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ORIGINAL ARTICLE

Magnification Endoscopy With Acetic Acid Enhancement and a Narrow-Band Imaging System for Pit Pattern Diagnosis of Colorectal Neoplasms

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Background and Goals: Pit pattern (PP) analysis of colorectal neoplasms using magnification chromoendoscopy with crystal violet (CV-MCE) is useful for predicting histologic features, but it is time consuming. Capillary pattern analysis by magnification endoscopy with narrow-band imaging (NBIME) is a useful and simpler procedure, but its diagnostic accuracy may be inferior to CV-MCE. NBIME with acetic acid enhancement (A-NBIME) is effective for rapid visualization of gastric mucosal microstructures. We performed a prospective study to compare the diagnostic reliability and feasibility of A-NBIME and CV-MCE in PP diagnosis of colorectal neoplasms.

Study: The present study consisted of 3 protocols: Study-1 assessed 56 colorectal lesions photographed with A-NBIME and CV-MCE, and the endoscopic images were reviewed by 3 experts to compare the diagnostic concordance; study-2 assessed 202 colorectal lesions photographed with A-NBIME in 116 consecutive patients and the correlation between PP and histologic findings; study-3 randomly allocated 100 patients with colorectal lesions equally to A-NBIME and CV-MCE, and compared the procedure time and visible ratio of PP.

Results: The κ value for interobserver agreement for A-NBIME and CV-MCE was 0.71 (0.66 to 0.75) and 0.80 (0.75 to 0.85), respectively. Intraobserver agreement between modalities for each reviewer was 0.79 (0.70 to 0.88), 0.80 (0.71 to 0.90), and 0.74 (0.67 to 0.82). Non-neoplastic polyps and massively invasive submucosal adenocarcinomas were statistically related to type II and type VI-H/VN. The procedure time was statistically shorter with A-NBIME than with CV-MCE (31 vs. 81 s), and the visible ratio of PP was equivalent (98.9% vs. 98.3%).

Conclusions: A-NBIME is comparable with CV-MCE in PP diagnosis of colorectal neoplasms and is a simpler technique.

Key Words: pit pattern, narrow-band imaging, acetic acid, magnification endoscopy, colorectal neoplasm

(*J Clin Gastroenterol* 2014;00:000–000)

Received for publication October 26, 2013; accepted April 8, 2014.

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The authors declare that they have nothing to disclose.

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Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Website, www.jcge.com.

Magnification chromoendoscopy using crystal violet staining (CV-MCE) has made it possible to visualize the pit patterns (PPs) (the shape of the opening of a glandular crypt) of colorectal neoplasms clearly and to predict their histologic features.[1–8] Kudo et al[1] initially classified the PPs into 6 types (I, II, IIIs, IIIL, IV, V), and suggested that type I/II, type IIIL/IIIs/IV, and type V were indicators of non-neoplastic polyps, adenoma, and adenocarcinoma, respectively. The type V PP was further subclassified into irregular structure (VI) and nonstructure (VN) types to identify adenocarcinoma with submucosal massive invasion (invasion depth $>1000\,\mu m$) showing a high risk of regional lymph node metastasis.[9–12] To improve the diagnostic accuracy, the type VI PP was subclassified into low-grade and high-grade types. A meeting of a research project, funded by the Japanese Ministry of Health, Labor and Welfare, was held in December 2005 to discuss the subclassification of the type VI PP, and based on several reports, the type VI-high grade was defined as a condition in which the existing pit has been destroyed or severely damaged.[3,4,13,14] However, when we use CV-MCE as a diagnostic modality, the colorectal lesion must be skillfully stained with 0.05% crystal violet solution dripped from a dedicated spraying tube, which is a laborious and very time-consuming procedure in many cases.

Recently, it was reported that magnification endoscopy with narrow-band imaging (NBIME) is useful for predicting the histologic features of colorectal lesions.[15–21] It allows detailed visualization of capillary patterns without any staining, but the histologic predictability of this new diagnostic tool may be inferior to that of CV-MCE.[22]

Magnification endoscopy with acetic acid–enhanced narrow-band imaging (A-NBIME) has been proposed as an effective method for visualizing superficial mucosal microstructures of early gastric cancers rapidly.[23–25] This modality enables vivid observation of the crypts of the glandular epithelium as deep brown and of their intervening part (stromal area) as whitish, appearances that are considered to be due to reversible alterations of the molecular structure of cellular proteins persisting from several seconds to several minutes.[26,27] However, the efficacy of this diagnostic modality for colorectal neoplasms has not been fully elucidated. Therefore, we performed a prospective study to investigate the efficacy of A-NBIME for PP diagnosis of colorectal neoplasms compared with CV-MCE.

MATERIALS AND METHODS

A total of 219 patients (M:F = 129:90; median age = 68 y) examined by colonoscopy at Tottori Municipal

Hospital were enrolled in the present study. The enrolled patients were unselected populations who needed colonoscopy for their medical check-up or for the investigation of their lower gastrointestinal symptoms, such as diarrhea, constipation, positive occult blood test of the stool, etc.

This analysis consisted of 3 protocols: study 1 compared the diagnostic concordance of PPs of colorectal neoplasms between A-NBIME and CV-MCE; study 2 assessed the ability of PPs diagnosed by A-NBIME for the histologic prediction of colorectal neoplasms; and study 3 evaluated the feasibility of A-NBIME compared with CV-MCE. The protocol of this study was approved by the medical ethics committee of Tottori Municipal Hospital, and written informed consent was obtained from all participants.

Study 1: Diagnostic Concordance of PPs of Colorectal Neoplasms Between A-NBIME and CV-MCE

Between October 2010 and March 2011, 51 patients with a total of 56 colorectal lesions (7 hyperplasias, 28 adenomas, 21 adenocarcinomas) were enrolled in this study, and the PPs of each lesion was clearly photographed with both A-NBIME and CV-MCE (Fig. 1). First, the lesions were instilled with 1.5% acetic acid solution and observed by NBIME under acetic acid enhancement (supplementary videos 1 and 2, Supplemental Digital Contents 1 and 2, http://links.lww.com/JCG/A143, http://links.lww.com/JCG/A144). Second, after complete recovery from the acetic acid enhancement, the lesions were stained with 0.05% crystal violet solution, and the same portion checked by A-NBIME was observed by magnifying endoscopy under crystal violet staining. A single expert endoscopist (K.S.), who had experience with over 2000 cases of magnifying colonoscopies, classified the PPs in CV-MCE images into 8 types: type I, II, IIIs, IIIL, IV, VI-L, VI-H, and VN.[1,2,13]

In the present study, the lesions with type I PP were excluded, as this pattern is treated as a standardized pattern for the other PPs. Furthermore, as an increase in PPs with simple shapes, such as type II, IIIs, IIIL, and IV, may possibly raise the κ value for the interobserver diagnostic agreement, 8 lesions each with type II, IIIs, IIIL, IV, VI-H, VI-H, and VN PPs diagnosed by CV-MCE (total 56 cases) were enrolled in this study. Once 8 lesions in each PP with fine endoscopic images were collected, the enrollment of a lesion with the PP was terminated. CV-MCE images and corresponding A-NBIME images were each randomly arranged and independently reviewed by 3 experienced endoscopists (Y.A., N.I., and T.Y.), who were well versed in PP diagnosis by CV-CME, without any prior knowledge of the histologic findings. They judged the PPs of each modality at a 1-week interval. The PP of CV-MCE images was judged according to the criteria mentioned above, and the PP of A-NBIME images was also diagnosed principally according to that of CV-MCE images. However, as the staining degree of the stromal area, which is an important criterion for subclassification of the type V PP in CV-MCE, cannot be diagnosed with A-NBIME because of good discoloration by acetic acid, type V PPs were originally subclassified by our criteria as follows. The type VI-L PP shows irregularly arranged pits with various sizes and forms but with clear contours; the type VI-H PP shows highly destroyed pits with severely irregular arrangement and without clear contours; and the type VN PP is almost amorphous and difficult to recognize as a glandular structure.

The κ statistics with 95% confidence intervals were calculated as an interobserver agreement of PP diagnosis among the 3 reviewers for A-NBIME and CV-MCE, and intraobserver diagnostic agreement between modalities for each lesion was also analyzed for each reviewer. Although the adequate sample size for the κ statistics is still controversial,[28–30] it is reported that ≥ 50 items are necessary for calculating interobserver reliability.[28]

Study 2: Ability of PPs Recognized by A-NBIME to Predict Histologic Features

Between November 2009 and August 2011, 116 consecutive patients with a total of 214 colorectal lesions were prospectively enrolled in this study. The PPs of the lesions were photographed by A-NBIME, and their histologic features were assessed from endoscopically or surgically resected specimens. Endoscopic photographs were reviewed by the 3 experienced endoscopists (the same ones as in study 1), and the PP was judged independently. Also in this study, the κ statistics with 95% confidence intervals were calculated as an interobserver agreement of PP diagnosis among the 3 reviewers for all lesions. When 2 or all 3 reviewers agreed upon the PP, it was diagnosed as the inherent PP of the lesion. When the lesion was diagnosed as different patterns by all 3 reviewers, it was excluded from the present study as a disagreed lesion. The histologic diagnosis was based on the classification of the Japanese Research Society for Cancer of the Colon and Rectum.[12] The correlation between PPs visualized by A-NBIME and histologic features was analyzed.

Study 3: Feasibility of A-NBIME and CV-MCE

Between November 2009 and September 2010, a total of 100 patients with colorectal polyps were enrolled in study 3, and alternately allocated to the A-NBIME and CV-MCE groups. For A-NBIME, 1.5% acetic acid solution was injected directly from the forceps channel to contact the lesions, and PPs were diagnosed by NBIME under acetic acid enhancement. For CV-MCE group, a dedicated tube was inserted from the forceps channel, and the crystal violet solution was dripped onto the lesions. Finally, the subjects were washed out to eliminate excess crystal violet solution and the PPs were diagnosed by magnifying endoscopy under crystal violet staining. The procedure time, which was defined as the time from acetic acid injection or insertion of the spraying tube for crystal violet dye from the forceps channel to when the PP was diagnosed, was compared between groups. Furthermore, both endoscopic images were reviewed by 2 experienced endoscopists (K.S. and H.T.) regarding the visibility of the PP, and the visible ratio of PPs was compared between groups.

The first 30 lesions enrolled for each group were analyzed as a pilot study to calculate the sample size with a statistical power of 80% at a 2-sided α level of 0.05. In this pilot study, the mean procedure time and the visible ratio of the PP in A-NBIME versus CV-MCE were 33.1 ± 19.6 seconds (mean ± SD) versus 88.0 ± 36.2 seconds and 96.7% (29/30) versus 96.7% (29/30), respectively. Concerning the procedure time, to confirm the clinically meaningful difference of 30 seconds for each lesion, a sample size of 27 lesions would be needed to demonstrate the superiority of A-NBIME to CV-MCE. Concerning the visible ratio of the PP, to confirm the inferiority limit of

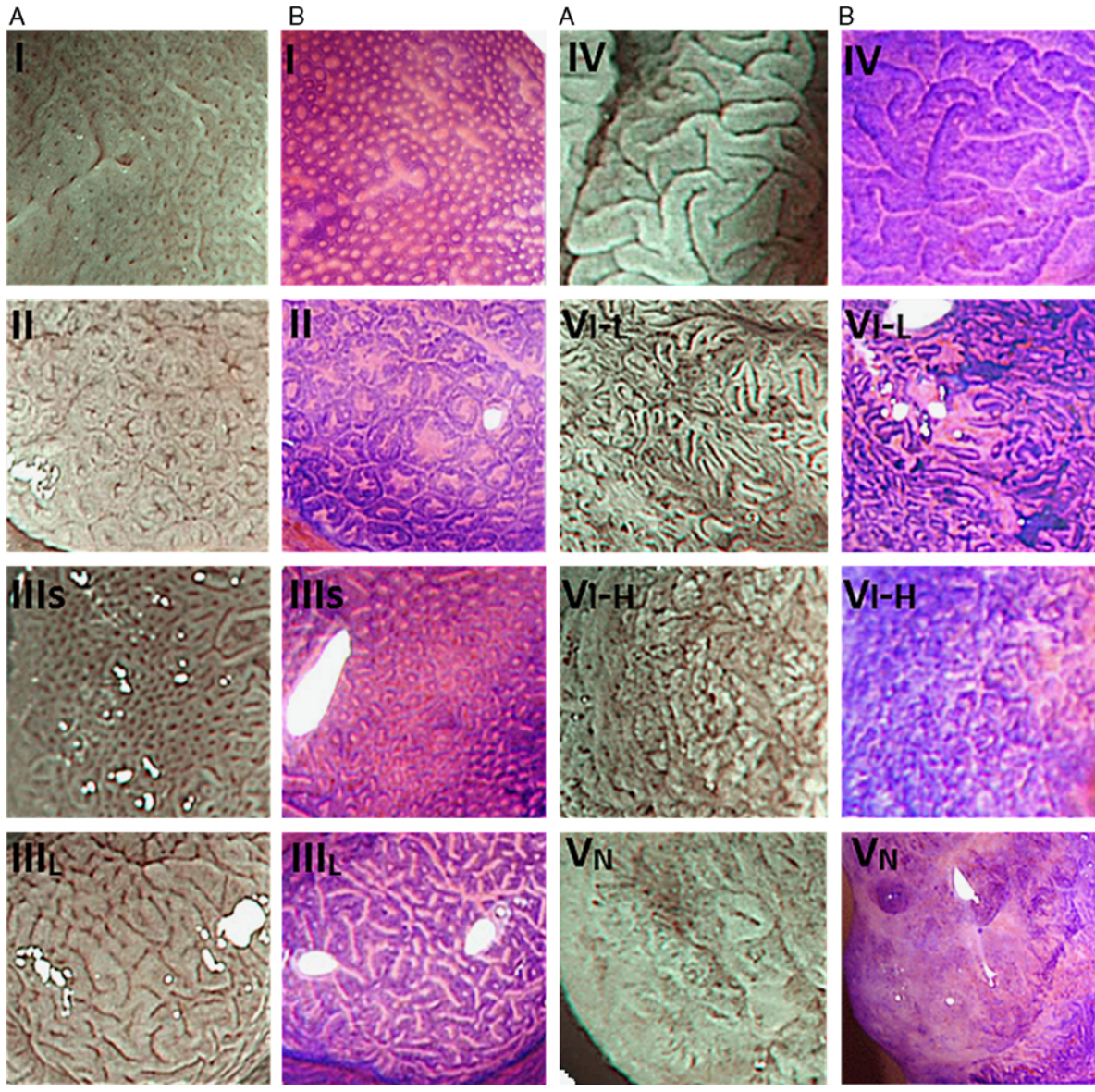


FIGURE 1. Comparison of pit pattern classifications of colorectal neoplasms by A-NBIME (A) and CV-MCE (B). Using A-NBIME, pit patterns were divided into the following 8 types as established by CV-MCE[1,2,13]: type I, round pit; type II, asteroid pit; type IIIs, tubular or round pit smaller than the normal pit; type IIIL, tubular pit larger than the normal pit; type IV, dendritic or gyrus-like pit; type VI-L, irregularly arranged pits with various sizes and forms but with clear contours; type VI-H, highly destroyed pits with severely irregular arrangement and without clear contours; and type VN, almost amorphous and difficult to recognize as a glandular structure. A-NBIME indicates magnification endoscopy with acetic acid–enhanced narrow-band imaging; CV-MCE, magnification chromoendoscopy using crystal violet staining.

AQ2 – 10% for A-NBIME, a sample size of 40 lesions would be needed to demonstrate the noninferiority of A-NBIME to CV-MCE. Therefore, the sample size allocated to each group was considered to be sufficiently large for each statistical analysis.

Colon Preparation

All patients were prepared for colonoscopy with 150 mg of sodium picosulfate hydrate administered on the night before the examination and with 2 to 3 L of polyethylene glycol-electrolyte solution administered on the morning of the examination. Most of the patients were administered with scopolamine butylbromide (10 mg) or glucagon (0.5 mg) to inhibit their bowel peristalsis.

Endoscopic System

The instruments used in these studies were a magnification videoendoscope (PCF-240ZI; Olympus Medical Systems Co. Ltd, Tokyo, Japan) and a standard optical videoendoscopic system (Evis Lucera Spectrum System; Olympus Medical Systems Co. Ltd). In this system, 1 light source projects standard broadband white lights and narrow-banded short wavelength lights with insertion of the NBI filter to the light path.

Statistical Analysis

Diagnostic concordance of PP was evaluated with the κ coefficient of reliability as follows: 0.00 to 0.20, poor agreement; 0.21 to 0.40, fair agreement; 0.41 to 0.60, moderate agreement; 0.61 to 0.80, substantial agreement; and 0.81 to 1.00, almost perfect agreement.[31] The χ^2 and either the Student *t* test or Welch test were used to test for significant differences of all data. In the analysis by unpaired *t* test, when there were unequal variances in the analyzed data, a statistically significant difference was calculated with Welch test instead of Student *t* test.

RESULTS

Study 1

The κ values of interobserver diagnostic concordance for PP among the 3 reviewers for A-NBIME and CV-MCE were 0.71 (0.66 to 0.75) and 0.80 (0.75 to 0.85), both showing good diagnostic agreement without statistical significant difference between modalities. The κ values of the intraobserver agreement of the 3 reviewers for each lesion between A-NBIME and CV-MCE were 0.79 (0.70 to 0.88), 0.80 (0.71 to 0.90), and 0.74 (0.67 to 0.82), showing statistically good concordance between modalities.

Study 2

A total of 214 colorectal lesions were photographed by A-NBIME and resected endoscopically or surgically. The endoscopic images of 9 lesions were of poor quality (5 out of focus, 3 insufficient acetic acid enhancement, and 1 covered with mucus). The histologic findings were difficult to diagnose in 3 lesions due to electrically coagulated damage on the resected specimen. These 12 lesions were excluded from the present study, and therefore, 202 lesions, including 27 hyperplasias, 144 adenomas, and 31 adenocarcinomas, were finally analyzed. The median (range) size was 10 (3 to 60) mm, and the macroscopic types were the protruded type (n = 151) and the flat type (n = 51).

The PP judgment was agreed upon by 2 or all 3 reviewers for all lesions, and the κ value for interobserver agreement was 0.69 (0.65 to 0.73), showing statistically good agreement also in this study, as in study 1. The relationship between PP diagnosed by A-NBIME and histologic features is listed in Table 1. Hyperplasias, adenomas, and adenocarcinomas were statistically related to type II ($P < 0.01$), type IIIs/IIIL/IV ($P < 0.01$), and type V ($P < 0.01$), respectively. The relationship between subclasses of type V (VI-L, VI-H and VN) and histologic findings is shown in Table 2. Intramucosal or slightly invasive submucosal adenocarcinoma (SMs: submucosal invasion depth $< 1000\,\mu m$) and massively invasive submucosal adenocarcinoma (SMm: submucosal invasion depth $\geq 1000\,\mu m$) were statistically related to type VI-L ($P < 0.01$) and type VI-H/VN ($P < 0.01$), respectively.

When type II was used as an indicator of non-neoplastic polyps, the diagnostic sensitivity, specificity, positive predictive value, and negative predictive value were 74.1%, 97.7%, 83.3%, and 96.6%, respectively. When type VI-H and VN were used as indicators of SMm, the sensitivity, specificity, positive predictive value, and negative predictive value were 90.0%, 97.4%, 64.3%, and 99.5%, respectively.

Study 3

The clinicopathologic features of the colorectal lesions of each group are shown in Table 3. There were no significant differences in macroscopic type, size, location, and histopathology between groups.

A total of 101 lesions and 119 lesions were observed with A-NBIME and CV-MCE, respectively. Six endoscopic images of poor quality (3 out of focus and 1 covered with mucus in A-NBIME group, and 2 out of focus in CV-MCE group) were excluded from the present study. Consequently, 97 lesions in A-NBIME group and 117 lesions in CV-MCE group were finally analyzed. The median (range) procedure time was 31 (10 to 218) seconds with A-NBIME and 81 (43 to 349) seconds with CV-MCE, showing a statistically significant difference ($P < 0.01$). The visible ratio of PPs was 98.9% (96/97) with A-NBIME and 98.3% (115/117) with CV-MCE ($P = 0.926$).

DISCUSSION

Magnification endoscopy with acetic acid enhancement or A-NBIME was reported to be a useful method for visualizing mucosal microstructure patterns of Barrett esophagus and the stomach.[23–25,32–39] In the diagnostic yield for colorectal lesions, a few literatures had addressed the efficacy of the combined use of acetic acid enhancement with colonoscopy or magnification colonoscopy.[40,41] However, in these studies, the efficacy of acetic acid enhancement was tested only for differentiating small adenomatous or hyperplastic polyps. Therefore, we designed the present study for investigating the value of A-NBIME for predicting histologic diagnosis of colorectal neoplasms including carcinoma in large number of samples. We

TABLE 1. Correlation Between Pit Patterns Visualized by A-NBIME and Histologic Features of Colorectal Lesions

	n (%)		
Pit Pattern	**Hyperplasia**	**Adenoma**	**Adenocarcinoma**
Type II (n = 24)	20 (83.3)*	4 (16.7)	0 (0)
Type IIIs (n = 11)	0 (0)	11 (100)**	0 (0)
Type IIIL (n = 88)	7 (8.0)	80 (90.9)**	1 (1.1)
Type IV (n = 36)	0 (0)	34 (94.4)**	2 (5.6)
Type V (n = 43)	0 (0)	15 (34.9)	28 (65.1)***

*$P < 0.01$, hyperplasia versus others.
**$P < 0.01$, adenoma versus others.
***$P < 0.01$, carcinoma versus others.
A-NBIME indicates magnification endoscopy with acetic acid–enhanced narrow-band imaging.

TABLE 2. Correlation Between Subclasses of the Type V Pit Pattern Visualized by A-NBIME and Histologic Features of Colorectal Lesions

	n (%)		
		Adenocarcinoma	
Pit pattern	**Adenoma**	**M or SMs**	**SMm**
Type VI-L (n = 29)	14 (48.3)	14 (48.3)*	1 (3.4)
Type VI-H (n = 12)	1 (8.3)	4 (33.3)	7 (58.3)**
Type VN (n = 2)	0 (0)	0 (0)	2 (100)**

*$P < 0.01$, M or SMs versus others.
**$P < 0.01$, SMm versus others.
A-NBIME indicates magnification endoscopy with acetic acid–enhanced narrow-band imaging; M, intramucosal adenocarcinoma; SMm, massively invasive submucosal adenocarcinoma; SMs, slightly invasive submucosal adenocarcinoma.

TABLE 3. Clinicopathologic Features of Colorectal Lesions

	A-NBIME (n = 97)	CV-MCE (n = 117)
Macroscopic type		
Protruded	70	81
Flat	26	35
Depressed	1	1
Median size (range) (mm)	6.0 (3-40)	6.0 (3-68)
Location		
Right side colon	47	60
Left side colon	37	42
Rectum	13	15
Histopathology		
Hyperplasia	5	11
Adenoma	87	99
Adenocarcinoma	5	7

A-NBIME indicates magnification endoscopy with acetic acid–enhanced narrow-band imaging; CV-MCE, magnification chromoendoscopy using crystal violet staining.

consider the contrast between the glandular crypts and intervening parts between them is more conspicuous in A-NBIME, because they are, respectively, visualized as red and white in the magnification endoscopy with acetic acid enhancement, and deep brown and white in A-NBIME. We expected that A-NBIME would have good efficacy for PP diagnosis of colorectal neoplasms and performed a prospective study to investigate this hypothesis. Consequently, we have concluded that A-NBIME is a useful and simple diagnostic tool for the PPs of colorectal neoplasms.

PP classification of colorectal neoplasms by CV-MCE is currently a pervasive method to predict histologic features. In contrast, NBIME has also been reported as a possible alternative diagnostic tool for histologic features of colorectal neoplasms.[15–21] As NBIME enables the detailed visualization of capillary patterns without any staining, the examination procedure is simpler and faster than CV-MCE. However, the capillary pattern analysis by NBIME aims to estimate histologic structural atypia indirectly through capillary form, whereas the PP analysis by CV-MCE is a direct estimation. Sakamoto et al[42] reported that the interobserver agreement in the capillary pattern analysis was inferior to that in the PP analysis. Wada et al[22] suggested that capillary pattern analysis was not sufficient for precise diagnosis, especially in submucosal invasive cancer, and recommended the combined use of PP diagnosis. Thus, capillary pattern analysis by NBIME shows good clinical feasibility, but it can be inferior to PP analysis by CV-MCE in the diagnostic concordance and accuracy.

The shape and arrangement of pits are indifferently observed between A-NBIME and CV-MCE, although the pit visualized by A-NBIME may be recognized smaller and more 3-dimensional than that by CV-MCE. The colorectal epithelium has numerous goblet cells that secrete mucus with high hydrophilicity.[43,44] According to Fick's law, the diffusion coefficient more effectively increases via smaller molecular weight compounds when the epithelia are instilled by enhancing solutions such as acetic acid or crystal violet.[45] Acetic acid is a hydrophilic carboxylic organic acid with a small molecular weight, and crystal violet is a hydrophobic dye with a large molecular weight (Fig. 2). Therefore, acetic acid is considered to infiltrate the crypt easily, despite the mucous barrier, by its small molecular

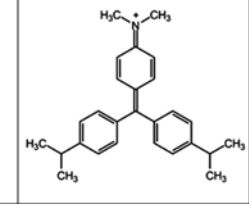
	acetic acid	crystal violet
molecular weight	60.05	373.53
structural formula	CH3—COOH	

FIGURE 2. Molecular weight and structural formula of acetic acid and crystal violet. Acetic acid has a smaller molecular weight and a more hydrophilic character than crystal violet.

weight and hydrophilic character, and it quickly discolors the intervening part between crypts and the marginal crypt epithelium to visualize pits as hollows of crypts in themselves. In contrast, crystal violet gradually infiltrates the crypts because of its large molecular weight and hydrophobicity, and it stains only the intervening part between crypts to visualize pits as unstained areas including crypts and marginal crypt epithelium. Therefore, the pits visualized by A-NBIME may be somewhat smaller and more 3-dimensional than those visualized by CV-MCE (Fig. 3). However, we consider these differences are small and possibly ignored in our clinical practice. A-NBIME makes the target enhancement of the PP possible, and the enhancement is rapid and vivid compared with CV-MCE. In addition, acetic acid removes the adherent mucus on the colorectal polyps by breaking the disulfide bonds of mucus[26] and enables the good visualization of the PPs even in case with the colorectal polyps covered by strongly adhering mucus which makes PP analysis difficult in magnification chromocolonoscopy,[40] suggestive of another advantage of A-NBIME compared with CV-MCE.

The κ value of the interobserver agreement for PP diagnosis by A-NBIME was somewhat smaller than that by CV-MCE, barely without statistical difference. As a reason for this result, we consider that the difference in PP appearance between modalities might have confused the reviewers who were well versed in CV-MCE but inexperienced in A-NBIME for PP diagnosis. It is necessary to investigate whether the interobserver diagnostic agreement of A-NBIME improves with accumulation of experience in future studies. However, A-NBIME showed statistically good interobserver agreement both in studies 1 and 2 in itself, suggestive of the good applicability of this modality for PP diagnosis of colorectal neoplasms. In addition, the κ value of the intraobserver agreement for the PP diagnosis between A-NBIME and CV-MCE showed statistically good agreement for each reviewer, which suggested that the PPs are similarly observed in principle between both modalities. Moreover, a good correlation between the PP and the histologic characteristics was found in A-NBIME, as proven by CV-MCE,[1–8,13,14] suggestive of the actual applicability of this diagnostic method in the therapeutic strategy for colorectal neoplasms. And above all, the primary advantage of A-NBIME was that this procedure was technically simpler and consequently less time consuming than CV-MCE. Thus, this newly developed diagnostic method showed good diagnostic performance and benefit for clinical practice. However, the endoscopic procedure in

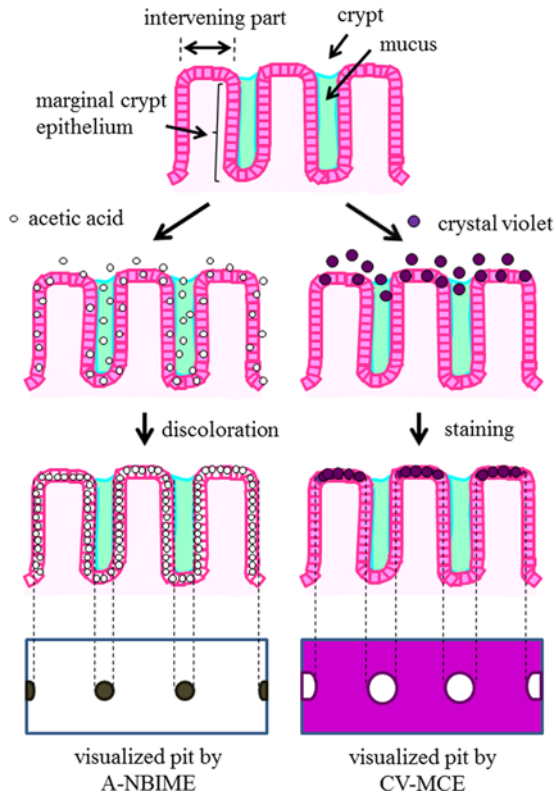


FIGURE 3. Acetic acid can easily infiltrate the crypt despite the mucus barrier, and quickly discolors the intervening parts and the marginal crypt epithelium. Crystal violet gradually infiltrates the crypt filled with mucus, and only stains the intervening parts. Therefore, at the early stage of enhancement, the pits visualized by A-NBIME are smaller than those visualized by CV-MCE. A-NBIME indicates magnification endoscopy with acetic acid–enhanced narrow-band imaging; CV-MCE, magnification chromoendoscopy using crystal violet staining.

this prospective study was performed at a single center, and therefore, a multicenter, prospective, randomized controlled trial with a large number of patients may be necessary to demonstrate the efficacy of this new diagnostic method sufficiently.

A-NBIME shows good interobserver agreement for PP diagnosis and good predictability of the histologic features of colorectal lesions despite its simplicity relative to CV-MCE. In conclusion, A-NBIME is a useful and feasible tool for the PP diagnosis of colorectal neoplasms.

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