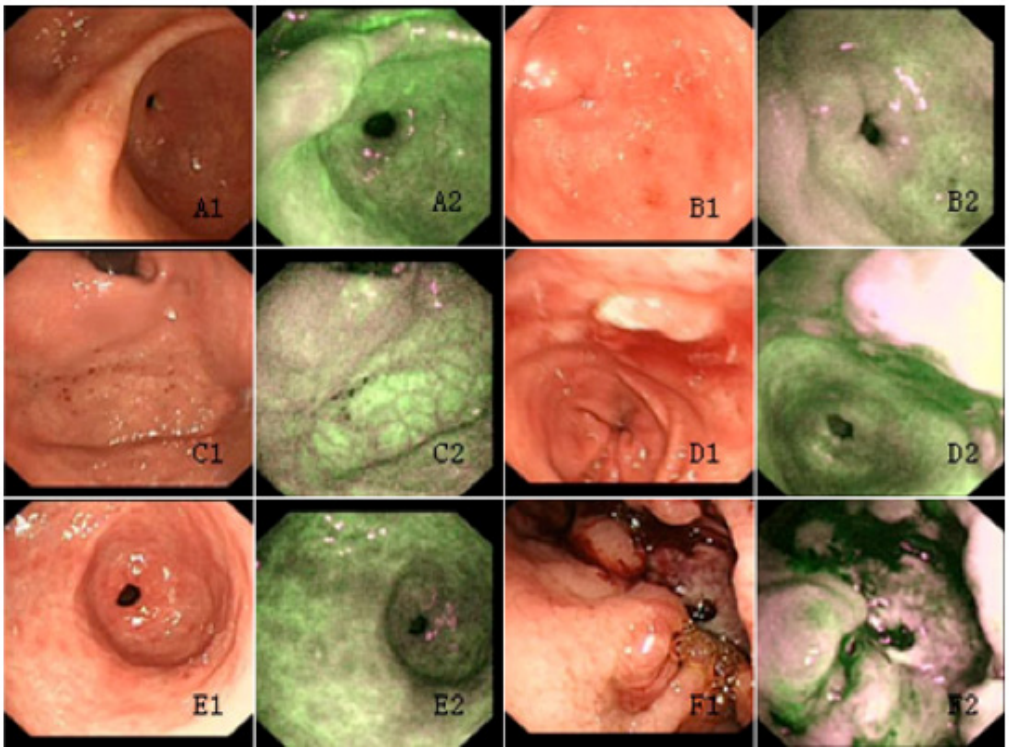

Figure 1. Endoscopic images with WLI (**1**) and AFI (2) mode. **A**: benign ulcer, **B** and **C**: inflammation, **D** and **F**: malignant lesions, **E**: normal mucosa.
For abbreviations see text

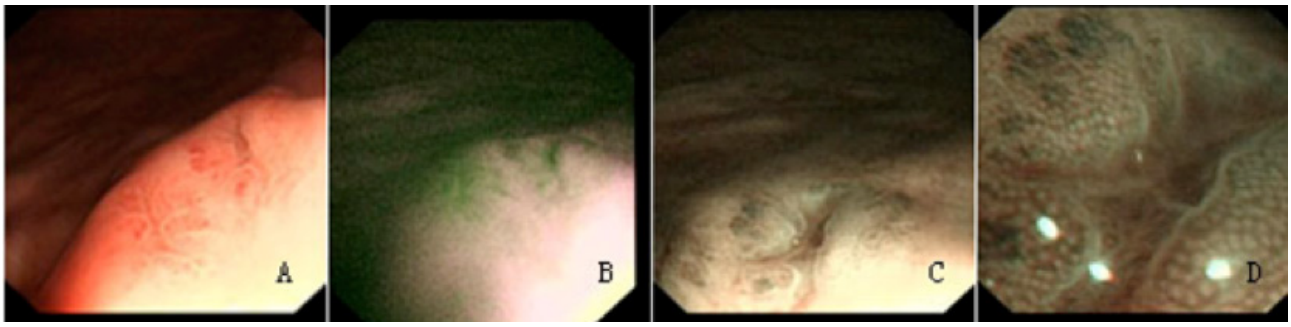

Figure 2. Endoscopic images of flat lesions. **A**: The lesions are rough with erosion under WLI; the image could not differentiate between benign or malignant lesions. **B**: AFI shows abnormal changes in red and indicates existence of suspicious lesions. **C**: under NBI mode the lesions are clearly outlined. **D**: ME-NBI mode reveals clearly the structures of the surrounding gastric pits and mucosal microvessels, suggesting the lesions are benign.
For abbreviations see text

AFI endoscopy

Under the AFI mode, the normal gastric mucosa showed green fluorescence, while erosion, inflammation and benign ulcer was light purple, bleeding dots were dark red, malignant lesions were dark red or deep red, the white fur that covered an ulcer surface was still white, with clear distinction from the surrounding normal mucosa. The adherent mucus and bile appeared as pink change in the AFI mode, and the mucosal blood vessels also exhibited the vascular network structure with clear boundaries in the AFI mode (Figure 1).

AFI-NBI combination diagnosis

The combination of AFI-NBI could much more clearly diagnose the flat lesions, which simply appeared as anabrotic and rough surfaces under the

Table 2. The accuracy assessment of AFI combined NBI for the diagnosis of precancerous lesions and early gastric cancer

Group	*Sensitivity (%)*		*Specificity (%)*		*Youden index*	
	AFI	*AFI+MBI*	*AFI*	*AFI+NBI*	*AFI*	*AFI+NBI*
Intestinal metaplasia	71.11	88.89	90.53	91.58	0.62	0.80
Dysplasia	66.67	83.33	97.01	98.51	0.64	0.82
Early gastric cancer	63.64	90.91	98.45	99.22	0.62	0.90

white light, and would easily be misdiagnosed, owing to the difficulty of determining whether they were benign or malignant. In the AFI mode, the lesions showed abnormal red changes, improving thus the detection rate for biopsy. In the NBI mode, the lesion outlines were clearly visible, with depression on the surface, showing no gastric pits when amplified; the microvascular structure was disordered, while the structures of surrounding gastric pits and mucosal microvessels were clear, allowing to consider them as benign, a fact confirmed by pathology. Therefore, AFI-NBI combination could improve the detection rate of flat lesions and the diagnostic accuracy (benign or malignant) (Figure 2).

AFI-NBI combination could also help the diagnosis in intestinal metaplasia and dysplasia (Figure 3A-1); the WLI observation showed the formations of mucosal bulges, erosion and ulceration, while the boundaries of mucosal lesions and normal tissue were unclear. The AFI mode revealed that the mucosal lesions were red, with clear boundaries with the normal mucosa while magnifying endoscopy combined with NBI (ME-NBI) mode revealed that the shapes of gastric pits were disordered and the normal pit structures disappeared. The biopsy of the corresponding lesion showed dysplastic appearance, like formation of irregular small glands, and partially fused glands. Figure 3B1-3 shows the corresponding endoscopic images under WLI, AFI and NBI. The AFI mode shows that the mucosal lesions were red, with clear boundaries with the normal mucosa. The ME-NBI mode revealed that the villi of gastric pits exhibited finger-like projections, and the biopsy indicated intestinal metaplasia-like changes. Therefore, the AFI-NBI combination could enhance the contrast between mucosal lesions and normal mucosa, leading to successful biopsy, and improving the detection rate of intestinal metaplasia and dysplasia (Figure 3B1-3).

Relationship of gastric pits basic forms and histology

The 45 cases with intestinal metaplasia mainly appeared as C, D and E type under the endoscope, among which 62.2% was of the E-type; the 6 cases of dysplasia showed mild depression, bumps or flat lesions, associated with the disordered or disappeared gastric pits structure. The important feature of early gastric cancer was the pleomorphism of gastric pits, mainly as F type, and the shapes of small pits were various, irregular and dendritic (Table 3).

Relationship of gastric microvascular morphology and histology

Forty-five cases with intestinal metaplasia showed type I (91%) and type II (9%) microvascular morphology, while dysplasia was more frequently seen as type III in 66.7% of the cases (4/6 cases). Early gastric cancer showed irregular or thickened tumor vasculature (Table 4).

Discussion

This study used the electronic endoscope, which can smoothly switch to the three modes of detection simply through a button on the handle, namely WLI, AFI and ME-NBI. The AFI system uses the blue light (395-475 nm wavelength), as well as the green and red light (540-560 nm and 600-620 nm wavelength, respectively) as the excitation source, and a filter, which allows the light to pass only at a wavelength range of 400-625 nm, and which was installed in front of the charged-coupled device (CCD) fluorescence endoscope, thus cutting and blocking the blue light. The CCD collects the generated autofluorescence, reflects the green and red light to construct the fluorescence images. The NBI imaging system uses the narrow band interference blue/green filter, which produces the 30 nm narrow band blue-green light, with the center wavelength as 415

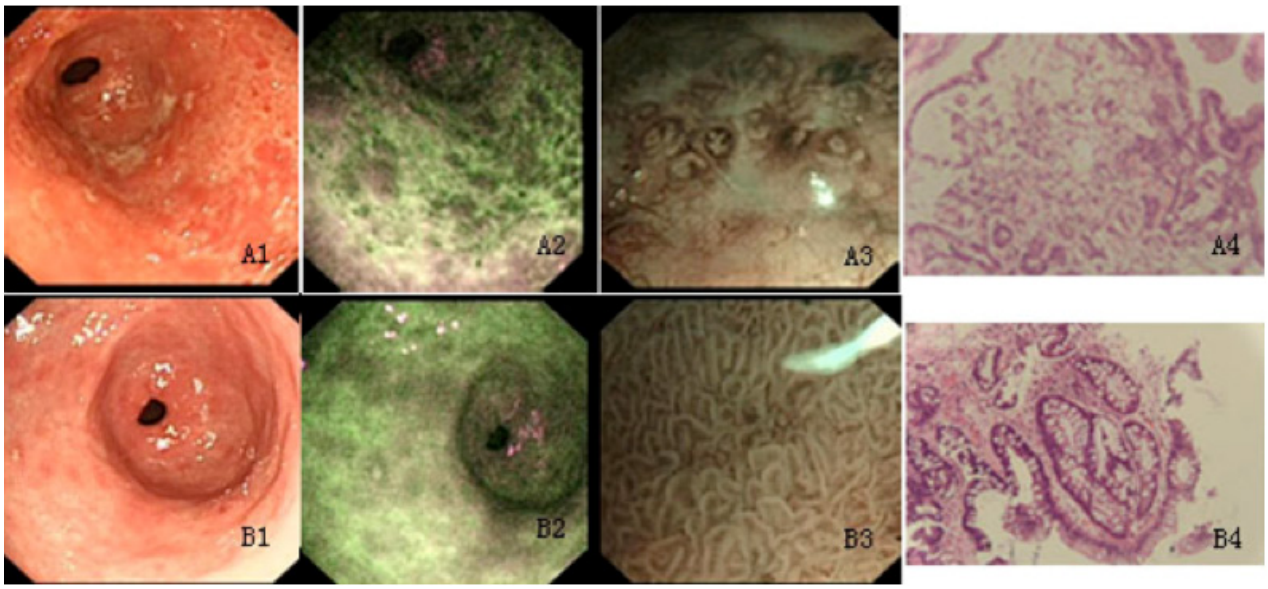

Figure 3. Endoscopic images under 1: WLI; 2: AFI; 3: ME-NBI. 4: Pathology (H&E stainning ×40). **A1** image under WLI mode shows no clear boundary between the lesions and normal mucosa. **A2** shows clear boundary between the lesions and normal mucosa under AFI mode. **A3** shows gastric pits of lesions are disordered using ME-NBI mode. **A4** shows that pathology revealed abnormal changes of the glands.
B1 shows unclear image, unable to discriminate between benign and malignant lesions under WLI mode. **B2** shows that the lesions have a clear demarcation from the normal mucosa under AFI mode. **B3** reveals that the patterns of gastric pits changed significantly under ME-NBI mode. **B4** shows that pathology indicated intestinal metaplasia.
For abbreviations see text

Table 3. The accuracy assessment of AFI combined NBI for the diagnosis of precancerous lesions and early gastric cancer

Group	*Cases*	*A*	*B*	*C*	*D*	*E*	*F*
Gastritis	78	49	28	1	0	0	0
Intestinal metaplasia	45	0	0	2	17	28	0
Dysplasia	6	0	0	0	0	0	6
Early gastric cancer	11	0	0	0	0	1	10

For A-F see text

Table 4. The relationship between the capillary epithelium pattern and pathology

Group	*Cases*	*I*	*II*	*III*	*IV*
Gastritis	78	75	3	0	0
Intestinal metaplasia	45	41	4	0	0
Dysplasia	6	0	1	4	1
Early gastric cancer	11	0	0	7	4

For I-IV see text

and 540 nm as the light source for the lighting, and is supported with a magnifying endoscope for the diagnosis.

When WLI reveals that the mucosal lesions have roughness, erosion, plaques, abnormal color, slight ample or depression, the AFI mode should be performed for the observation. When the excitated light shines the submucosa, the generated strong fluorescence reduces and weakens when it meets the abnormal lesions (e.g. abnormal aggregation or mucosal thickening of superficial vessels), so these subtle changes are converted into color information, and make the subtle differences between normal mucosa and lesions distinguishable.

After recording the results of fluorescence endoscopy, the ME-NBI mode is switched for observation, and this mode can significantly improve the contrast of mucosal capillaries and microvessels, and mainly focuses on the microglandular

and fine capillary morphologies on the gastrointestinal mucosal surface, thus it can guide the biopsy much more precisely, and compare the results of endoscopy and tissue pathologic diagnosis.

The study found that AFI-NBI combination achieved sensitivity 88.89% and specificity 91.58% in diagnosing intestinal metaplasia, with the Youden index as 0.80 (>AFI 0.62); for dysplasia the corresponding figures were 83.33% and 98.51%, with the Youden index as 0.82 (>AFI 0.64); and for early gastric cancer 90.91% and 99.22%, with the Youden index as 0.90 (>AFI 0.62), which were all significantly higher than the simple fluorescence endoscopy. The positive predictive value of AFI-NBI combination was 90.91% for early gastric cancer, the negative predictive value was 99.22%, the missed diagnosis rate was 9.1%, and the misdiagnosis rate was 0.78%. The consistency coefficient kappa of AFI-NBI with the final pathological results was 0.928, indicating that these two had good consistency. The results showed that AFI-NBI combination was more accurate to guide the biopsy, and could find some lesions that would be hard to find under the ordinary endoscope, thus it could help improve the detection rate of early gastric cancer and precancerous lesions. These conclusions were similar to the Kato et al. study [12]. There are also other reports indicating that the combined AFI-NBI can also help improve the diagnostic accuracy of early cancerization of Barrett's esophagus [13-16].

The diagnostic value of AFI-NBI combination in precancerous lesions and early gastric cancer is higher compared to the simple fluorescence endoscopy, because the current fluorescence endoscopes still lack sensitivity for the autofluorescence generated by the tissues, and the image quality still needs to be improved. Furthermore, the simple fluorescence endoscopy is often affected by some confounding factors. The study found that, under the AFI mode, the normal mucosa was green, while the inflammation, erosion, depression and ulcers were purple or dark red. Of note, during the research, some parts were found as suspicious red lesions, which exhibited no obvious changes of gastric pits and microvessels under the NBI mode, and this might be related to: 1) necrotic tissues, mucus and bile attached to the stomach, thus interfering with the autofluorescence information; and 2) possible shaded areas caused by geometric factors when constructing the autofluorescence images. These shaded areas might be likely to be misdiagnosed as abnormal mucosa. Several studies which reported that because of the difference between the molecular structures of normal and tumor tissues, their characteristics of fluorescence spectrum were easy to be distinguished, so the combination of fluorescence endoscopy and fluorescence spectroscopy could significantly improve the diagnostic reliability and sensitivity of fluorescence endoscopy [17-20]. The autofluorescence characteristics represent the biochemical structure of the tissues, and the changes of tissues' biochemical structure were the main cause of the changes of the autofluorescence features. The characteristics of emission spectrum of tumor tissues and normal tissues could thus be detected to distinguish the cancerous tissues.

This study found that the AFI-NBI combination could identify the gastric mucosal abnormalities or lesions, thus improving the diagnostic reliability and sensitivity. Through observing the morphological changes of gastric pits and microvessels, ME-NBI could real-timely distinguish the neoplastic and non-neoplastic lesions during the examination process. The capillaries of normal mucosal surface that surrounded the gastric neoplastic lesions extended and ended at the edge of the lesions, so the boundary between the neoplastic lesions and the surrounding normal mucosa were much more clear. Meanwhile, the density of blood vessels within the neoplastic lesions was high, while the structure of the neoplastic lesions was disordered, so that under the narrow wave, the lesions' color was much darker, and much more prominent in the view field, and the contour of lesions was much more clear.

AFI-NBI could diagnose the flat lesions much more clearly under the white light; the relatively flat lesions exhibited only the surface erosion and roughness, which would be easily misdiagnosed, and it was also difficult to determine the benign or malignant nature of the lesions. AFI could make the contour of focus displaying much more clearly, thus improving the detection rate of biopsy. And under the ME-NBI mode, the analysis of morphological changes of gastric pits and microvessels could accurately determine the benign or malignant nature of the lesions.

AFI-NBI was considerably accurate in diagnosing intestinal metaplasia and dysplasia. This study found that the intestinalized lesions appeared as the villous finger-like projections of gastric pits under the ME-NBI mode, consistent with the pathological results of biopsy. Dysplasia appeared as mild depressions, bumps or flat lesions, accompanied with structural disorder of gastric pits or disappearance consistent with the

final pathological results, and suggesting that AFI-NBI is of important value in the diagnosis of precancerous lesions.

High-grade dysplasia and early cancerized lesions might appear as irregular changes of superficial capillaries. In this study, gastritis more frequently showed type I microvascular changes in ME-NBI; type II microvascular changes only occurred in the normal gastric mucosa or benign lesions; mucosal microvascular morphology of patients with early gastric cancer met the type III or IV changes, and 66.7% of the patients with dysplasia exhibited type III mucosal microvascular morphology. Besides the irregular changes of superficial capillaries, high-grade dysplasia and early cancerized lesions exhibited changes of gastric pits' appearance. Gastric pits, as gland openings, are the basic units of the gastric mucosal surface. When gastric mucosal lesions occur, it is the gastric pits that would first exhibit the morphological changes. One study has assessed this classification and clinicopathological significance [21]. Currently, according to the classification criteria of Sunjin et al. the gastric pits are divided into 6 basic types [10]. This study found that gastric atrophy mainly appeared as coarse and sparse gastric pits. In intestinal metaplasia the gastric pits appeared as C, D and E shapes. Dysplasia appeared as mild depressions, bumps or flat lesions, accompanied with disappeared fine structure, rough and disordered tiny pits or fine structures. The important feature of early gastric cancer was the pleomorphism of gastric pits, exhibiting smaller and irregular pits and dendritic shapes.

In summary, the advantages of AFI-NBI-guided biopsy were: 1) it could reduce the numbers of biopsies; 2) the objectivity was good, and not restricted by the doctor's experience; 3) the sensitivity and specificity in severe dysplasia and carcinoma in situ were high, thus significantly increasing the positive rate of biopsy. Considerable relevant information was obtained from this small-sample study, but the reliability and clinical value of this technology still needs further large-scale randomized controlled trials for accurate validation.

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