Magnifying endoscopy for diagnosing and delineating early gastric cancer

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Bibliography
DOI 10.1055/s-0029-1214594
Published ahead of print
Endoscopy 2009; 41:
462–467 © Georg Thieme
Verlag KG Stuttgart · New York
ISSN 0013-726X

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We describe the basic principles and clinical usefulness of modern magnifying endoscopy techniques, using white-light imaging or narrow-band imaging, for precise diagnosis of small flat gastric cancers. Regarding technology, first, the resolution provided by the endoscope is important in order to consistently visualize the precise morphology of microvascular architecture, and second, the use of a distal attachment (soft hood or cap) is essential in order to maintain a constant distance between the tip of the scope and the mucosal surface. Regarding methodology, a systematic but simple classification system based on microvascular pattern and microsurface pattern (the "VS classification") is proposed. The technique based on the principles described here can be applied not only in routine endoscopic examination but also in the detailed preoperative assessment of the lateral extent of early gastric cancer, before endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD).

Objectives

In the past, magnifying endoscopy in the stomach was considered difficult. The wide lumen of the stomach makes it difficult to obtain a very close view; movement due to peristalsis, aortic pulsation, and respiration, disturbs focusing; and gastric mucus often impairs magnifying observation. More importantly, the optical resolution of endoscopes was insufficient for clear visualization of the mucosal surface and blood vessels, and the principles and guidelines for understanding magnified endoscopic findings had not been established [1]. In recent years, however, progress in magnifying endoscopy has enabled the endoscopist to visualize both the microvascular architecture and the microsurface structure within superficial gastric lesions without the use of contrast material [1]. Herein we describe the clinical application of magnifying endoscopy to the detection and delineation of early gastric cancer.

Basic principles: technological features

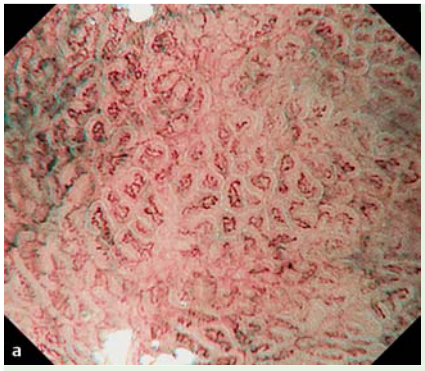
Resolving power of magnifying endoscopes

For the analysis of gastric microvascular architecture it is necessary to visualize the morphology of the mucosal capillaries. Since the minimal diameter of the gastric mucosal capillaries is reported to be 8 micrometers [2], the resolution provided by the scope needs to be at least 8 micrometers. The maximal resolutions of the optically magnifying GIF-Q240Z and GIF-H260Z instruments (Olympus Co., Tokyo, Japan) are 7.9 micrometers [3] and 5.6 micrometers [unpublished data], and that of the EG-590ZW (Fujinon Corp, Saitama, Japan) is 6.2 micrometers [4]. Therefore, these endoscopes have enough resolving power to clearly visualize the gastric mucosal capillaries.

Techniques for enhancing vascular imaging

Several enhancement techniques are available for clear visualization of both the microvascular architecture and the microsurface structure. The adaptive hemoglobin index color enhancement technique has been reported in a previous article [5], and will not be discussed in this paper.

Narrow-band imaging (NBI) is an optical technique that uses blue and green light, each delivered using a relatively narrow bandwidth, for illumination. This gives better visualization of blood vessels, due to the high absorption of blue and green light by hemoglobin. In addition, it also provides better visualization of more superficial mucosal structures due to the shorter penetration depth and better optical features of the short-wavelength light delivered within the narrow bandwidth [6,7].



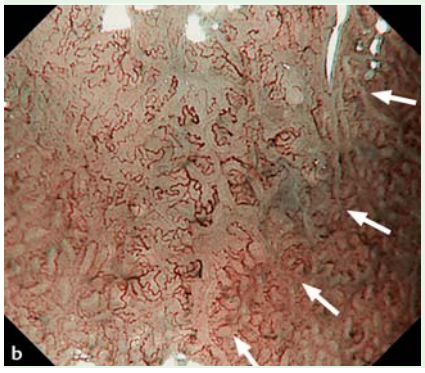
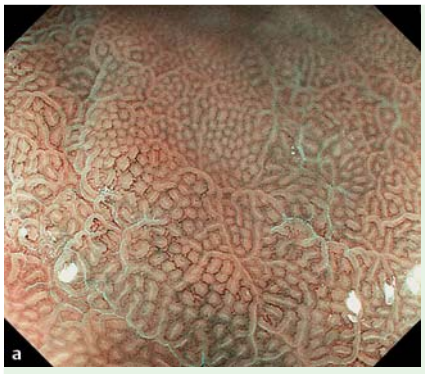


Fig. 1 Magnifying endoscopy with narrow-band imaging (NBI): an early gastric cancer (diameter 18mm), superficial flat (0-IIb), differentiated (intestinal) type within the distal part of the gastric body. **a** Background noncarcinomatous mucosa: regular microvascular pattern (open-loop) plus regular microsurface pattern (tubular). **b** Carcinomatous mucosa: irregular microvascular pattern (closed-loop/open-loop/tortuous/branched/bizarre) plus absent microsurface pattern, with a demarcation line (arrows) between cancerous and noncancerous mucosa.



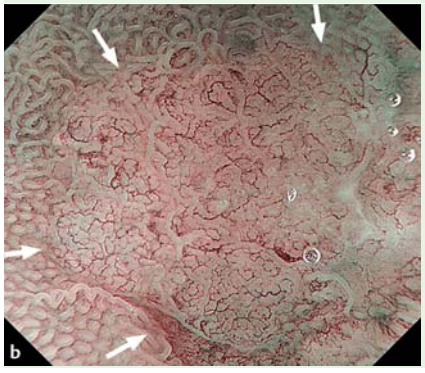
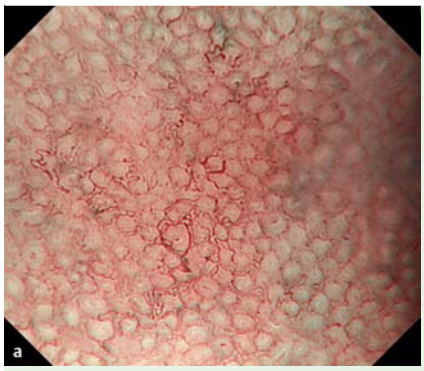


Fig. 2 Magnifying endoscopy with NBI: an early gastric cancer (diameter 3mm), superficial flat (0-IIb) type, differentiated (intestinal) type within the gastric cardia. **a** Background noncarcinomatous mucosa surrounding carcinoma: regular microvascular pattern (closed-loop) plus regular microsurface pattern (tubular). **b** Carcinomatous mucosa: irregular microvascular pattern (open-loop/closed-loop) plus irregular microsurface pattern (curved), with a demarcation line (arrows) between cancerous and noncancerous mucosa.

Other image-enhancement techniques such as the optimal band imaging (OBI) technique (Fuji Intelligent Color Enhancement [FICE]; Fujinon, Saitama, Japan) [4,8] or the post-processing digital filter technique (i-Scan; Hoya Pentax, Tokyo, Japan) [9] are also available to improve vascular imaging for the diagnosis of early neoplasia, However, since our experience is limited to NBI, we will only describe the clinical application of magnifying endoscopy with NBI, with regard to early gastric cancer.



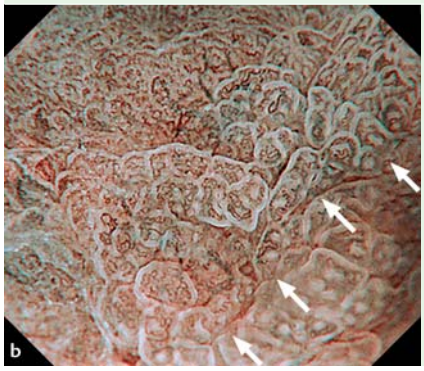


Fig. 3 Magnifying endoscopy with NBI: an early gastric cancer (diameter 25mm), superficial elevated (0-IIa) type, differentiated (intestinal) type within the gastric cardia. **a** Background noncarcinomatous mucosa: regular microvascular pattern (closed-loop) plus regular microsurface pattern (oval). **b** Carcinomatous mucosa: irregular microvascular pattern (open-loop/closed-loop) plus irregular microsurface pattern (tubular), with a demarcation line (arrows) between cancerous and noncancerous mucosa.

Basic principles: analysis of magnified endoscopy findings

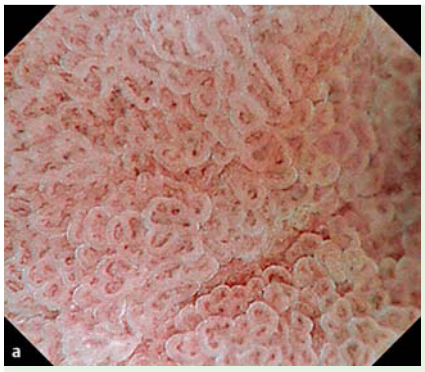
The microvascular architecture and microsurface structure are analyzed [7]. With white-light imaging (WLI) alone, only the microvascular architecture can be assessed, but with NBI, both the microvascular architecture and the microsurface structure (such as the crypt epithelial pattern) can be clearly visualized. For optimal evaluation these two findings should be described independently. Throughout this article, we will consistently describe magnifying endoscopy findings according to the "VS classification" system [7].

VS classification: definitions (Fig. 1–5)

Vascular pattern ("V"). The basic anatomical components for the analysis of vascular findings at magnifying endoscopy are (i) capillaries, (ii) collecting venules, and (iii) microvessels, where "microvessel" is a generic term for a minute vessel that cannot be distinctly classified. A microvessel can be either a capillary or collecting venule; it can also be neovascularization in a neoplastic area. Three types of microvascular pattern are defined:

- *Regular:* The mucosal capillaries have a uniform shape that can be closed-loop (polygonal) or open-loop. They have a consistent size and their arrangement and distribution are regular and symmetrical (**Fig. 1a, 2a, 3a, 4a, 5a**).
- *Irregular:* The vessels differ in shape, being closed-loop (polygonal), open-loop, tortuous, branched, bizarrely shaped, with or without a network. The size of the vessels also varies and their arrangement and distribution are irregular and asymmetrical (**Fig. 1b, 2b, 3b, 4b**).
- *Absent:* The subepithelial microvascular pattern is obscured by the presence of an opaque substance (for example "white opaque substance" [10]), within the superficial part of the mucosa (**Fig. 5b**).

Surface pattern ("S"). The basic anatomical components for the analysis of surface microstructure findings at magnifying endos-



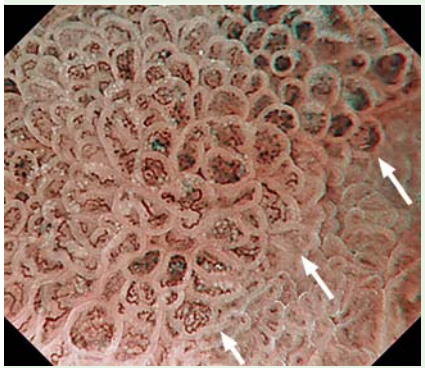
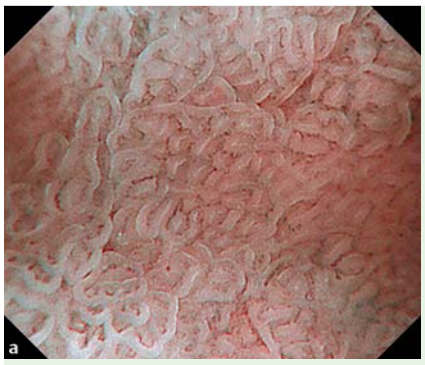


Fig. 4 Magnifying endoscopy with NBI: an early gastric caner (30 mm in diameter), superficial elevated (0 – IIa) type, differentiated (intestinal) type within the gastric antrum . **a** Background noncarcinomatous mucosa: regular microvascular pattern (open-loop) plus regular microsurface pattern (tubular). **b** Carcinomatous mucosa: irregular microvascular pattern (open-loop/closed-loop) plus regular microsurface pattern (papillary), with a demarcation line (arrows) between cancerous and noncancerous mucosa.



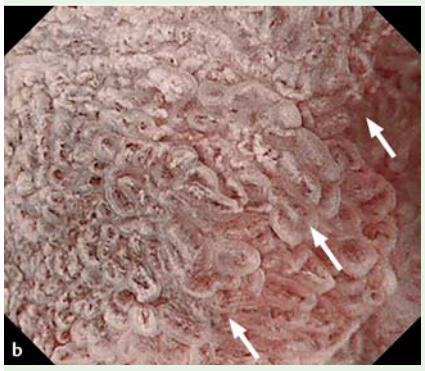


Fig. 5 Magnifying endoscopy with NBI: an early gastric cancer (diameter 15mm), superficial elevated (0-IIa) type, differentiated (intestinal) type within the gastric body. **a** Background noncarcinomatous mucosa: regular microvascular pattern (open-loop) plus regular microsurface pattern (tubular). **b** Carcinomatous mucosa: absent microvascular pattern (white opaque substance [WOS] obscured the microvascular architecture) plus irregular microsurface pattern (irregular WOS, with disorganized arrangement of speckled WOS which varies in size and shape), with a demarcation line (arrows) between cancerous and noncancerous mucosa.

copy are (i) crypt epithelium and (ii) white opaque substance (WOS). Three types of surface pattern are defined:

- *Regular:* The individual morphology of crypt epithelium shows a uniform round/oval/tubular/linear/curved/papillary structure. The width and length of the crypt epithelium are constant. The arrangement and distribution are regular and symmetrical (**Fig. 1a, 2a, 3a, 4a, 5a**). When WOS is present, regular WOS can be an additional marker of regular microsurface pattern, defined as well-organized and symmetrical distribution of the WOS in a regular reticular/maze-like/speckled pattern.
- *Irregular:* The individual morphology of crypt epithelium shows an irregular tubular/linear/curved/papillary/villous structure. The width and length of the crypt epithelium vary. The arrangement and distribution are irregular and asymmetrical (**Fig. 2b, 3b**). When WOS is present, irregular WOS can be an additional marker of irregular microsurface pattern, which is defined as disorganized and asymmetrical distribution of the WOS in an irregular reticular/speckled pattern (**Fig. 5b**).
- *Absent:* No epithelial structure is visible at magnifying endoscopy (**Fig. 1b**).

Fig. 6 Upper gastrointestinal magnifying endoscope with soft black hood attachment. (From reference [6], with permission of Elsevier Inc.).

The magnifying endoscopy appearance of early gastric cancer

Retrospective and prospective studies have shown that early gastric cancer is associated with the presence of either an irregular microvascular pattern with a demarcation line, or the presence of an irregular microsurface pattern with a demarcation line [7, 10 – 13]. Accordingly, we provisionally set our criterion for early gastric carcinoma as

- the presence of an irregular microvascular pattern with a demarcation line

or

- the presence of an irregular microsurface pattern with a demarcation line.

We will describe magnifying endoscopy findings according to these criteria throughout this article.

Materials and description of the procedure

Magnifying endoscopy with a hood attachment

A soft black hood (MB-162 for GIF-Q240Z, or MB-46 for GIF-H260Z and GIF-Q160Z; Olympus, Tokyo) is essential for optimal magnifying endoscopy.

Prior to the examination, the hood is mounted on the tip of the endoscope to enable the endoscopist to consistently fix the mucosa at a distance of approximately 2 mm – at which maximal magnification of the endoscopic image can be obtained (**Fig. 6**). Since the depth of the hood is very shallow, it does not disturb the visual field even during nonmagnifying observation. In addition, since the hood is soft, it does not injure the mucosa. In fact, when upper gastrointestinal magnification endoscopy was done in more than 600 screening endoscopy cases using this kind of soft black hood, there were no complications such as contact bleeding, or any untoward incidents such as hood dislocation [12].

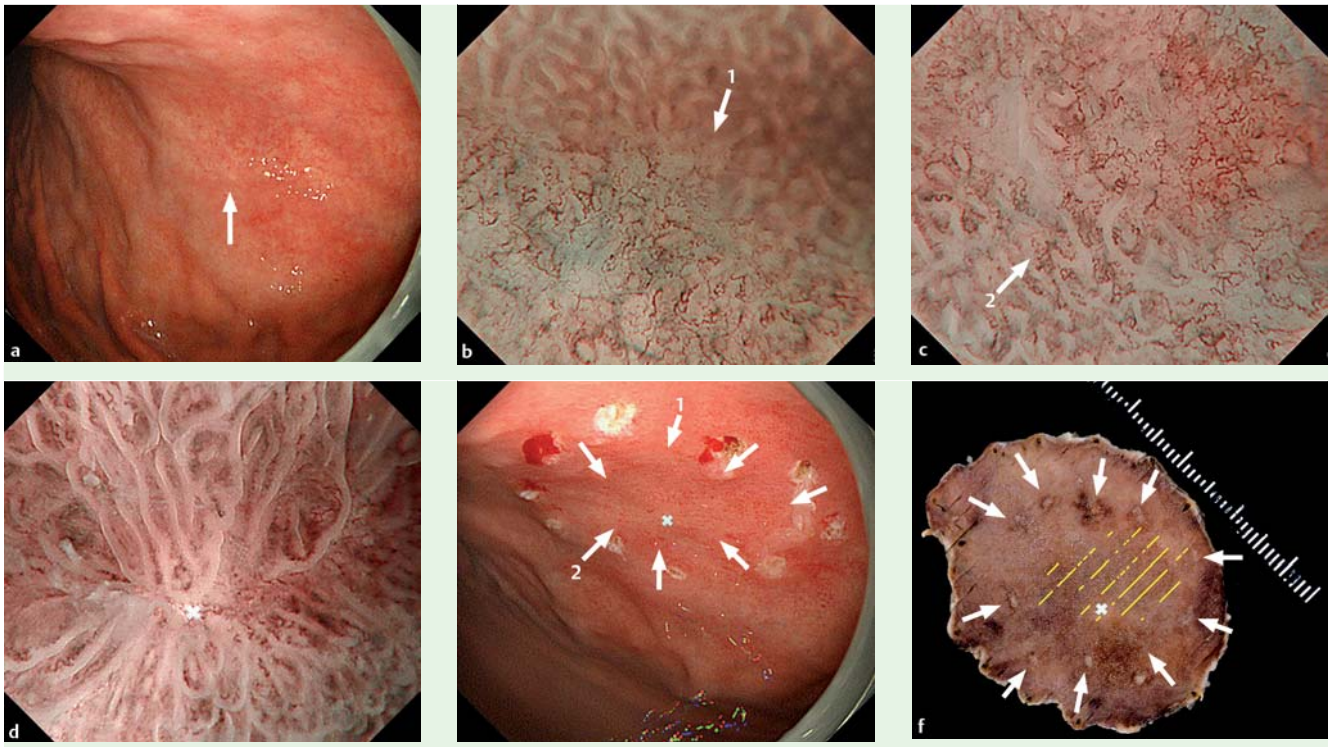


Fig. 7 How to evaluate early gastric cancer, in the case of occult cancer, by magnifying endoscopy with NBI. **a** Findings from the proximal gastric body with ordinary endoscopy. The arrow shows a tiny scar from previous biopsy. **b** Characterization and confirmatory diagnosis of the carcinoma by magnifying endoscopy with NBI. **c** Delineation of the lateral margin by magnifying endoscopy with NBI. **d** Detection of the tiny scar due to previous biopsy (cross) . **e** Markers placed just outside the demarcation line, using electrocoagulation (arrows correspond to those in the images in **b** and **c**, from magnifying endoscopy with NBI). **f** Resected specimen.

How to obtain a magnifying endoscopy image with optimal resolution

In addition to standard preparations for upper gastrointestinal endoscopy, it is important to clear all mucus and bile from the stomach. In Japan, patients are therefore given the following mixture 30 minutes before the endoscopic procedure: 100 ml of water with 10 000 units of pronase (Kaken Pharmaceutical, Tokyo, Japan), 1 g of sodium bicarbonate, and 10 ml of dimethylpolysiloxane (20 mg/ml, Horii Pharmaceutical Ind., Osaka Japan). Pronase, however, is not uniformly available for human use in the rest of world. An alternative mixture consists of 100 ml of water mixed with 2 ml of acetylcysteine (200 mg/ml Parvolex; Celltech, UK or Mucomyst, Bristol-Myers Squibb, USA), and 0.5 ml (40 mg/ml) activated dimethicone (Infacol; Forest Laboratories, UK).

Before detailed inspection, adherent mucus is removed by water flushing. When a mucosal lesion is found during nonmagnifying observation with WLI, the lesion is visualized using maximal magnification, employing gradual movement of the tip of the endoscope to bring the image into focus and the distally attached soft black hood to stabilize the tip of the endoscope onto the tissue. Instead of pressing the tip of the hood, gentle suction should be applied, without causing mucosal injury, and the lesion is observed by magnifying endoscopy with both WLI and NBI.

Evaluation of lesions suspicious for early gastric cancer.

Magnifying endoscopy evaluation of early gastric cancer has four steps: (i) detection, (ii) characterization, (iii) making a confirmed diagnosis, and (iv) delineation. This sequence in magnifying endoscopy is shown in **Fig. 7**, in a patient in whom cancer was diagnosed in a biopsy taken from a flat lesion in the gastric body that showed easy friability.

In the overview, high-resolution endoscopy does not indicate the presence of a carcinoma (**Fig. 7a**). The only landmark is a tiny scar from the previous biopsy (arrow). After primary detection, the lesion is further characterized using magnifying endoscopy. A clear demarcation line between mucosa with a regular microvascular/microsurface pattern and an area with an irregular microvascular pattern and an absent microsurface pattern was noted (**Fig. 7b**). These findings confirmed the diagnosis of a carcinoma. Subsequently, the lateral margin of the carcinoma was delineated (**Fig. 7b, 7c**), and the tiny scar due to the previous biopsy was identified **Fig. 7d**).

After delineation the lesion was resected en bloc by endoscopic submucosal dissection (ESD) together with the surrounding normal mucosa (**Fig. 7e, 7f**).

Limitations and success rate

Table 1 shows the results of inspection of 100 consecutive early gastric cancers with magnifying endoscopy and NBI, according to the VS classification (unpublished data). A demarcation line was identified in 97 out of 100 carcinomas (97 %). Overall, 97 out of 100 early carcinomas showed either an irregular microvascular pattern or an irregular microsurface pattern with a demarcation line. Therefore, 97 % of the lesions met the criteria for carcinoma according to the VS classification system and could be correctly discriminated from noncancerous mucosa. The three carcinomas which did not fulfill the criteria were macroscopically flat or de-

VS classification			Demarcation line, n	
V pattern	S pattern	n	Present	Absent
Regular	Regular	1	0	1
Regular	Irregular	0	0	0
Regular	Absent	2	0	2
Irregular	Regular	7	7	0
Irregular	Irregular	56	56	0
Irregular	Absent	30	30	0
Absent	Regular	0	0	0
Absent	Irregular	4	4	0
Absent	Absent	0	0	0
Total		100	97	3

Table 1 Magnification endoscopy with narrow-band imaging (NBI): frequency of findings according to the VS classification system (microvascular architecture ["V"] and microsurface structure ["S"]), and presence/absence of a demarcation line, in 100 consecutive early gastric cancers.

pressed type lesions with a pale color and histologically undifferentiated (diffuse)-type cancer. Histologically this type of carcinoma invades the lamina propria mucosa sparsely and diffusely underneath the surface epithelium, which makes it impossible to determine either changes in the microvascular or microsurface pattern or a distinct demarcation line.

The use of magnifying endoscopy and NBI for characterization and delineation of early gastric cancer has been studied at only a few centers, and more prospective studies would contribute to our further understanding of this field.

Indications

Routine screening endoscopy: distinguishing between small early gastric cancer and focal gastritis (Fig. 8)

It has already been reported that magnifying endoscopy using a soft black hood is useful for correctly distinguishing, on the basis of microvascular architecture, between an early gastric cancer and focal gastritis when a flat reddened lesion is seen at routine screening endoscopy [11,12,14]. With regard to diagnostic accuracy, according to a prospective blinded study [9], the negative predictive value for ruling out carcinoma is remarkably high (100%) when a demarcation line between the lesion and the surrounding mucosa is absent at magnifying endoscopy. It is a helpful marker for the endoscopist, avoiding multiple unnecessary biopsies from a noncancerous lesion in order to identify a small flat gastric cancer.

The positive predictive value for carcinoma is also high (93%) when an irregular microvascular pattern is present within the lesion. Therefore, it is useful for the endoscopist in deciding where the target biopsy should be taken. Accordingly, when we apply the magnifying endoscopy technique to flat or depressed reddened lesions during routine endoscopy, we can avoid taking unnecessary biopsies from noncancerous lesions and can target biopsy in cases where there is a strong suspicion of carcinoma even though the lesion is very small and flat.

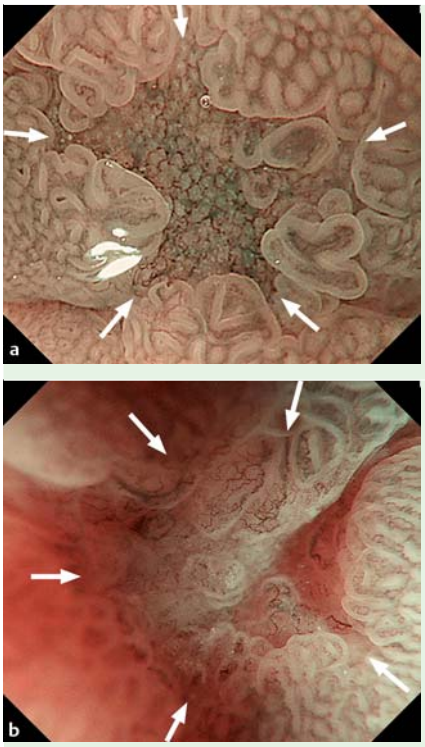


Fig. 8 Differential diagnosis between focal gastritis and gastric cancer of a small flat lesion. **a** Magnifying endoscopy with NBI: an example of findings of focal gastritis in the gastric body. There is a demarcation line between the lesion and the surrounding mucosa. Within the demarcation line, the regular microvascular pattern (open-loop) plus regular microsurface pattern (tubular) have disappeared; however, the lesion shows only a regular microvascular pattern (closed polygonal loop with a network) plus a regular microsurface pattern (oval). These findings do not fulfill the criteria for carcinoma and are characteristic for focal gastritis. **b** Magnifying endoscopy with NBI: example of findings of a small early gastric cancer in the gastric antrum. There is an irregular demarcation line between the lesion and the surrounding mucosa. Within this area, the regular microvascular pattern (coil-shaped) plus regular microsurface pattern (tubular) have disappeared; instead an irregular microvascular pattern (branched/open-loop/close-loop) and absent microsurface pattern can be identified. These findings meet the criteria for carcinoma.

Preoperative assessment of the lateral extent of early gastric cancer, for curative endoscopic resection

Magnifying endoscopy with NBI may allow reliable delineation of the lateral extent of carcinomatous tissue prior to endoscopic removal by endoscopic mucosal resection (EMR) or ESD [11,15]. As described above, this technique has already been applied in clinical practice, and has been shown to assure the endoscopist of curative resection without taking any biopsies from the noncancerous mucosa surrounding the carcinoma [11].

One of the limitations of this technique is evident when we apply this to early gastric carcinoma of undifferentiated (diffuse) type. This type of carcinoma is not a standard indication for endoscopic resection and hence may not be clinically relevant. However, since the indications for endoscopic resection are being constantly reviewed and extended, especially by Japanese endoscopists, it is mandatory to have several negative biopsies from the back-

ground mucosa surrounding the carcinoma when this type of carcinoma is endoscopically resected.

Conclusions

An irregular microvascular pattern and/or an irregular microsurface pattern together with a clear demarcation line are the hallmarks of early gastric cancer. Magnifying endoscopy with NBI is a reliable imaging technique for the characterization and delineation of early gastric cancer.

Acknowledgments

We wish to thank Dr. Kazuhiro Gono (Olympus, Tokyo, Japan) for his technical advice, Professor Akinori Iwashita (Department of Pathology, Fukuoka University Chikushi Hospital, Fukuoka, Japan) for his academic contribution as a pathologist, and Miss Katherine Miller (Royal English Language Centre, Fukuoka, Japan) for correcting the English used in this manuscript.

Competing interests: Dr Ragunath has received research support in the form of endoscopy equipment, educational grants, and speaker's honorarium from Olympus-Keymed UK.

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