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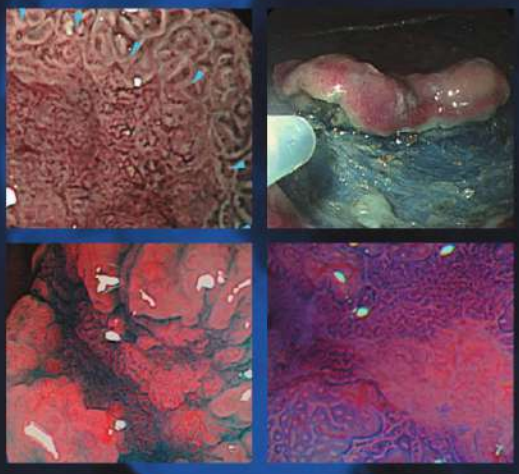
New Challenges in Gastrointestinal Endoscopy



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New Challenges in Gastrointestinal Endoscopy

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Image Enhanced Endoscopy (IEE) Using NBI During Screening Colonoscopy: Usefulness and Application

Yasushi Sano

Summary. We review magnified observations of the microvascular architecture of colorectal lesions, and discuss the utility of detailed observations of this architecture for differential diagnosis during narrow-band imaging (NBI) colonoscopy. Angiogenesis is critical to the transition of premalignant lesions in a hyperproliferative state to the malignant phenotype. Therefore, diagnosis based on angiogenic or vascular morphological changes might be ideal for the early detection or diagnosis of neoplasms. In this review, we propose the term "meshed capillary" for nonneoplastic lesions in order to distinguish them from neoplastic lesions, and the capillary classification "capillary pattern" for the differential diagnosis of colorectal lesions. We believe that the combined use of NBI optical equipment-based image-enhanced endoscopy (IEE) and real chromoendoscopy decreases the time and cost of screening colonoscopy. To assess the feasibility and efficacy of using the NBI system, further studies are required for colorectal lesions and other lesions of the gastrointestinal tract.

Key words. Narrow-band imaging system, Colonoscopy, Microvascular architecture, Capillary pattern, Optical equipment-based image-enhanced endoscopy (IEE)

Introduction

The detection and subsequent removal of neoplastic colorectal lesions, including adenomatous polyps and early cancers, have been reported to reduce the incidence of colorectal cancers, based on the concept of the adenoma–carcinoma sequence [1]. Therefore, the roles of screening colonoscopy and polypectomy are becoming more important because colorectal cancer is the third most common cause of cancer mortality, and the incidence of colorectal cancer in Japan is increasing [2]. Although efficacious colonoscopy is recommended, it has been reported that 10% to 30% of resected polyps are nonneoplastic lesions that did not need to be removed [3]. Therefore, distinguishing between nonneoplastic lesions and neoplastic lesions

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can increase the efficiency of treatment by eliminating the time and cost of unnecessary polypectomy [4,5]. The narrow-band imaging (NBI) system is based on modifying spectral features by narrowing the bandwidth of spectral transmittance with optical filters. Since 1999, we have been developing our own NBI system with support from a Grant for Scientific Research Expenses for Health and Welfare Programs, Japan. NBI modification provides a unique image emphasizing the capillary pattern and the surface structure [6–8]. In our pilot study, the NBI system was sufficient to distinguish between nonneoplastic lesions and neoplastic lesions, and had a special feature allowing otherwise invisible endoscopic findings to be visualized without a dye solution. [8–11].

In this chapter, we describe the usefulness of NBI in screening colonoscopy and target optical IEE, and discuss the utility of detailed observations of the microvascular architecture for differential diagnosis during colonoscopy.

Improvement of Visibility

Our pilot study found that, compared with normal observations, clearer observation of the capillary vessels in the network on the surface layer of the mucosa is possible using the NBI system. [9] Therefore, recognizing the lesion becomes easier, since the permeable image of the vessels is interrupted. On normal mucosa, a regular hexagonal or honeycomb-like pattern is found around the crypt of the gland. On the other hand, in a neoplastic lesion these vessels become thicker, and disruption of the vessels, differences in the diameters of the vessels, and a rise in vessel density can be found when the abnormality gets worse. Since the filter of NBI is adjusted to Hb absorption characteristics, a brownish area can be found if the observation area contains a large number of capillary vessels (Fig. 1). Contrast enhancement of the lesion makes the disruption of the normal vessel network in colonic lesions obvious, and improves the visualization [11,22].

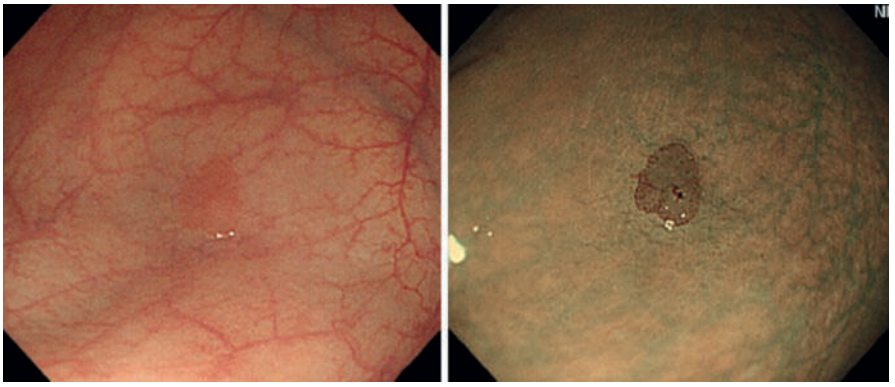


Fig. 1. Brownish area and typical endoscopic features of a flat adenomatous polyp on narrow-band imaging (NBI). **a** Standard colonoscopy. A 0–IIa type lesion, 4 mm in size, can be seen in the rectum. **b** NBI without any dye spraying. The lesion can be seen as a dark brown lesion (*brownish area*)

Improvement in the Observation of the Surface Structure (Pit Pattern) and the Microcapillaries (Capillary Pattern [CP])

Several studies have reported that observations using chromoendoscopy, as well as chromoendoscopy with a magnifying function, is helpful for differentiating neoplasia from nonneoplasia. In our pilot study [9], the accuracy of endoscopic diagnosis was 79.1% with conventional colonoscopy and 93.4% with NBI colonoscopy. This was similar to that with chromoscopy. Therefore, by combining the NBI system with the magnifying function, it is expected that it will be possible to infer the pit pattern on the surface layer of the mucosa without any staining, and obtain as accurate a diagnosis as that obtained with optical chromoendoscopy.

The NBI modification provides a unique image which emphasizes the capillary pattern as well as the surface structure. Angiogenesis is critical to the transition of premalignant lesions in a hyperproliferative state to the malignant phenotype [12–14]. Therefore, a diagnosis based on the angiogenic or vascular morphological changes might be ideal for the early detection or diagnosis of neoplasms. We have described the utility of detailed observations of microvascular architecture for differential diagnosis during NBI colonoscopy [10,15]. We named the mucosal capillary meshwork which is arranged in a honeycomb pattern around the mucosal glands "meshed capillary" (MC), and using NBI colonoscopy with magnification we classified the microvascular architecture into 3 types, i.e., capillary pattern (CP) types I, II, and III [15,20,21,22]. These capillary vessels, which can be observed clearly by NBI, are thought to be similar to observations of capillary vessels of around 300 μm, according to the Monte Carlo simulation that we conducted [16]. The definition of each CP is summarized in Fig. 2 and described in detail below.

Normal Colonic Mucosa (CP: Type I)

Using NBI colonoscopy without magnification, not only thick veins and capillaries but also fine capillaries can be seen as a brown color. The vessel network of the mucosa is well visualized in much finer detail on NBI colonoscopy than on standard colonoscopy. However, the mucosal capillary meshwork (MC) arranged in a honeycomb pattern around the mucosal glands is invisible, or only faintly visible, under magnifying observations using NBI colonoscopy (Fig. 3a), because the endoscopic resolution is not sufficient to visualize the network. The diameter of the vessels was reported to be from 8.6 ± 1.8 μm to 12.4 ± 1.9 μm (range 6.4–20.9 μm) [13,14].

Hyperplastic Polyp (CP: Type I)

Most hyperplastic polyps can be seen as light brown lesions without neovascularization on NBI colonoscopy. A Kudo's type II pit pattern can be seen by magnifying observations using NBI without any dye solution [17]. In many cases the mucosal capillary meshwork is invisible, or only faintly visible, under magnifying observations using NBI colonoscopy because the endoscopic resolution is not sufficient to visualize

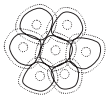
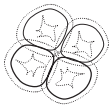
	Schematic micro-vessel architecture	Capillary characteristics	Vessel diameter (μm) (minimum – maximum)	Visibility using NBI (Capillary pattern classification)
Normal mucosa		Mucosal capillary network (meshwork) arranged in a honeycomb pattern around the mucosal glands.	8.6±1.8 to 12.4±1.9 (6.4 - 20.9)	MC vessel: Invisible ~ faintly visible (Capillary pattern type I)
Hyperplastic		Mucosal capillary network (meshwork) arranged in a honeycomb pattern around the mucosal glands.	< 10	MC vessel: Invisible ~ faintly visible (Capillary pattern type I)
Adenoma		Vascular casts showed that the microvasculature have a similar organization to the normal colon. However, capillaries are elongated and have increased diameters compared to normal.	13.1+3.3	MC vessel: Clearly visible Slightly thicker capillary Capillary density: loose (Capillary pattern type II)
Carcinoma	 	Vascular casts of colonic carcinoma is characterized by a disorganized structure and increased density of microvessels. The increased number and density of microvessels results in formation of nodular clusters of capillaries.	18.3±0.1 to 19.8±7.6 (2.2 – 84.5)	MC vessel: Clearly visible thicker capillaries, unevenly sized with branching and curtailed irregularity. (Capillary pattern type IIIA) MC vessel: Presence of a nearly avascular or loose microvascular area due to histological desmoplastic changes in the stromal tissue (Capillary pattern type IIIB)

Fig. 2. Sano's endoscopic microvascular classification of colorectal lesions using NBI (Sano's classification of capillary patterns)

the network (Fig. 3b). We have previously reported that intratumor microvessel density in a small hyperplastic polyp was significantly higher than that in normal mucosa, but that the vessel diameter was not significantly larger than in normal mucosa [18]. However, MC vessels are sometimes recognized in parts of hyperplastic polyps such as large hyperplastic polyps [5,15] or hyperplastic polyps with serrated adenomatous changes [5,15].

Adenomatous Lesion (CP: Type II)

Adenomatous lesions, including the flat and depressed types, can be seen as dark brown neovascular lesions (a brownish area) on NBI colonoscopy without magnification, and are easily detected while withdrawing from NBI colonoscopy. A Kudo's type III or IV pit pattern, demarcated by the appearance of MC vessels, can be seen by magnifying observations using NBI without the application of any dye solution [8,15]. MC vessels are clearly visible because the capillaries are elongated and have increased diameters compared with normal capillaries (Fig. 3c). The vessel diameter has been reported to be 13.1 ± 3.3 μm [13,14].

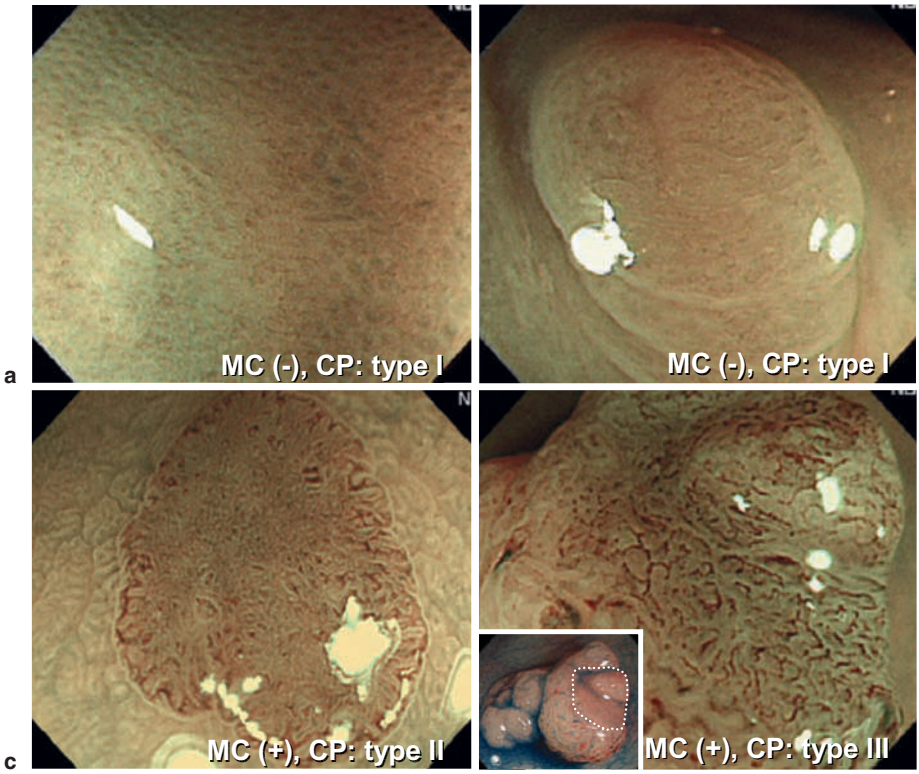


Fig. 3. Magnifying endoscopic findings of macrocapillary vessels using NBI in normal colonic mucosa, hyperplastic polyps, adenomas, and carcinomas. **a** Normal colonic mucosa. In many cases the mucosal capillary meshwork arranged in a honeycomb pattern around the mucosal glands is invisible, or only faintly visible, with magnifying observation using NBI colonoscopy, because the endoscopic resolution is not high enough to visualize the network (MC (−), CP: type I). **b** Hyperplastic polyps. In many cases the mucosal capillary meshwork is invisible, or only faintly visible, with magnifying observation using NBI colonoscopy, because the endoscopic resolution is not high enough to visualize the network (MC (−), CP: type I). **c** Adenomatous polyps. MC vessels are clearly visible, because these capillaries are elongated and have larger diameters than normal capillaries. The honeycomb-like pattern of capillaries on the surface of the tumor is retained (MC (+), CP: type II). **d** Carcinoma in adenomas (magnified view of the demarcated area *lower left*, chromoendoscopic view). The microvascular architecture of colonic carcinoma is characterized by a disorganized structure and an increased density of microvessels. MC vessels are clearly visible and show unevenly sized, thicker capillaries which are branching, curtailed, and irregular (MC (+), CP: type IIIA)

Intramucosal and Superficial Submucosal Cancer (CP type IIIA)

The MC vessels are clearly visible and show unevenly sized thicker capillaries (diameter: >18 μm) with branching and curtailed irregularity when compared to adenomatous polyps. MC vessels of intramucosal and superficial submucosal cancer (Sm1) are

characterized by a lack of uniformity (blind ending, branching) and an increased density of microvessels. Therapeutically, lesions diagnosed as CP type IIIA should be resected by snare polypectomy, EMR or ESD (Fig. 3d).

Deep Submucosal Invasive Cancer (CP type IIIB)

Microvascular observation of colorectal cancer lesions under magnifying NBI has demonstrated that, in addition to the characteristics shown by CP type III lesions, a lesion showing a clear distinction between normal/cancerous mucosa on the surface and, presence of a nearly avascular or loose microvascular area due to histological desmoplastic changes in the stromal tissue, are highly associated to deep submucosal invasion or beyond [23,24]. Therapeutically, lesions diagnosed as CP type IIIB should be removed surgically.

Recently, Katagiri et al. reported that capillary patterns observed by NBI with magnification provided high accuracy for distinction between low grade dysplasia (CP-II) and high grade dysplasia/invasive cancer (CP-III). Sensitivity and specificity were 90.3% and 97.1% respectively. The overall accuracy was 95.5% [20].

Histological Findings of Microvascular Proliferation

We evaluated microvascular proliferation with CD-31 immunohistochemical staining in normal colonic mucosa, hyperplastic polyps, adenomas, and carcinomas (Fig. 4). Many microcapillary vessels measuring less than 10 μm could be seen in the stroma at the surface of normal colonic mucosa and hyperplastic polyps. However, adenomatous and cancerous lesions with thicker capillary vessels (20–30 μm) could be seen surrounding glands just under the basal membrane at the surface. These findings suggest that MC vessels were histologically confirmed to be dilated, with increased microvasculature and vessel diameters in the superficial portion of adenomatous and cancerous lesions, by immunohistochemical staining with antihuman monoclonal CD-31 antibody [19].

A Bench Study: Comparison Between Endoscopic Resolution and MC Vessels

MC vessels in normal colonic mucosa and hyperplastic polyps are invisible, or only faintly visible, under magnifying observation using NBI colonoscopy. To evaluate the correlation between endoscopic resolution and the visibility of MC vessels, a square plate (TOPPAN-TEST-CHART-NO1) was used in this bench study. As previously reported, the diameter of MC vessels ranges from 8 to 12 μm in normal colonic

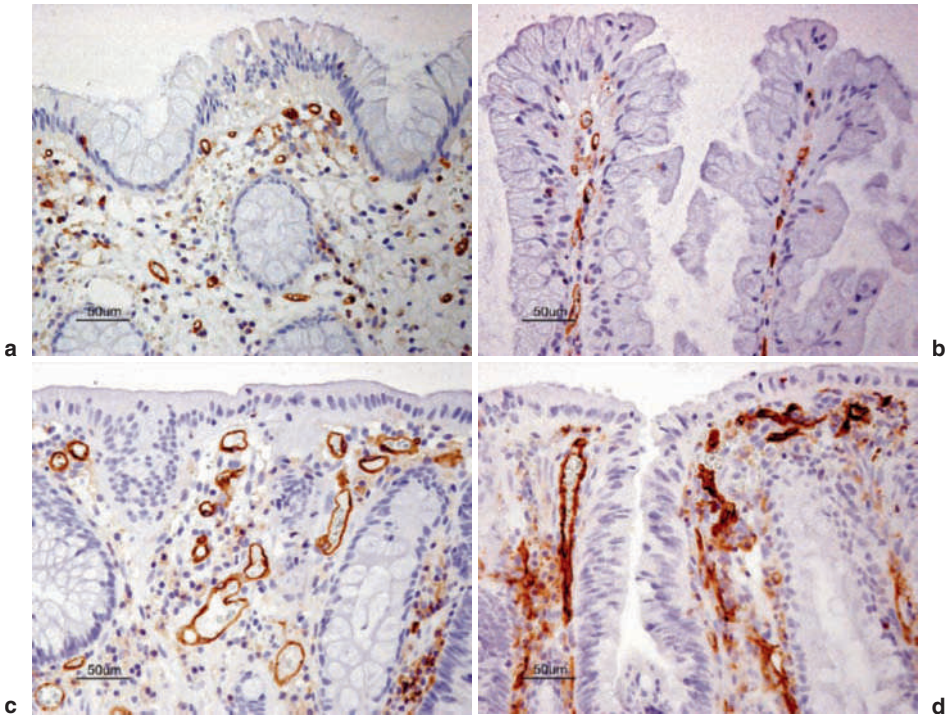


Fig. 4. Histological findings of macrocapillary vessels in normal colonic mucosa, hyperplastic polyp, adenoma, and carcinoma. All specimens are stained for endothelial cells with an anti-CD31 antibody (clone JC/70A, DAKO, dilution 1:20). Original magnification ×100. **a** The superficial portion of normal colonic mucosa. Many microcapillary vessels, measuring approximately 10 μm, can be seen in the stromal tissue. **b** The superficial portion of a hyperplastic polyp. Many microcapillary vessels, measuring approximately 10 μm, can be seen in the stromal tissue as in normal mucosa. **c** The superficial portion of an adenomatous polyp. Thicker capillary vessels can be seen surrounding the adenomatous glands. **d** The superficial portion of a well-differentiated adenocarcinoma. Thicker capillary vessels can be seen surrounding the cancerous glands

mucosa and hyperplastic polyps [12–14]. As shown in Fig. 5a, the bars on the square plate, which are approximately 8–12 μm when adjusted to the same scale as the polyp, are not clearly visible or distinguishable owing to the endoscopic resolution. On the other hand, MC vessels in adenomatous or cancerous lesions are in the range 13–20 μm [12–14]. These vessels are clearly visible on NBI colonoscopy with magnification (Fig. 5c). In this bench study, the bars on the square plate, which are approximately 14–20 μm when adjusted to the same scale as the polyp, are clearly visible. Therefore, the presence of MC vessels on magnifying endoscopy using NBI is a useful indicator for distinguishing between hyperplastic polyps and adenomatous polyps.

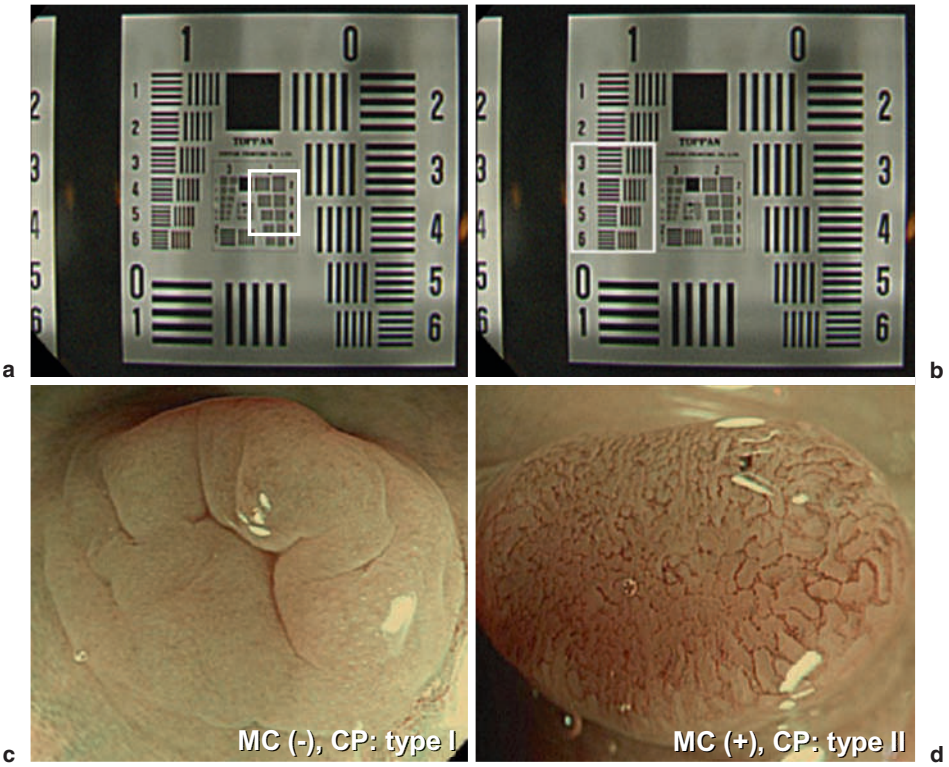


Fig. 5. Comparison between endoscopic resolution and meshed capillary vessels. **a** Magnified observation of a square plate (TOPPAN-TEST-CHART-NO1), 3 mm in size. The area highlighted relates to the bars, which are approximately 8–12 μm, which are not clearly visible or distinguishable due to the endoscopic resolution. **b** Magnified observation of a hyperplastic polyp, also 3 mm in size, MC (−), CP: type I. At this magnification, it is not possible to identify the MC vessels which are only 8–12 μm in diameter, as shown in Fig. 6a. **c** Magnified observation of a square plate (TOPPAN-TEST-CHART-NO1), 3 mm in size. The area highlighted relates to the bars, which are approximately 14–20 μm, which are clearly visible at this magnification. **d** Magnified observation of an adenomatous polyp, also 3 mm in size, MC (+), CP: type II. It is possible to identify the MC vessels which are 14–20 μm, as shown in Fig. 5c

Future Prospects

Diagnoses on the basis of mucosal patterns have been reported to be correlated with histological diagnoses. Chromoendoscopy is often used, as it is a contrast staining method using a biocompatible dye agent such as indigo carmine. In mucosa with glands, the dye agents accumulate within crypt orifices. Although chromoendoscopy is effective in many applications, it is still only an optional diagnostic method because of the time needed, the additional cost, and the necessity of complete mucus removal. In this review, we have described the utility of detailed observations of the microvas-

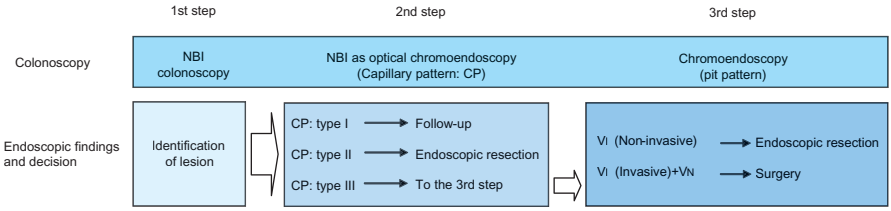


Fig. 6. Three-step strategy for the management of colorectal lesions using conventional colonoscopy, NBI colonoscopy, and chromoendoscopy. When you find a lesion in a normal observation, observe it with NBI mode. If the result is CP: Type I, follow-up is recommended, if it is CP: Type II, resection is recommended, and if it is CP: Type III, conduct chromoendoscopy and observe the pit pattern (VI or VN) carefully before deciding on the treatment policy

cular architecture for differential diagnosis during NBI colonoscopy. An NBI modification provides a unique image that emphasizes the capillary pattern and the surface structure. Our initial data indicate that NBI may be as effective, or more effective, than chromoscopy without the same problems [9].

Angiogenesis is critical to the transition of premalignant lesions in a hyperproliferative state to a malignant phenotype. Therefore, a diagnosis based on the angiogenic or vascular morphological changes might be ideal for the early detection or diagnosis of neoplasms. In this review, we have proposed the term "meshed capillary" (MC) to distinguish between nonneoplastic and neoplastic lesions, and the capillary classification "capillary pattern" (CP) for the differential diagnosis of colorectal lesions. On the basis of previous investigations, the surface microvascular architecture in colorectal lesions can be divided into three patterns: (1) honeycomb-like capillaries in the normal mucosa and hyperplastic polyps (8–12 μm); (2) elongated meshwork capillaries with a greater diameter in adenomatous lesions (approximately 13 μm); (3) disorganized meshwork capillaries with an increased density of microvessels in cancerous lesions (18–19 μm) [12–14]. These capillary patterns can easily be recognized using NBI colonoscopy, and we believe that the combined use of NBI and real chromoendoscopy decreases the time and cost of screening colonoscopy. The three-step strategy for the management of colorectal lesions using these procedures is shown in Fig. 6. However, at the present time, NBI colonoscopy may not be superior to chromoendoscopy for distinguishing between endoscopically treatable early invasive cancers and untreatable cancers. We should use the three different procedures without getting them confused.

In the near future, we hope that NBI procedures will become standard for screening and surveillance colonoscopy. To assess the feasibility and efficacy of using the NBI system, further studies are required for colorectal lesions and other lesions of the gastrointestinal tract.

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