Effectiveness of narrow-band imaging magnification for invasion depth in early colorectal cancer

Masakatsu Fukuzawa, Yutaka Saito, Takahisa Matsuda, Toshio Uraoka, Takao Itoi, Fuminori Moriyasu

Abstract
AIM: To evaluate the surface microvascular patterns of early colorectal cancer (ECC) using narrow-band imaging (NBI) with magnification and its effectiveness for invasion depth diagnosis.

METHODS: We studied 112 ECC lesions [mucosal/submucosal superficial (m/sm-s), 69; sm-deep (sm-d), 43] ≥ 10 mm that subsequently underwent endoscopic or surgical treatment at our hospital. We compared microvascular architecture revealed by NBI with magnification to histological findings and then to magnification colonoscopy pit pattern diagnosis.

RESULTS: Univariate analysis indicated vessel density: non-dense (P < 0.0001); vessel regularity: negative (P < 0.0001); caliber regularity: negative (P < 0.0001); vessel length: short (P < 0.0001); and vessel meandering: positive (P = 0.002) occurred significantly more often with sm-d invasion than m/sm-s invasion. Multivariate analysis showed sm-d invasion was independently associated with vessel density: non-dense [odds ratio (OR) = 402.5, 95% confidence interval (CI): 12.4-13133.1] and vessel regularity: negative (OR = 15.9, 95% CI: 1.2-219.1). Both of these findings when combined were an indicator of sm-d invasion with sensitivity, specificity and accuracy of 81.4%, 100% and 92.9%, respectively. Pit pattern diagnosis sensitivity, specificity and accuracy, meanwhile, were 86.0%, 98.6% and 93.8%, respectively, thus, the NBI with magnification findings of non-dense vessel density and negative vessel regularity when combined together were comparable to pit pattern diagnosis.

CONCLUSION: Non-dense vessel density and/or negative vessel regularity observed by NBI with magnification could be indicators of ECC sm-d invasion.

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Key words: Colorectal neoplasms; Narrow-band imaging; Microvasculature

Peer reviewer: Dr. Oliver Mann, MD, Senior Attending Physician and Deputy Director, Department of General, Visceral and Thoracic Surgery, University of Hamburg, Martini Str. 52, D-20246 Hamburg, Germany

INTRODUCTION
Magnified colonoscopy and the development of pit pattern diagnosis[1] not only permits us to distinguish neoplastic from non-neoplastic colorectal lesions,[2-5] but also helps to assess the invasion depth of early colorectal cancers (ECC).[6-9] Similarly, vascular findings on the surface of gastric lesions have also been observed by
magnification endoscopy, and the usefulness in predicting the histological nature of such lesions and assessing their invasion depth has also been reported in the upper gastrointestinal (GI) tract[10-12].

The recently developed narrow-band imaging (NBI) system is a noninvasive optical technique that uses reflected light that provides clearer images of surface microvascular architecture than the conventional observation modality[13]. To date, the use of magnification endoscopy with the NBI system has been studied in the upper GI tract[14-20] and the suitability of this new modality for differentiating neoplastic from non-neoplastic lesions and its potential for pit pattern diagnosis have also been reported for the lower GI tract[21-23].

As previously indicated, colorectal lesions with mucosal (m) or submucosal (sm) superficial invasion < 1000 μm (sm-s) have an extremely low risk of lymph-node metastasis and are good candidates for endoscopic treatment[24]. It is helpful therefore, to differentiate endoscopically between m/sm-s and deeper sm invasion (sm-d ≥ 1000 μm) lesions. There have been only a few reports concerning invasion depth diagnosis using NBI with magnification in a large series of cases, however, a number of questions remain regarding the comparative effectiveness of a diagnosis based on NBI observation and one using pit pattern analysis by dye chromoendoscopy for determining invasion depth.

Using magnification colonoscopy with the NBI system, we evaluated the characteristics of the surface microvascular architecture of ECC and investigated the effectiveness of this new optical modality for the diagnosis of invasion depth. In addition, we evaluated the comparative relationship between NBI with magnification and pit pattern diagnoses.

MATERIALS AND METHODS

NBI system

NBI is a novel technique that uses spectral narrow-band optical filters instead of the full spectrum of white light. It is based on the phenomenon that the depth of light penetration depends on its wavelength, with a short wavelength penetrating only superficially and a longer wavelength penetrating into deeper layers. In the NBI mode, optical filters that allow narrow-band light to pass at wavelengths of 415 and 540 nm are mechanically inserted between a xenon arc lamp and a red/green/blue rotation filter. Thin blood vessels such as capillaries on the mucosal surface can be seen most clearly at 415 nm, which is the wavelength that corresponds to the hemoglobin absorption band, while thick vessels located in the deep layer of the mucosa can be observed at 540 nm. Current NBI technology limits mucosal surface light penetration, thereby enhancing visualization of the fine capillary vessel structure on the surface layer.

Patients and evaluation methods

We studied a total of 112 ECC lesions ≥ 10 mm analyzed with NBI with magnification colonoscopy examination, which then underwent endoscopic or surgical treatment at the National Cancer Center Hospital between January 2006 and February 2007. All colonoscopies were performed with a PCF-Q240ZI or CF-H260AZI endoscope (Olympus Optical Co. Ltd., Tokyo, Japan) by three experienced endoscopists (MF, YS, TM) each of whom had annually performed more than 1000 magnifying chromoendoscopy examinations and at least 500 NBI examinations per year. Endoscopic images of each lesion were taken in the following order: conventional colonoscopy, NBI with magnification, chromoendoscopy and magnification chromoendoscopy. When a lesion was detected by conventional colonoscopy, its surface was washed with proteinase to remove excess mucus. Magnification NBI views of the microvascular architecture concentrated on those portions of the lesion where invasion seemed to have permeated the deepest regions, such as depressed areas and large nodules[22,23].

After completion of NBI with magnification, the pit pattern of each lesion was assessed with magnification chromoendoscopy performed using 0.4% indigo-carmine (IC) dye spraying. When high magnification observation with IC dye did not permit us to determine adequately the surface structure for pit pattern analysis, 0.05% crystal violet was applied for staining[24]. The visible pit pattern was then assessed during the course of the examination by the endoscopist conducting the procedure. All lesions were resected subsequently endoscopically or surgically and histological diagnosis was performed by three experienced pathologists based on the Vienna classification[25,26]. The depth of sm invasion was determined as being either sm-s < 1000 μm or sm-d ≥ 1000 μm[27]. After pathological diagnosis was completed on all resected lesions, three endoscopists (Fukuzawa M, Saito Y and Matsuda T) who performed the examination individually reviewed the endoscopic images of the NBI findings that were taken prior to treatment. All endoscopic images were chosen by one of these endoscopists. Their evaluation of the NBI images of the m/sm-s and sm-d lesions focused on the suspected areas, respectively, of higher grade dysplasia and deepest suspected invasion. Each characteristic of microvascular architecture was finally determined based on the agreement of at least two of the three reviewing endoscopists. Microvascular findings with a high frequency of sm-d were assessed as to whether those were significant sm-d indicators by univariate and multivariate analysis. In addition, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy were calculated for each microvascular architectural feature observed during NBI, as well as every pit pattern diagnosis determined by magnification chromoendoscopy. We then compared the various types of microvascular architectural characteristics revealed by NBI with magnification to the chromoendoscopy pit pattern diagnoses.

The protocol for this study was approved by our institutional review board and all patients gave written informed consent.

Chromoendoscopy with magnification

Our pit pattern evaluation method relied on the clinical classification system proposed by Fuji et al[28] and Matsuda et al[29], with reference to the Kudo Classification System. Lesions were categorized into noninvasive and invasive...
patterns. The noninvasive pattern included regular crypts with or without a demarcated area (e.g. depression, large nodule, or reddened area) and irregular pits without a demarcated area, and are usually observed in Kudo’s types IIIa, IIIb, IV and V1 without demarcated areas (e.g. adenomatous polyps, m and sm-s cancers), with endoscopic resection being the appropriate treatment. The invasive pattern was characterized by irregular and distorted crypts in a demarcated area, as observed in Kudo’s type V2s and V1 with a demarcated area (e.g. sm-d), and should be treated by surgical resection. As indicated, Kudo’s type V1 can be observed in either noninvasive or invasive patterns. Those differences are dependent on the presence or absence of a demarcated area.

**Microvascular architecture of ECC**

Microvascular architectural images taken during magnification colonoscopy with NBI were reviewed retrospectively by three endoscopists who referenced the microvascular architectural features of superficial esophageal carcinoma[^8^], and included the following characteristics: (1) caliber, narrow or wide; (2) caliber regularity, positive or negative; (3) meandering, positive or negative; (4) vessel regularity, positive or negative; (5) vessel length, short or long; and (6) vessel density, non-dense or dense. These characteristics were evaluated by comparing the NBI with magnification images to representative photographs of model examples (Figure 1).

**Statistical analysis**

We compared microvascular architecture as revealed by NBI with magnification to histological findings using the $\chi^2$ test of independence or Fisher’s exact test for univariate analysis. Variables with a $P$ value of $< 0.05$ in our univariate analysis were subsequently included in a logistic regression multivariate analysis. The StatView program, version 5.0 (SAS Institute, Cary, NC, USA), was used for data analysis and $P < 0.05$ was considered to be statistically significant.

**RESULTS**

**Clinicopathological features of patients and lesions**

The clinicopathological details of the patients and colorectal lesions involved in this study are shown in Table 1.

**Univariate analysis**

Univariate analysis indicated characteristics involving vessel density: non-dense ($P < 0.0001$); vessel regularity: negative ($P < 0.0001$); caliber regularity: negative ($P < 0.0001$); vessel length: short ($P < 0.0001$); and vessel meandering: positive ($P = 0.002$) occurred significantly more often with sm-d invasion than m/sm-s invasion (Table 2).

**Multivariate analysis**

Multivariate analysis demonstrated that sm-d invasion was independently associated with vessel density: non-dense [odds ratio (OR) = 402.5, 95% confidence interval (CI): 12.4-13133.1]; and vessel regularity: negative (OR = 15.9, 95% CI: 1.2-219.1) (Table 2). The sensitivity, specificity, PPV, NPV and diagnostic accuracy rate for each characteristic are shown in Table 3. The two vascular findings that were confirmed by multivariate analysis had the highest values for specificity, PPV and accuracy (non-dense vessel density: specificity 0.99, PPV 0.95, accuracy 90.2%; negative vessel regularity: specificity 0.99, PPV 0.95, accuracy 90.2%).

**Pit pattern diagnosis**

The pit patterns of 21 m/sm-s lesions were evaluated following IC dye spraying, whereas the pit patterns of the other 48 m/sm-s lesions and all 43 sm-d lesions were assessed after crystal violet staining. We subsequently calculated the sensitivity, specificity, PPV, NPV and accuracy in differentiating m/sm-s from sm-d for: (1) the pit patterns that were diagnosed as being invasive; and (2) the NBI with magnification characteristic findings of (a) non-dense vessel density and/or negative vessel regularity and (b) non-dense vessel density and negative vessel regularity, which were both considered to be indicators for sm-d invasion. Pit pattern analysis sensitivity, specificity, PPV, NPV and diagnostic accuracy were 0.86 (95% CI: 0.72-0.95), 0.99 (0.92-0.99), 0.97 (0.86-0.99), 0.92 (0.83-0.97) and 93.8%, respectively. The NBI with magnification characteristic findings of non-dense vessel density and negative vessel regularity were comparable to pit pattern diagnosis results [0.81 (0.67-0.92), 1.00 (0.95-1.00), 1.00 (0.90-1.00), 0.90 (0.81-0.95), 92.9%] (Table 4). Seven of the lesions in this study were incorrectly diagnosed using pit pattern analysis including six sm-d lesions mistakenly diagnosed as m/sm-s invasion depth. In two of these cases, however, both non-dense vessel density and negative vessel regularity had also been observed by magnification NBI, which suggests its potential use as a supplementary diagnostic tool to pit pattern diagnosis (Figures 2 and 3).

**DISCUSSION**

It has been reported previously that observation of intra-

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**Table 1** Clinicopathological features of evaluated colorectal lesions

| Lesions (n = 112) | m/sm-s | sm-d |
|------------------|--------|------|
| Gender (male/female) | 42/27  | 24/19 |
| Age (range, yr) | 63.2 (57-79) | 62.5 (52-80) |
| Location | Right colon | 29 | 15 |
| Morphology[^1^] | Ip/Is/Isp | 21 | 18 |
| Ip/IIa + Ip/Ic | 10 | 16 |
| Isp-G | 20 | 5 |
| Isp-NG | 18 | 4 |
| Mean size (range, mm) | 32.3 (10-100) | 24.4 (10-90) |

[^1^] Update on the Paris classification of superficial neoplastic lesion in the digestive tract[^10^]. LST-G: Laterally spreading tumor-granular type; LST-NG: Laterally spreading tumour-non granular type; m/sm-s: Mucosal/submucosal superficial; sm-d: Submucosal-deep.
papillary capillary loops by magnification endoscopy is useful in the diagnosis of invasion depth of superficial esophageal cancer\cite{[10],[11]}. The intra-papillary capillary loops can be seen in the normal esophageal mucosa by mag-

Table 2  Microvascular architecture & invasion depth

| Variables             | Univariate analysis | Multivariate analysis |
|-----------------------|---------------------|-----------------------|
|                       | P-value\(^1\)       | Odds ratio            | 95% CI                |
| Vessel density        | Non-dense/dense     | < 0.001               | 0.001                 | 402.5 | 12.4-13133.1 |
|                       | m/sm-s              | 1/68                  |                       |       |               |
|                       | sm-d                | 33/10                 |                       |       |               |
| Vessel regularity     | Negative/positive   | < 0.001               | 0.038                 | 15.9  | 1.2-219.1    |
|                       | m/sm-s              | 8/61                  |                       |       |               |
|                       | sm-d                | 38/5                  |                       |       |               |
| Caliber regularity    | Negative/positive   | < 0.001               | 0.056                 | 17.3  | 0.9-323.4    |
|                       | m/sm-s              | 44/25                 |                       |       |               |
|                       | sm-d                | 42/1                  |                       |       |               |
| Vessel length         | Short/long          | < 0.001               | 0.161                 | 0.2   | 0.01-2.10    |
|                       | m/sm-s              | 20/49                 |                       |       |               |
|                       | sm-d                | 37/6                  |                       |       |               |
| Meandering            | Positive/negative   | 0.002                 | 0.110                 | 0.1   | 0.01-1.60    |
|                       | m/sm-s              | 49/20                 |                       |       |               |
|                       | sm-d                | 41/2                  |                       |       |               |
| Caliber               | Wide/narrow         | NS                    |                       |       |               |
|                       | m/sm-s              | 62/7                  |                       |       |               |
|                       | sm-d                | 41/2                  |                       |       |               |

\(^1\)\(\chi^2\) or Fisher’s test. 95% CI: 95% confidence interval; NS: Not significant.
In cancerous lesions, characteristic changes of the intrapapillary capillary loops can be seen in the superficial mucosa according to the depth of tumor invasion. There have been few studies to assess invasion depth in cancerous lesions from microvascular architecture. However, the NBI system enabled observation of such the estimated depth was intramucosal and this LST-NG lesion was treated by endoscopic submucosal dissection.

Figure 2  35 mm laterally spreading tumor, non-granular (LST-NG) type, located in the ascending colon. A: Conventional colonoscopy image; B: Conventional colonoscopy image following 0.4% IC dye spraying; C: Narrow-band imaging (NBI) with magnification image at center of the lesion enclosed by the red box in A. Microvascular architecture consisted of non-dense vessel density and negative vessel regularity; D: Crystal violet staining image; E: Magnification view of the portion enclosed by the red box in D revealed a noninvasive pattern; F: Magnification view of the portion enclosed by the yellow box in D also revealed a noninvasive pattern, such the estimated depth was intramucosal and this LST-NG lesion was treated by endoscopic submucosal dissection.

Figure 3 Stereomicroscopic view and histological images. A: Stereomicroscopic view; B: Red lines indicate submucosal penetration of the tumor; C: Histological diagnosis at dotted line in A was a well-differentiated adenocarcinoma and depth of invasion was sm (1300 mm) shown with the arrow. Invasion depth diagnosis using NBI with magnification was correct, based on findings of non-dense vessels and negative vessel regularity, but pit pattern diagnosis of this lesion was inaccurate.
Table 3  Assessment of the carcinomatous invasion depth based on microvascular architecture

| Microvascular architecture | Sensitivity (95% CI) | Specificity (95% CI) | PPV (95% CI) | NPV (95% CI) | Accuracy (%) |
|---------------------------|----------------------|----------------------|--------------|--------------|--------------|
| Vessel density            | 33/43                | 0.86 (0.72-0.95)     | 0.97 (0.85-0.99) | 0.87 (0.78-0.94) | 90.2         |
| Non-dense                 | 38/43                | 0.99 (0.92-0.99)     | 0.88 (0.80-0.99) | 0.84 (0.76-0.94) | 87.5         |
| Vessel regularity          | 38/43                | 0.99 (0.92-0.99)     | 0.88 (0.80-0.99) | 0.84 (0.76-0.94) | 87.5         |
| Negative                  | 38/43                | 0.99 (0.92-0.99)     | 0.88 (0.80-0.99) | 0.84 (0.76-0.94) | 87.5         |
| Caliber regularity         | 42/43                | 0.99 (0.92-0.99)     | 0.88 (0.80-0.99) | 0.84 (0.76-0.94) | 87.5         |
| Negative                  | 42/43                | 0.99 (0.92-0.99)     | 0.88 (0.80-0.99) | 0.84 (0.76-0.94) | 87.5         |
| Vessel length              | 37/43                | 0.99 (0.92-0.99)     | 0.88 (0.80-0.99) | 0.84 (0.76-0.94) | 87.5         |
| Short                      | 37/43                | 0.99 (0.92-0.99)     | 0.88 (0.80-0.99) | 0.84 (0.76-0.94) | 87.5         |
| Meandering                | 41/43                | 0.99 (0.92-0.99)     | 0.88 (0.80-0.99) | 0.84 (0.76-0.94) | 87.5         |
| Positive                  | 41/43                | 0.99 (0.92-0.99)     | 0.88 (0.80-0.99) | 0.84 (0.76-0.94) | 87.5         |
| Caliber                    | 41/43                | 0.99 (0.92-0.99)     | 0.88 (0.80-0.99) | 0.84 (0.76-0.94) | 87.5         |
| Wide                      | 41/43                | 0.99 (0.92-0.99)     | 0.88 (0.80-0.99) | 0.84 (0.76-0.94) | 87.5         |

PPV: Positive predictive value; NPV: Negative predictive value.

Table 4  Assessment of the carcinomatous invasion depth: comparison between microvascular architecture & pit pattern analysis

| Microvascular architecture | Sensitivity (95% CI) | Specificity (95% CI) | PPV (95% CI) | NPV (95% CI) | Accuracy (%) |
|---------------------------|----------------------|----------------------|--------------|--------------|--------------|
| Non-dense vessel density  | 38/43                | 0.86 (0.72-0.95)     | 0.97 (0.85-0.99) | 0.87 (0.78-0.94) | 90.2         |
| and/or negative vessel regularity | 35/43 | 0.99 (0.92-0.99) | 0.88 (0.80-0.99) | 0.84 (0.76-0.94) | 87.5         |
| Non-dense vessel density  | 38/43                | 0.99 (0.92-0.99)     | 0.88 (0.80-0.99) | 0.84 (0.76-0.94) | 87.5         |
| and negative vessel regularity | 37/43 | 0.99 (0.92-0.99) | 0.88 (0.80-0.99) | 0.84 (0.76-0.94) | 87.5         |
| Pit pattern               | 37/43                | 0.99 (0.92-0.99)     | 0.88 (0.80-0.99) | 0.84 (0.76-0.94) | 87.5         |
| (Invasive pattern)        | 37/43                | 0.99 (0.92-0.99)     | 0.88 (0.80-0.99) | 0.84 (0.76-0.94) | 87.5         |

microvascular architecture of the tumor surface in the GI tract. In a similar fashion, we used NBI with magnification to investigate whether or not quantitative ECC invasion depth diagnosis was possible based on analysis of capillary vessel patterns instead of pit patterns. Based on our results, it appeared that non-dense vessel density and negative vessel regularity, as observed by NBI with magnification, could be diagnostic indicators of sm-d invasion, as effectively as pit pattern analysis.

Regular hexagonal or honeycomb-like capillary patterns are formed around the crypts of normal colorectal mucosa. In contrast, it has been reported that these capillaries are larger in tumor adenomas, whereas vascular disruption, caliber irregularity and dense vessels have been observed in severe atypical cases. In addition, vascular changes do not generally occur in non-neoplastic lesions such as hyperplastic polyps, with the exception of inflammatory polyps. The NBI technique provides clearer observation of microvascular architectural characteristics, therefore, it has been reported that differentiation of neoplastic from non-neoplastic lesions on the basis of different vascular patterns is equally possible using NBI or chromoendoscopy, and pit pattern diagnosis has likewise been explored using NBI. Previous studies have shown that the accuracy of pit pattern diagnosis of invasion depth by magnification endoscopy was 98.8%, whereas such diagnostic accuracy in this study was 93.8%.

The area surrounding crypts in the superficial layer of the mucosa is covered with capillaries and has previously been recognized as a pit using the NBI technique. Machida et al have reported that NBI pit pattern diagnosis is significantly more useful (P < 0.001) than conventional observation, but inferior to chromoendoscopy (P < 0.05). Hirata et al have reported that overall diagnostic consistency in pit patterns between magnification NBI and dye-spraying observations was 84%, but even higher for types II, III, IV and V pit patterns, although somewhat lower at 78%, for the type V pit pattern. In addition, Tischendorf et al have reported that there is no significant difference in the PPVs for neoplastic lesions as determined by pit pattern and vascular findings using NBI. There was a discrepancy, however, between two endoscopists in their NBI pit pattern diagnosis of types III-V neoplastic lesions. This may have been because the actual pit structure was not observed using the NBI technique, unlike the results from the contrast and staining methods; or, it could have been caused by the NBI pit pattern diagnosis of types III-V lesions, which are considered particularly important in determining the most suitable method of treatment, not having been performed accurately.

More recently, Katagiri et al have reported that capillary patterns observed by NBI with magnification are highly accurate in distinguishing between low-grade and high-grade dysplasia/invasive cancer, and thus could be used to predict the histopathological features of colorectal neoplasia. In addition, Hirata et al have reported vascular findings of significant sm-d invasion based on their NBI observation of thick blood vessels with irregularity on the surface of tumors. This differs somewhat from the results of our investigation, but the difference could be caused by a number of factors, such as variations in our respective definitions of vascular findings, and the macroscopic types of lesions involved in the two studies.
Magnification observation with dye spraying and staining, in particular crystal violet staining, however, can be time-consuming. Patient symptoms including abdominal discomfort and peristalsis are more likely to appear in longer duration colonoscopy examinations, which may render detailed observation more problematic. In contrast, the press of a single button on the handle of the endoscope with the NBI system can almost immediately change from NBI to the conventional view and back again, thereby shortening examination times and reducing the burden on patients and endoscopists alike. A mucous attachment on the endoscope can also interfere with diagnosis, and washing the surface of a lesion with pronase solution takes additional time during pit pattern diagnosis by magnification colonoscopy with IC dye spraying or crystal violet staining. Hirata et al.14 have further reported that NBI observation results in more accurate pit pattern diagnosis than dye spraying observation in cases with mucous attachment.

Our study suffered from some limitations. First, the NBI assessments were made on still images by three endoscopists, whereas the pit pattern diagnosis was done in real time after initial inspection with NBI, which could account for some further bias. Second, the different NBI features of the microvasculature are not independent: the endoscopist is not blinded to one feature if he scores the other. In addition, lesions that were diagnosed histologically as cancer had a diameter of at least 10 mm, thus lesions < 10 mm in diameter were not assessed in this study. Accordingly, future prospective studies will require that relevant data be accumulated and analyzed on a more objective basis.

In conclusion, the results of this study indicated that two microvascular architectural characteristics, non-dense vessel density and negative vessel regularity, observed using NBI with magnification during colonoscopy examinations could be reliable indicators of ECC sm-d invasion.

ACKNOWLEDGMENTS
The authors wish to thank Christopher Dix for his assistance in helping to edit this manuscript.

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