

## REVIEW

## MAGNIFYING ENDOSCOPY WITH NARROW BAND IMAGING FOR EARLY DIFFERENTIATED GASTRIC ADENOCARCINOMA

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We have been using magnifying endoscopy with narrow band imaging (NBI) to study early differentiated gastric adenocarcinomas and to assess the relationship between microvessel pattern, pit pattern and histological pattern. The magnified view of the cancerous area showed three types of pattern: (i) a mesh pattern, consisting of mesh-like connected microvessels; (ii) a loop pattern, consisting of loop-like microvessels that were not connected and had tubule-like or villus-like mucosal structures along them; and (iii) an interrupted pattern, consisting of interrupted thick or thin vessels without mucosal structures. The mesh type of microvascular pattern showed a round pit pattern in 88.9% of cases (32/36) and the loop type of microvascular pattern showed a non-round pit pattern in 100% of cases. Among lesions that showed a mesh pattern or a loop pattern, 94.9% (56/59) were mucosal cancer and 5.1% (3/59) were submucosal cancer. However, 92.3% (12/13) of lesions that showed an interrupted pattern were submucosal differentiated adenocarcinoma and 7.7% (1/13) were mucosal differentiated adenocarcinoma. The present findings provide basic data on the characteristics of mucosal differentiated gastric adenocarcinoma revealed by magnifying endoscopy with NBI, as well as invasive changes such as submucosal invasion.

**Key words:** gastric cancer, interrupted pattern, magnifying endoscopy, narrow band imaging.

## INTRODUCTION

Recently, there have been a number of reports describing endoscopic diagnosis of lesions in the gastrointestinal tract using the narrow band imaging (NBI) system.<sup>1–3</sup> NBI is a unique sequential electronic endoscopy technique with an ordinary lighting system, in which the wavelength ranges of the new RGB filters are 485–515 nm for red (R), 430–460 nm for green (G), and 400–430 nm for blue (B).<sup>4</sup> This system, in combination with a magnifying endoscope, can yield very clear images of microvessels on the mucosal surface.<sup>1</sup> Details of the magnified appearance of microvessels in gastric cancer have been reported by Tajiri *et al.*<sup>5</sup> and Yao *et al.*<sup>6</sup> Magnifying endoscopy with NBI has been reported to give more detailed information on microvessels in gastric mucosa including cancerous tissue.<sup>1,7–9</sup> Sumiyama *et al.* reported that magnified views of differentiated adenocarcinoma showed a fine network pattern in 66.1% of cases.<sup>7</sup>

We have been studying the magnified view of differentiated gastric adenocarcinomas using NBI and the relationship between microvessels pattern, pit pattern and histological pattern. Here we report the characteristics of mucosal differentiated gastric adenocarcinoma revealed by magnifying endoscopy with NBI, including invasive changes such as submucosal invasion.

## PATIENTS AND METHODS

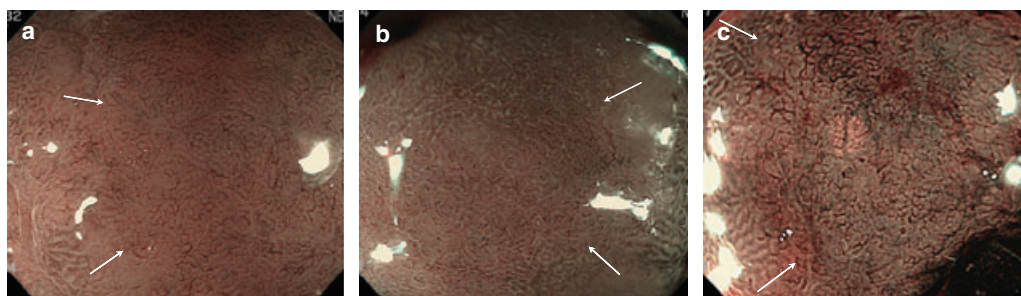
Between October 2005 and November 2007, 105 patients with early-stage gastric cancer were consecutively enrolled. All the patients had been found to have early-stage gastric differentiated adenocarcinoma by endoscopic examination and biopsy. After conventional endoscopy, magnifying endoscopy with NBI was carried out to clarify the extent of the cancer in order to prepare for endoscopic submucosal dissection (ESD) or surgical operation. The protocol was approved by the ethics committee of our institution. All enrolled patients gave their written informed consent to participate in the study. Thirty-three patients among the 105 were not chosen for this study because of insufficient quality of the magnifying endoscopic imaging. The endoscopic pictures of these patients did not have detailed information of microvascular pattern. Therefore, the magnifying endoscopic and histological findings for 72 patients were studied.

## Endoscopic procedure

To dissolve the mucus layer of the stomach, each patient ingested a solution containing 20 000 U pronase (Pronase MS; Kaken Pharmaceutical Products Inc., Tokyo, Japan) and 1 g NaHCO<sub>2</sub> in 50 mL water, 10 min before endoscopy. The procedure was carried out with a magnifying endoscope (GIF-Q240Z or GIF-H260Z; Olympus Optical Co., Tokyo, Japan). Gastric carcinomas were initially observed by conventional endoscopy, followed by magnifying endoscopy with NBI. The microvascular pattern of the cancerous mucosa and the non-cancerous mucosa was observed by magnifying endoscopy with NBI.

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**Fig. 1.** (a) Complete mesh pattern (white arrows). (b) Incomplete mesh pattern (white arrows). (c) Irregular mesh pattern (white arrows).

All of the magnifying endoscopic examinations and recordings of all of the endoscopic findings were carried out by a single endoscopist (KY). On all occasions, endoscopic photographs were taken and recorded on digital videotape.

#### Examination of pit pattern of gastric differentiated adenocarcinomas by magnifying endoscopy after acetic acid sprinkling

All specimens resected by ESD were extended on boards with pins and observed by magnifying endoscopy after acetic acid sprinkling. Close attention was paid to the cancerous mucosa, non-cancerous mucosa and the borderline between them and several pictures were taken. To compare the microvascular pattern of the cancerous area recorded using NBI with the pit pattern of cancerous tissue on the resected specimen, it was important to identify the same area that had been observed by magnifying endoscopy using NBI. For identification of the same area, the shape of the cancerous margin was recorded initially in detail and then two endoscopists (KY and AN) confirmed the area when the resected specimen was later observed by magnifying endoscopy.

#### Histopathology

After pictures had been obtained by magnifying endoscopy, the resected specimens were fixed in 20% formalin. The lesions, together with the surrounding non-carcinomatous mucosa, were cut into 2 mm-wide serial-step sections on the specimens resected by ESD and 5 mm-wide serial-step sections on the specimens resected surgically; these dimensions were determined by the endoscopist who performed the study (KY) to correspond to the correct portion of the magnified endoscopic images. The histopathological diagnosis was done by a pathologist (HU) who was blinded to the endoscopic findings.

#### Statistical analysis

The correspondence of each pit pattern with each microvascular pattern was studied using a contingency table. When the *P*-value was less than 0.05, the difference was considered statistically significant.

## RESULTS

### Macroscopic features of the lesions

Ten of the 72 lesions were elevated, 27 were flat and 35 were depressed. All of the lesions were diagnosed as differentiated adenocarcinomas from biopsy specimens and resected specimens.

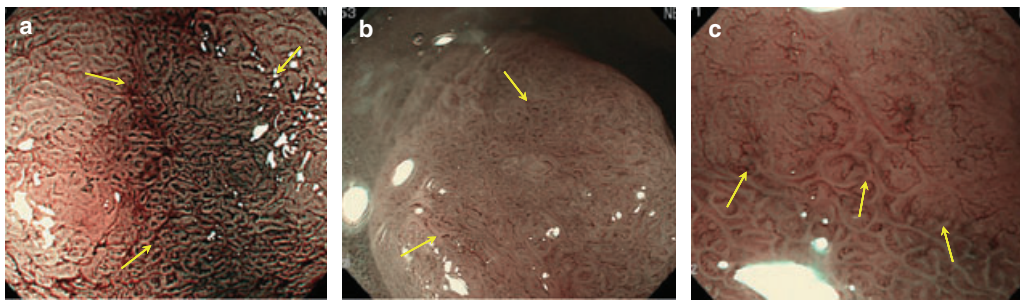
### Appearance of microvessels by magnifying endoscopy using NBI

The magnified view of the cancerous area was divided into three patterns: (1) a mesh pattern, consisting of mesh-like connected microvessels; (2) a loop pattern, consisting of loop-like microvessels that were not connected and had tubule-like or villus-like mucosal structures along them; and (3) an interrupted pattern, consisting of interrupted thick or thin vessels without mucosal structures. Furthermore, the mesh pattern was subdivided into three types: (1a) a complete mesh pattern; (1b) an incomplete mesh pattern and (1c) an irregular mesh pattern.

The complete mesh pattern consisted entirely of connected microvessels with a mesh-like appearance (Fig. 1a) and was similar to the fine network pattern reported by Nakayoshi *et al.*<sup>1</sup> The incomplete mesh pattern consisted of microvessels with an incomplete mesh-like appearance (Fig. 1b) and low density resembling the microvascular pattern of adenoma. The irregular mesh pattern basically showed a mesh-forming microvessel pattern, but the microvessels were often broken and irregular (Fig. 1c). All of the lesions with an incomplete mesh pattern and a complete mesh pattern were mucosal-depth cancers, although three lesions with irregular mesh pattern were submucosal invasive cancers (Table 1).

The loop pattern showed loop-forming microvessels at the tips of tubule-like or villus-like mucosal structures which were associated with branched pits. This pattern was subdivided into three types on the basis of mucosal structures, and not the appearance of the microvessels: (2a) the villiform pattern; (2b) the gyriform pattern; and (2c) the fusion pattern.

The villiform pattern consisted of small granule-like or villus-like structures containing loop-like microvessels (Fig. 2a). The gyriform pattern (Fig. 2b) consisted of tubular or gyriform structures surrounded by branched pits. Loop-like microvessels appeared along these branched pits. The fusion pattern showed fusion of the villiform pattern and



**Fig. 2.** (a) Villiform pattern (yellow arrows). (b) Gyriform-like pattern (yellow arrows). (c) Fusion pattern (yellow arrows).

**Table 1.** Depth of cancerous lesion for each microvascular pattern

Depth	Mesh pattern	Loop pattern	Interrupted pattern	Total
Mucosal cancer	33	23	1	57
Sm1 (submucosal scanty invasion)	1 <sup>†</sup>	0	1	2
Sm2–3 (submucosal massive invasion)	2 <sup>†</sup>	0	11	13
Total	36	23	13	72

<sup>†</sup>Three cases with submucosal invasion showed an irregular mesh pattern.

**Table 2.** Distribution of the lesions showing the mesh pattern and loop pattern

	Mesh pattern			Loop pattern		
	Complete mesh pattern	Incomplete mesh pattern	Irregular mesh pattern	Villiform pattern	Gyriform pattern	Fused pattern
Total	19 (0)	6 (0) 36	11 (3) <sup>†</sup>	12 (0)	8 (0) 26	3 (0)

( ) number of submucosal cancers.

<sup>†</sup>Two lesions with an irregular mesh pattern were massive submucosal cancers and one lesion was a scanty submucosal cancer. All of the lesions except those with an irregular mesh were mucosal cancers.

gyriform pattern due to the absence of branched pits (Fig. 2c). Loop-like microvessels appeared inside these fused structures. All of the lesions with the loop pattern were mucosal-depth cancers (Table 1).

The distribution of the lesions comprising each mesh pattern and loop pattern subgroup is demonstrated in Table 2.

The interrupted pattern showed broken and short irregular microvessels, which differed from the mesh pattern or the loop pattern, and the mucosal structure could not be imaged from this microvessel pattern (Fig. 3a,b; see also Correlation between microvascular pattern and pit pattern below). Among the lesions that showed the interrupted pattern, 92.3% (12/13) were submucosal differentiated gastric cancers (Table 1).

The illustrations of a mesh pattern, a loop pattern and an interrupted pattern are shown (Fig. 3c–e).

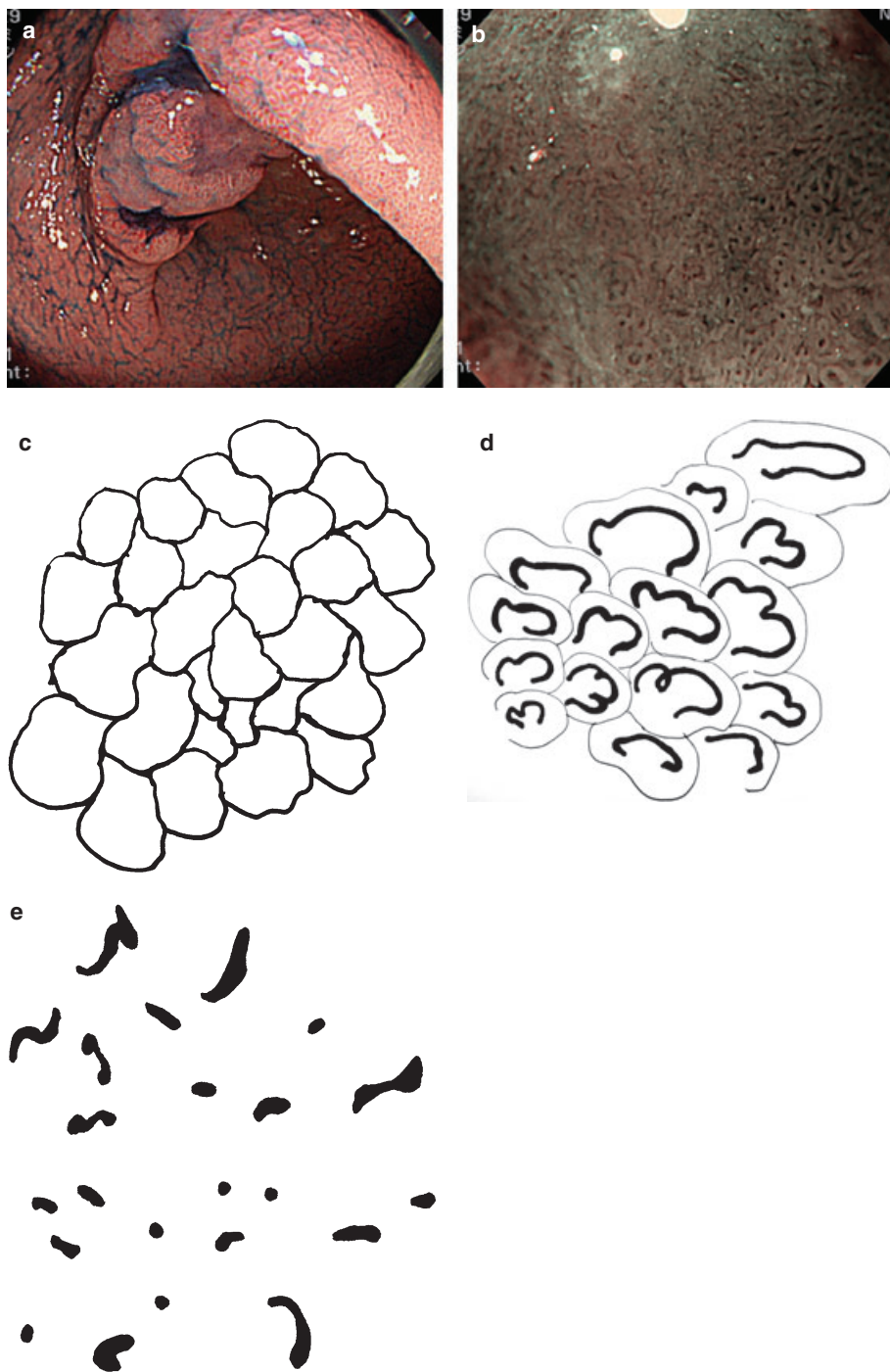
#### **Correlation between microvascular pattern and pit pattern**

The pit patterns revealed by acetic acid sprinkling in resected specimens were divisible into two types; round and non-round (branch-like pit). The round pit pattern was subdivided into

three patterns; small round pits (Fig. 4a), oval round pits (Fig. 4b) and long round pits (Fig. 4c). The non-round pit pattern was subdivided into granular and tubular types according to the mucosal structure surrounded by the branch-like pits. The granular pattern showed granular elevations surrounding branched pits (Fig. 4d), whereas the tubular pattern showed tubular elevations surrounding branched pits (Fig. 4e). Among the lesions with a mesh-type microvascular pattern, 88.9% (32/36) showed a round pit pattern, and 100% of the lesions with a loop-type microvascular pattern showed a non-round pit pattern (Table 3). The two cancerous pit patterns differed in their microvascular patterns ( $P < 0.001$ ). This result suggests that mesh-pattern microvascular vessels surround cancerous ducts with round pits.

#### **Correlation between microvascular pattern and histological findings including of depth of cancer**

Most cases with the complete mesh pattern (Fig. 5a) showed a round pit pattern (Fig. 5b) and, histologically, showed short and straight cancerous ducts (Fig. 5c). Furthermore, the histological type in all cases showing the complete mesh pattern was well-differentiated adenocarcinoma. Cases with the



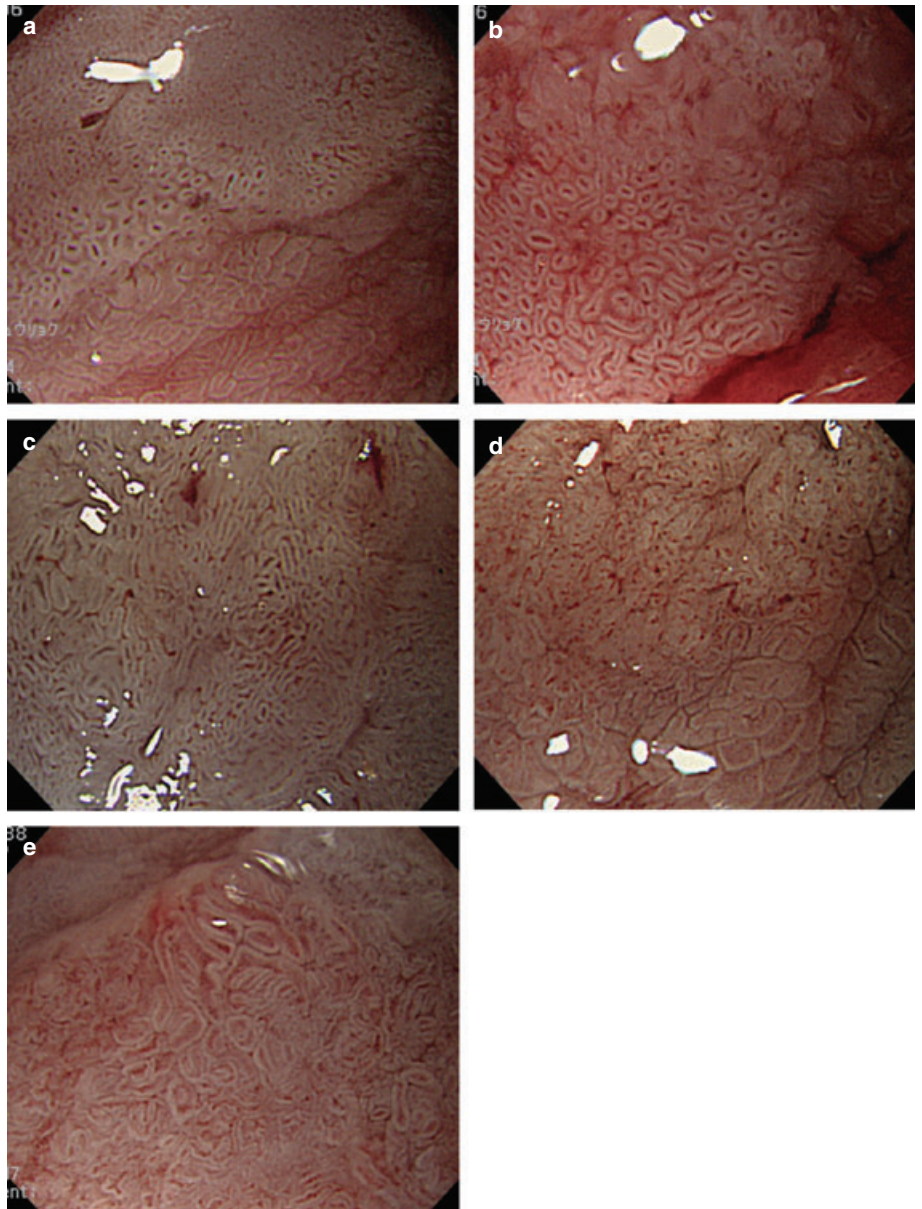
**Fig. 3.** (a) IIC lesion on the antrum. (b) Interrupted pattern. (c) Illustration of a mesh pattern. (d) Illustration of a loop pattern. (e) Illustration of an interrupted pattern.

incomplete mesh pattern also showed short and straight cancerous ducts, which were diagnosed as well-differentiated adenocarcinoma. However, 50% (3/6) of the cases with an incomplete mesh pattern had been diagnosed as adenoma by biopsy a few years ago.

Among cases with an irregular mesh pattern, 90.9% (10/11) were moderately differentiated adenocarcinomas. Furthermore, two cases with an irregular mesh pattern showed massive submucosal invasion and one case showed scanty submucosal invasion (Table 1).

The histological hallmark of the villiform pattern was cancerous tissue with club-shaped stroma (Fig. 5d), whereas that of the gyriform pattern was branched and had long cancerous glands (Fig. 5e).

Among the lesions showing an interrupted pattern, 92.3% (12/13) were submucosal differentiated adenocarcinomas and 7.7% (1/13) were mucosal differentiated adenocarcinomas. All of the cases showing an interrupted pattern were invasive differentiated adenocarcinomas, including intramucosal cancer. In cases of submucosal invasive cancer, submucosal



**Fig. 4.** (a) Small round pit pattern. (b) Oval round pit pattern. (c) Long round pit pattern. (d) Granular pattern. (e) Tubular pattern.

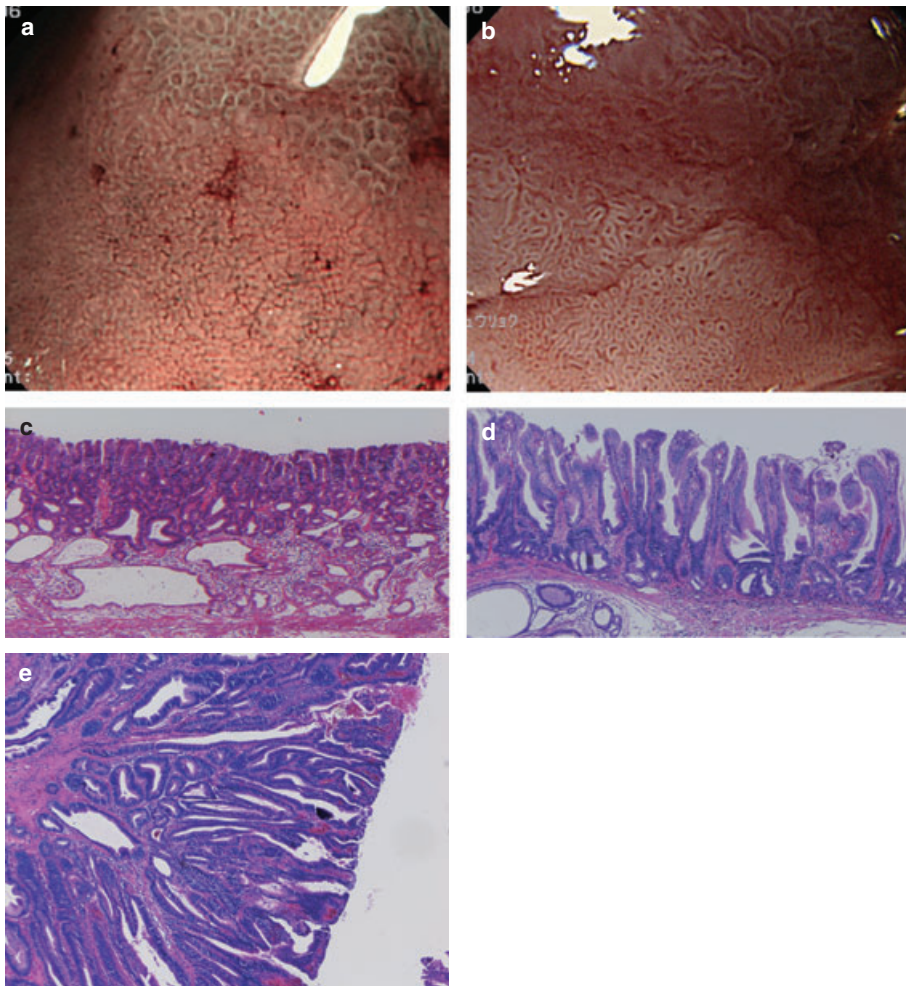
**Table 3.** Relationship between microvascular pattern and pit pattern

Pit pattern	Mesh pattern	Loop pattern	Total
Round pit pattern	32	0	32
Non-round pit pattern (Branch-like pit pattern)	2	23	25
Impossible to classify	2	0	2
Total	36	23	59

Contingency table:  $P < 0.001$ .

invasion was found approximately in the sites of interrupted pattern. Fig. 6a shows the endoscopic appearance of cardiac cancer, and it was difficult to diagnose submucosal invasive cancer from conventional endoscopic findings. The magnifying endoscopic view of Fig. 6a showed the interrupted pattern (Fig. 6b). Histological examination of the resected specimen

showed submucosal invasive cancer (Fig. 6c). Fig. 6d shows the endoscopic appearance of a IIc lesion in the antrum. The magnifying endoscopic view in Fig. 6d shows an interrupted pattern (Fig. 6e). Although histological examination of the resected specimen showed mucosal cancer, the cancerous tissue showed intramucosal invasive cancer (Fig. 6f).



**Fig. 5.** (a) Complete mesh pattern was shown on a IIb lesion by magnifying endoscopic observation with NBI. (b) Round pit pattern was observed on the resected specimen after instillation of acetic acid in the same area as that in (a). (c) Histologically, the areas in (a) and (b) indicate short and straight cancerous ducts. (d) Histologically, the villiform pattern shows cancerous tissue with club-like stroma. This is the histological view of the area in Fig. 2a. (e) Histologically, the gyriform pattern shows branched and long cancerous glands. This is the histological view of the area in Fig. 2c.

## DISCUSSION

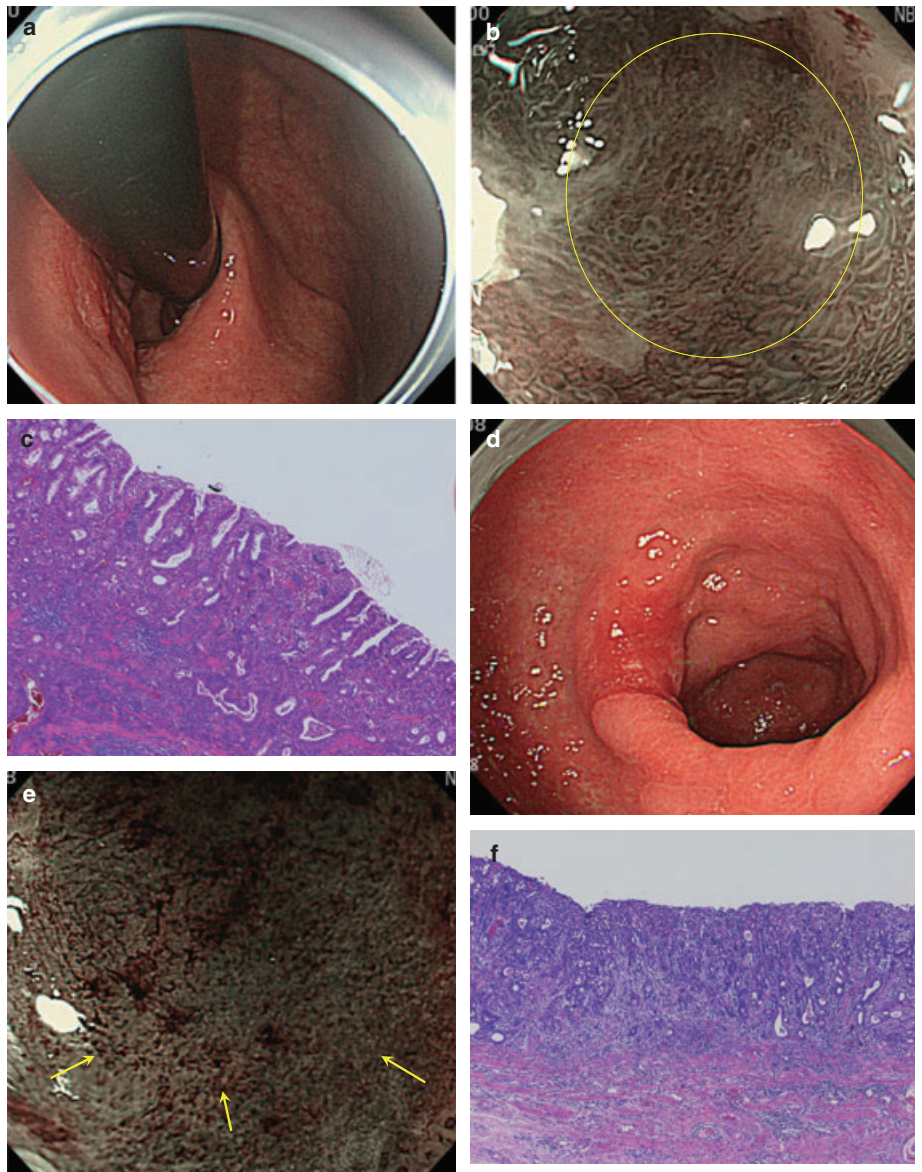
Narrow band imaging is a unique sequential electronic endoscopic technique using an ordinary lighting system, in which the wavelength ranges of the filters are 485–515 nm for red, 430–460 nm for green, and 400–430 nm for blue.<sup>10</sup> This system, in combination with a magnifying endoscope, can yield very clear images of microvessels on the mucosal surface.<sup>2,3</sup>

Several articles have already described the magnifying endoscopic view of gastric cancer obtained using NBI.<sup>1,7–9</sup> Nakayoshi *et al.*<sup>1</sup> reported that magnifying endoscopy with NBI was capable of predicting the histological characteristics of gastric cancer lesions on the basis of their microvascular pattern and found a fine network pattern in 66.1% of differentiated adenocarcinomas. Furthermore, they observed that microvessels were present in the surrounding cancerous ducts in the surface mucosa of specimens of differentiated cancer and that the same patterns as the 3-D structures of the microvessels could be reconstructed by laser scanning microscopy.

In the present study, the microvascular patterns of gastric mucosal and submucosal differentiated adenocarcinomas were divided into three types. The first type was the mesh pattern, which was divided into three subgroups: a complete

mesh pattern, which was thought to correspond to the fine network pattern reported by Nakayoshi *et al.*, an incomplete mesh pattern, which was not rich in microvessels; and an irregular mesh pattern, in which microvessels were often broken and irregular. All of the lesions showing the complete or incomplete mesh pattern were mucosal differentiated adenocarcinomas. However, 27% (3/11) of the lesions with an irregular mesh pattern were submucosal invasive cancers. The degree of microvessel irregularity might have some relationship to cancerous invasion.

The second type was the loop pattern, which was subdivided into a villiform pattern, a gyriform pattern and a fusion pattern. This pattern showed loop-forming microvessels that were not interconnected and had a dot-like or stick-like appearance. We analyzed the magnifying imaging and histological features of the lesions with each loop pattern. Histologically, the villiform pattern was characterized by a stick-like stroma with cancerous cells at the center. This histological feature was thought to be responsible for the villiform appearance on magnifying view. The gyriform pattern was characterized by more branched and elongated cancerous crypts on magnifying view. In both types, the loop-like microvessels appeared around branched grooves, which means that microvessels were present inside both villiform or gyriform lesions. The loop pattern sometimes



**Fig. 6.** (a) Endoscopic view of a cardiac cancer. (b) Magnifying endoscopic view of the lesion in (a). An interrupted pattern is shown (inside yellow circle). (c) Histological appearance of the resected specimen, showing submucosal invasive cancer. (d) Endoscopic view of IIC on the antrum. (e) Magnifying endoscopic view of (d) shows an interrupted pattern (yellow arrows). (f) Histological examination of the resected specimen shows mucosal cancer, although the cancerous tissue was invasive.

resembled intestinal metaplasia. More detailed analysis will be necessary for differential diagnosis of differentiated adenocarcinoma with a loop pattern and intestinal metaplasia.

The third type was the interrupted pattern showing broken and short irregular microvessels, which was different from the mesh pattern or the loop pattern. Among the lesions showing the interrupted pattern, 92.3% (12/13) were submucosal differentiated gastric cancers. One lesion showing the interrupted pattern was a mucosal differentiated adenocarcinoma, but the histological diagnosis was intramucosal invasive cancer. We think that the interrupted pattern is due to cancer cells invading the stroma surrounding cancerous glands, which, in turn, affects the appearance of microvessels. The interrupted pattern is thought to be a magnified feature of histological invasive change in the intramucosal layer. However, the number of submucosal cancers we investigated in this study was small. Other magnifying endoscopy features

of cases with submucosal invasion should be analyzed, and the definition of the interrupted pattern should be reconsidered. Furthermore, the intra-observer and interobserver variation should be assessed to generalize this classification in the near future.

We thought that the relationship between the microvascular pattern and the pit pattern would contribute to the interpretation of the microvascular pattern of differentiated adenocarcinomas. However, the pits of gastric cancerous lesions are difficult to observe by magnifying endoscopy *in vivo*, probably because of their very small size and abundant mucus. We realized that it was possible to reveal the pit patterns of cancerous lesions in resected specimens by magnifying endoscopy after sprinkling them with acetic acid.<sup>11</sup> Cancerous pits were divisible into two patterns: round and non-round. The round pit pattern was subdivided into small round, oval round and long round. The round pit pattern was characterized by a flat surface with numerous ducts of

cancerous glands. Among the lesions with a mesh pattern, 88.9% showed a round pit pattern. This suggested that the microvessels of cancerous tissue with a round pit pattern had a mesh-like structure. Cancerous lesions with a round pit pattern show a mesh-like microvascular structure because the crypts are short and straight, and surrounded by horizontally running microvessels.

However, 100% of the lesions with loop-like microvessels showed a non-round pit (branched pit) pattern with granular or tubular elevations surrounding branched pits. The relationship between microvessels and pits has been reported in *Helicobacter pylori*-free normal mucosa and gastritis mucosa.<sup>12,13</sup> In intramucosal differentiated gastric adenocarcinoma, the microvessels basically run around cancerous crypts, similar to the relationship between microvessels and pits of *H. pylori*-free gastric mucosa and gastritis mucosa. Both the mesh pattern and loop pattern have a characteristic feature of feeding vessels around a pit.

However, the interrupted pattern was completely different from these types of microvessels. As mentioned above, we think that the interrupted pattern is due to cancer cells invading the stroma surrounding cancerous glands, and that the appearance of microvessels is affected by this invasive change.

The characteristic features of the microvascular pattern of gastric differentiated adenocarcinoma have allowed endoscopists to diagnose gastric cancer more accurately, for example, the extent of cancer and confirmation of cancerous lesions before biopsy. Furthermore, if differential diagnosis of mucosal cancer and submucosal cancer by magnifying endoscopy becomes possible, then this approach would be very practical for selection of treatment (i.e. operation or endoscopic submucosal dissection). More cases of submucosal differentiated gastric cancer should be studied to confirm whether there are other magnified appearances of submucosal invasion apart from the interrupted pattern.

In conclusion, we have clarified the characteristic features of the magnified view of mucosal differentiated gastric adenocarcinoma and have begun to grasp the characteristics of invasive changes including submucosal invasion.

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