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ORIGINAL ARTICLE

Retrospective Study

Endocytoscopic narrow-band imaging efficiency for evaluation of inflammatory activity in ulcerative colitis

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Abstract

AIM: To assess the efficacy of endocytoscopic narrow-band imaging (EC-NBI) for evaluating the severity of inflammation in ulcerative colitis (UC).

METHODS: This retrospective study was conducted at a single tertiary care referral center. We included UC patients who underwent colonoscopy with endocytoscopy from July 2010 to December 2013. EC-NBI was performed, and the images were evaluated by assessing visibility, increased vascularization, and the increased calibers of capillaries and were classified as Obscure, Visible or Dilated. Obscure was indicative of inactive disease, while Visible and Dilated were indicative of acute inflammation. This study received Institutional Review Board approval. The primary outcome measures included the diagnostic ability of EC-NBI to distinguish between active and inactive UC on the basis of histological activity. The conventional endoscopic images were classified according to the Mayo endoscopic score. A score of 0 or 1 indicated inactive disease, whereas a score of 2 indicated active disease.

RESULTS: Fifty-two patients were enrolled. There was a strong correlation between the EC-NBI findings and the histological assessment (r = 0.871, P < 0.01). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of EC-NBI for diagnosing acute inflammation were 84.0%, 100%, 87.1%, 100%, and 92.3%, respectively, while those for the Mayo endoscopic score were 100%, 40.7%,

100%, 61.0%, and 69.2%, respectively. Compared with conventional endoscopy, EC-NBI was superior in diagnostic specificity, negative predictive value, and accuracy ($P < 0.001$, $P = 0.001$ and $P = 0.047$, respectively).

CONCLUSION: The EC-NBI finding of capillaries in the rectal mucosa was strongly correlated with histological inflammation and aided in the differential diagnosis between active and inactive UC.

Key words: Endosytoscopy; Narrow-band imaging; Magnified endoscopy; Ulcerative colitis; Mucosal healing; Histological healing

Core tip: Endocytoscopic narrow-band imaging (EC-NBI) is a new technique, in which ultramagnified EC images are used in combination with NBI. The EC-NBI finding associated with the capillaries showed strong correlations with the presence of histological inflammation and the ability to distinguish between inactive and active ulcerative colitis. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the EC-NBI findings for diagnosing acute inflammation were 84.0%, 100%, 87.1%, 100% and 92.3%, respectively. Compared with conventional endoscopy, EC-NBI was superior in diagnostic specificity, negative predictive value, and accuracy.

Maeda Y, Ohtsuka K, Kudo S, Wakamura K, Mori Y, Ogata N, Wada Y, Misawa M, Yamauchi A, Hayashi S, Kudo T, Hayashi T, Miyachi H, Yamamura F, Ishida F, Inoue H, Hamatani S. Endocytoscopic narrow-band imaging efficiency for evaluation of inflammatory activity in ulcerative colitis. *World J Gastroenterol* 2015; 21(7): 2108-2115 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i7/2108.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i7.2108

INTRODUCTION

Surveillance colonoscopy is important for patients with ulcerative colitis (UC) because endoscopic appearance is a predictor of future clinical relapse. Moreover, the goal of therapy in these patients has shifted from symptom control alone to clinical remission in conjunction with mucosal healing. Although most studies on mucosal healing have focused on endoscopic scores, it has been suggested that histological inflammation is a valuable therapeutic goal[1,2]. Studies have indicated a higher risk of relapse in patients with persistent active microscopic inflammation compared with that in patients with normal histology[3,4]. However, it has also been reported that endoscopic and histological assessments differ in patients with active and inactive disease. Therefore, the routine diagnosis of histological activity in UC requires multiple biopsy specimens[5]; however, the collection of biopsy specimens is invasive. Therefore, it is important to identify a surrogate marker of histological activity.

Endocytoscopy (EC; Olympus Medical Systems, Tokyo, Japan)[6] enables the real-time observation of cells and nuclei *in vivo* using × 450 ultramagnification. This device can facilitate the differentiation of neoplastic and non-neoplastic lesions, and it can also guide the observations of celiac disease, amebic colitis, serrated polyps, and rectal carcinoids[7-14].

Furthermore, a correlation between EC classification and paired histological sample findings in UC patients has been reported[15]. Narrow-band imaging (NBI; Olympus Medical Systems) is a technique that uses spectral narrow-band optical filters instead of the full spectrum of white light. The applied light wavelengths are restricted to those specific to hemoglobin absorption, thereby clarifying mucosal vascular patterns. The NBI system was developed as an *in vivo* approach for visualizing the morphological changes in microvessels located in the superficial neoplasia or inflammation[16-19]. Endocytoscopic NBI (EC-NBI) is a new technique in which ultramagnified EC images are used in combination with NBI. It can help in visualizing microvessel structures and assist in the differentiation of capillaries from ascending arterioles and descending veins (Figure 1)[20]. This pilot study aimed to assess the efficacy of EC-NBI for evaluating the severity of inflammation in UC.

MATERIALS AND METHODS

Patients

This study was conducted at the Digestive Disease Center of the Showa University Northern Yokohama Hospital from July 2010 to December 2013. Using EC-NBI images to distinguish active from inactive UC according to histological activity, a total of 52 patients with a confirmed diagnosis of UC and a Mayo endoscopic score[21] of 0-2 were included; patients with a Mayo endoscopic score of 3 were not recruited. Informed consent was obtained from all patients before the procedure was performed, and ethical approval was granted by the local ethics review committee. This study was conducted in accordance with the Declaration of Helsinki.

Procedure

In this study, total colonoscopy and routine observation were performed with conventional endoscopy (CF-H260AZI; Olympus Medical Systems) to define the Mayo endoscopic score and target area, which was the most severely inflamed area in the rectum. The selected active section of the rectal area was observed using EC-NBI. The rectal mucosa was washed with excess water, and EC-NBI was performed without spraying or staining. Subsequently, a biopsy specimen

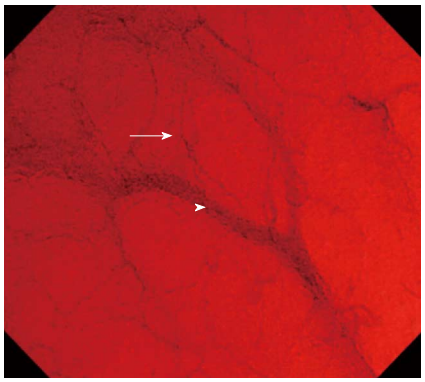

Figure 1 Differentiation between capillaries (arrow) and descending vein (arrow head).

was obtained from the rectal mucosa for histological analysis of the same area.

Instrument

As mentioned in a previous publication from our facility[10], the integrated-type EC (CF-Y-0020; Olympus Medical Systems) has an adjustable scope with an outside diameter of 13.6 mm at the distal end and a working length of 1330 mm. This scope enables consecutive conventional and ultramagnified endoscopic observation using one-touch switch operation. In the endocytoscopic mode, the scope has a magnification capability of × 450 displayed on a 14-inch monitor; the light focusing depth of field is 50 μm, and the surface field of view is 400 μm × 400 μm. Moreover, EC-NBI facilitates the increased visualization of microvessel structures, allowing for the differentiation of capillaries from ascending arterioles and descending veins. The principle of the endocytoscopic mode is similar to that of contact endoscopy and is set up with a fixed focus. The scope tip is applied to the target area after switching to the NBI mode. The EC-NBI images are immediately obtained using the mode-changing switch on the handle.

EC-NBI and conventional endoscopy image analysis

For each case, multiple EC-NBI images were obtained because the diameters of capillaries may change gradually. These images were obtained using the integrated image capture system and saved on the server that hosted the database in JPEG format with a pixel array of 640 × 480 and 16-bit color (Olympus Medical Systems). The EC-NBI and conventional endoscopic images for each case were separately downloaded from the server for analysis by a reader (Ya M), who was a trained endoscopist blinded to the findings of the histological analysis. From the multiple images obtained for each case, the reader selected the image that showed the most microvessel distension. All EC-NBI and conventional endoscopic images from the target area were randomly allocated. The EC-NBI images were classified by grade of visibility, increased vascularization, and the increased calibers of capillaries as follows: Obscure (Figure 2A), the capillaries were not clearly visible; Visible (Figure 2B), the capillaries were clearly visible and/or increased vascularization was observed; Dilated (Figure 2C), the caliber of the capillaries was unusually large (three times as large as that of the surrounding capillaries). Obscure was indicative of inactive disease, while Visible and Dilated were indicative of acute inflammation in our EC-NBI findings. The conventional endoscopic images were classified according to the Mayo endoscopic score (Table 1). A score of 0 or 1 indicated inactive disease, whereas a score of 2 indicated active disease[22].

Table 1 Mayo endoscopic score for ulcerative colitis

0	Normal or inactive disease
1	Mild disease: erythema, decreased vascular pattern, mild friability
2	Moderate disease: marked erythema, absent vascular pattern, friability, erosions
3	Severe disease:spontaneous bleeding, ulceration

Histological assessment

All biopsy specimens were fixed in 10% formalin, embedded in paraffin, serially sectioned, and stained using hematoxylin and eosin (HE). Histological examination was performed by an experienced pathologist (S.H.) who was blinded to both the clinical and endoscopic data.

Histological assessment was based on the Geboes index (Table 2)[23]. The scale included six grades, and each grade was divided into 4-5 subgroups[23,24]. The patients were divided into two groups according to their final indices; one group was comprised of those with an index of $\leqslant$ 3.0, and the other contained those with an index of > 3.0. A grade of 3.1 indicated the presence of neutrophils in the epithelium, which was representative of acute inflammation and a predictor of relapse[25]. A Geboes index of $\leqslant$ 3.0 indicated inactive disease, while an index of > 3.0 indicated active disease.

Date analysis

Diagnoses obtained by conventional endoscopy and EC-NBI were compared with those based on the Geboes index, and the diagnostic abilities of conventional endoscopy and EC-NBI to differentiate between inactive and active disease were assessed. Next, the Spearman rank correlation coefficient between the Mayo endoscopic score and the Geboes index and that between EC-NBI findings and the Geboes index were calculated. We compared the EC-NBI findings with the Sutherland index for the clinical severity of inflammation in UC. The Spearman rank correlation coefficient between the EC-NBI findings and Sutherland index was calculated[26]. All clinical data were collected from medical records.

In a subanalysis, the inter- and intraobserver

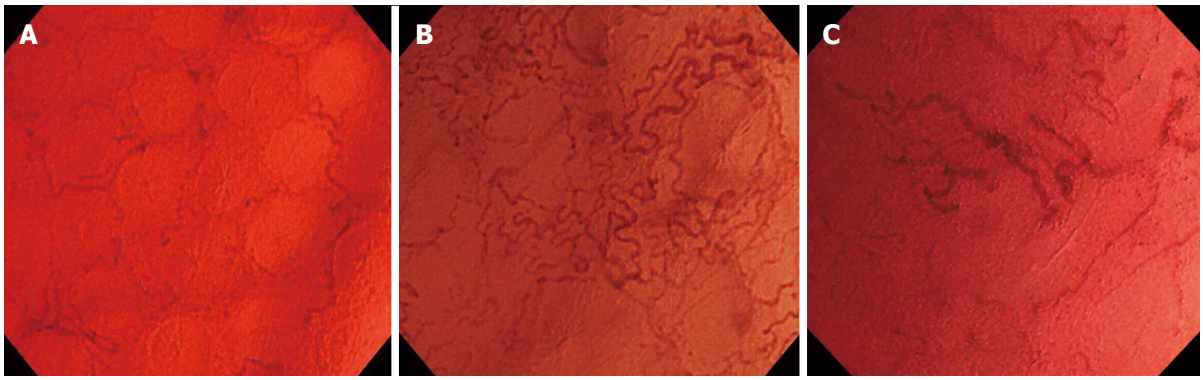

Figure 2 Endocytoscopic narrow-band imaging findings were classified into three groups. A: Obscure; B: Visible; C: Dilated.

Table 2 Geboes index

Grade 0	Structural (architectural change)
Subgrades	
0.0	No abnormality
0.1	Mild abnormality
0.2	Mild or moderate diffuse or multifocal abnormalities
0.3	Severe diffuse or multifocal abnormalities
Grade 1	Chronic inflammatory infiltrate
Subgrades	
1.0	No increase
1.1	Mild but unequivocal increase
1.2	Moderate increase
1.3	Marked increase
Grade 2	Lamina propria neutrophils and eosinophils
2A Eosinophils	
2A. 0	No increase
2A.1	Mild but unequivocal increase
2A.2	Moderate increase
2A.3	Marked increase
2B Neutrophils	
2B. 0	None
2B.1	Mild but unequivocal increase
2B.2	Moderate increase
2B.3	Marked increase
Grade 3	Neutrophils in epithelium
3.0	None
3.1	< 5% crypts involved
3.2	< 50% crypts involved
3.3	> 50% crypts involved
Grade 4	Crypt destruction
4.0	None
4.1	Probable-local excess of neutrophils in part of crypt
4.2	Probable-marked attenuation
4.3	Unequivocal crypt destruction
Grade 5	Erosion or ulceration
5.0	No erosion, ulceration, or granulation tissue
5.1	Recovering epithelium + adjacent inflammation
5.2	Probable erosion-focally stripped
5.3	Unequivocal erosion
5.4	Ulcer or granulation tissue

agreements for conventional endoscopy and EC-NBI were calculated for the three endoscopists (Ya M., K. W., and Yu. M.). Thirty images each from conventional endoscopy and EC-NBI were randomly selected from all images and randomly arranged for assessments among the three endoscopists. To assess intraobserver agreement, the same images were randomly allocated to the endoscopists for reassessment more than a month after the initial assessment. Interobserver agreement was calculated from the results of the first reading, and intraobserver agreement was calculated by comparing the first and second assessments and presented as the kappa value.

Statistical analysis

For the statistical analysis, a computerized database was designed using R (The R Foundation for Statistical Computing, Vienna, Austria, v. 2.13.0). The quantitative data were expressed as the mean ± SD values. Statistical significance was evaluated using Fisher's exact test or Student's *t*-test as appropriate. *P* values (two-tailed) of < 0.05 were considered statistically significant. The agreements were interpreted as follows: no agreement (0), slight agreement (< 0.20), fair agreement (0.21-0.40), moderate agreement (0.41-0.60), substantial agreement (0.61-0.80), and almost perfect agreement ($\geqslant 0.81$), as proposed by Landis and Koch[27].

RESULTS

Examination with the new prototype EC was uneventful in all cases. The clinical features of the 52 patients are shown in Table 3. The additional time required to perform a further examination with EC-NBI was approximately 3 min. According to the EC-NBI findings, the images were classified into 21 obscure cases, 17 visible cases, and 14 dilated cases. With regard to histological activity, 25 and 27 cases had Geboes indices of $\leqslant 3.0$ and > 3.0, respectively. The diagnoses obtained using EC-NBI were compared with the histological diagnoses. All obscure cases had Geboes indices of $\leqslant 3.0$. However, 76.5% (13/17) of the visible and all of the dilated cases had a Geboes indices of > 3.0. There was a strong correlation between EC-NBI finding and the Geboes index ($r = 0.871$, $P < 0.01$; Table 4). We also assessed the

Table 3 Profiles of enrolled patients

Total number of patients	40
Sex, M/F	19/21
Age, yr	46.7
Disease duration, yr	20
Type of UC	
Total colitis	20
Left-sided	6
Proctitis	14
Clinical course	
Relapsing-remitting type	21
Chronic continuous type	11
One attack only	8
Treatment	
5-ASA	39
SASP	10
Mesalazine	33
Prednisolone	2
AZA	4
CAP	1
No medication	1

UC: Ulcerative colitis.

Table 4 Correlation between the endocytoscopic narrow-band imaging findings and the Geboes index and between the Mayo endoscopic score and the Geboes index

Geboes index	EC-NBI			Mayo endoscopic score			Total
	Obscure	Visible	Dilated	0	1	2	
1	17	1	0	12	6	0	18
2	4	3	0	5	2	0	7
3	0	6	1	2	5	0	7
4	0	7	11	1	7	10	18
5	0	0	2	0	1	1	2
the Spearman rank correlation coefficient	$r = 0.871$, $P < 0.01$			$r = 0.665$, $P < 0.01$			

EC-NBI: Endocytoscopic narrow-band imaging.

correlation between conventional endoscopic findings and histological activity ($r = 0.665$, $P < 0.01$; Table 4). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the EC-NBI findings for diagnosing acute inflammation were 84.0%, 100%, 87.1%, 100%, and 92.3%, respectively (Table 5), while those for the Mayo endoscopic score were 100%, 40.7%, 100%, 61.0%, and 69.2%, respectively (Table 5). Compared with conventional endoscopy, EC-NBI was superior in terms of diagnostic specificity, negative predictive value, and accuracy (Table 6). The correlations between EC-NBI finding and the Sutherland index as an indicator of clinical disease activity are shown in Figure 3. The EC-NBI findings showed a positive correlation with the Sutherland index ($r = 0.721$, $P < 0.01$).

To assess the reproducibility of EC-NBI, the kappa values for the interobserver agreements were assessed for the three readers. A kappa value of 0.823 (95%CI: 0.682-0.965) and very high agreements were observed

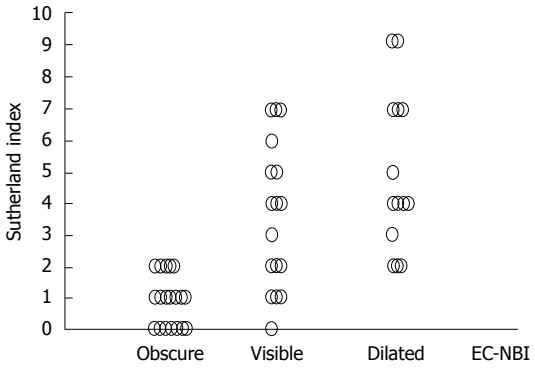

Figure 3 Correlation between the endocytoscopic narrow-band imaging findings and the Sutherland index.

Table 5 Differential diagnosis between inactive and active ulcerative colitis using the endocytoscopic narrow-band imaging finding and the Mayo endoscopic score

EC-NBI finding	Acute inflammation -	Acute inflammation +	Mayo score	Acute inflammation -	Acute inflammation +
Obscure	21	0	0/1	25	16
Visible/dilated	4	27	2	0	11

Geboes index ≤ 3.0; acute inflammation +: Geboes index > 3.0.

Table 6 Comparison of the diagnostic abilities for acute inflammation between the endocytoscopic narrow-band imaging finding and the Mayo endoscopic score

	EC-NBI	Mayo score	*P* value
Sensitivity	84.0%	100%	$P = 0.110$
Specificity	100%	40.7%	$P < 0.001$
PPV	87.1%	100%	$P = 0.568$
NPV	100%	61.0%	$P = 0.001$
Accuracy	92.3%	69.2%	$P = 0.047$

NPV: Negative predictive value; PPV: Positive predictive value. EC-NBI: Endocytoscopic narrow-band imaging.

in association with the EC-NBI findings. There was also excellent intraobserver agreement, with kappa values of 0.850 (95%CI: 0.689-1.011) for Ya M, 0.750 (95%CI: 0.549-0.950) for K.W., and 0.801 (95%CI: 0.620-0.983) for Yu M.

DISCUSSION

To our knowledge, this is the first study to show the potential applicability of the newly developed EC-NBI system for assessing the histological disease activity of UC. Recent studies have shown that an increase in the severity of inflammation, as detected both endoscopically and histologically, correlated with an increased frequency of relapse or of dysplasia[28,29]. However, the consistency between the endoscopic and histological findings in UC patients has not been elucidated. It has been suggested that conventional

colonoscopy is not reliable for assessing acute inflammation and the potential for relapse[1]. We confirmed a strong correlation between the EC-NBI findings and histological activity and also found that this system has a high diagnostic ability to differentiate between active and inactive UC. EC-NBI was superior to conventional endoscopy in terms of sensitivity, negative predictive value, and accuracy. The results obtained in this study may be serve as a simple and objective foundation for the optimization of therapeutic strategies for the treatment of UC.

Employing an approach similar to that used in the present study, Bessho *et al*[15] have shown the benefits of classifying the histological activity of UC using EC. In their report, the shape and distance of the crypt were also assessed, and an excellent correlation was revealed between EC and histological diagnosis. However, their study had some limitations because the EC observations required pretreatment with methylene blue or toluidine blue staining. The additional time required for EC observation was reported to be approximately 20 min in one area[15]. Therefore, a more practical procedure for assessing the histological activity of UC is necessary. EC-NBI images can be immediately obtained using the mode-changing switch on the handle without the need for spraying or for staining. EC-NBI can be performed in approximately 3 min; therefore, this procedure may be intuitive because it involves the evaluation of visibility, increased vascularization, and the increased calibers of capillaries in the target area. Both the inter- and intraobserver agreements for the EC-NBI finding were excellent in this study. However, there were only three types of EC-NBI finding, which may have contributed to its high reproducibility.

In this study, capillaries in the rectal mucosa were assessed. Previous studies have evaluated. The colorectal microvasculature with NBI [30], demonstrating a good correlation with Histological diagnosis. However, the difference between the capillaries and other types of microvasculature was not considered. This differentiation is very important for assessing the visibility and the increased calibers of microvessels. The mucosal capillary plexus of the large intestine is typically arranged in a regular, hexagonal, honeycomb pattern surrounding the mucosal glands. The plexus is supplied by arteries that are divided within the submucosa to form the subepithelial capillaries. Venous drainage occurs through the venules immediately originating under the mucosal surface and leading to the submucosal veins[20]. To our knowledge, this is the first report to assess the differences between the capillaries and other vessels using the ultramagnification afforded by EC in combination with the detailed microvessel visualization permitted by NBI.

Recent data have provided evidence that the differential regulation of angiogenic mediators involved in inflammatory bowel disease-associated chronic inflammation causes this pathological angiogenesis. Many factors are involved in this phenomenon, including growth factors/cytokines, chemokines, adhesion molecules, integrins, matrix-associated molecules, and signaling targets[31]. Our EC-NBI findings were based on the evidence of increased vascularization and the increased calibers of the capillaries in the target area.

This study has some limitations. First, the number of subjects was small. This was because there was only one integrated-type endocytoscope in the facility. Second, in the present study, the EC-NBI images were obtained *in vivo* but were not actually diagnosed *in vivo*. We aimed to assess the accuracy of diagnosis solely on the basis of EC-NBI, with the assessors blinded to the conventional endoscopic findings. Moreover, the lack of enrollment of patients with severe active UC may have biased the results. The presence of ulcers or the prominent spontaneous hemorrhaging of the colorectal mucosa is important for the diagnosis of the severe active stage. These lesions can be recognized easily with conventional endoscopy. Furthermore, the blue light emitted around the wavelength used for NBI is mainly absorbed by hemoglobin, and the prominent hemorrhaging of the surface mucosa can be a major disadvantage to NBI assessments. Therefore, patients with a Mayo endoscopic score of 3 were not recruited in this study. The EC-NBI findings were compared with histological activity as a predictive factor of long-term clinical prognosis; however, the findings were not compared directly with the long-term clinical prognosis.

In conclusion, the EC-NBI finding of capillaries in the rectal mucosa was strongly correlated with the presence of histological inflammation and the ability to distinguish between inactive and active UC. Furthermore, EC-NBI is easy to perform and has high reproducibility. EC-NBI findings can be effective in the on-site evaluation of inflammatory activity in UC. To assess the clinical efficacies of the EC-NBI findings, further multicenter prospective clinical trials involving larger patient samples and direct comparisons with long-term clinical prognosis are required.

COMMENTS

Background

Surveillance colonoscopy is important for patients with ulcerative colitis (UC) because endoscopic appearance is a predictor of future clinical relapse. Although most studies on mucosal healing have focused on endoscopic scores, it has been suggested that histological inflammation is a valuable therapeutic goal. However, it has also been reported that endoscopic and histological assessments differ in patients with active and inactive disease. Therefore, it is important to identify a surrogate marker of histological activity. The efficacy of endocytoscopic narrow-band imaging (EC-NBI) for evaluating the severity of inflammation in UC has not been evaluated.

Research frontiers

EC-NBI is a new technique in which ultramagnified endocytoscopy images are used in combination with NBI. It can help in visualizing microvessel structures and assist in the differentiation of capillaries from ascending arterioles and descending veins.

Innovations and breakthroughs

EC-NBI can help in visualizing microvessel structures and assist in the differentiation of capillaries from ascending arterioles and descending veins.

The additional time required toperform a further examination with EC-NBI was approximately 3 min. There was a strong correlation between EC-NBI findings and histlogical diagnosis. Compared with conventional endoscopy, EC-NBI was superior in terms of diagnostic specificity, negative predictive value, and accuracy. The correlations between EC-NBI findings and the Sutherland index as an indicator ofclinical disease activity. The EC-NBI findings showed a positive correlation with the Sutherland index.

Applications

The study results suggest that the EC-NBI finding of capillaries in the rectal mucosa was strongly correlated with the presence of histological inflammation and the ability to distinguish between inactiveand active UC. EC-NBI findings can be effective in the on-site evaluation of inflammatory activity in UC.

Terminology

EC (Olympus Medical Systems, Tokyo, Japan) is a novel endoscopy enables the real-timeobservation of cells and nuclei *in vivo* using 450 × ultramagnification. NBI (Olympus Medical Systems) is a technique that uses spectral narrow-band optical filters instead of the full spectrum of white light. The applied light wavelengths are restricted to those specific to hemoglobin absorption, thereby clarifying mucosal vascular patterns.

Peer-review

Maeda *et al* have assessed the efficacy of endocytoscopic narrow-band imaging findings to evaluate the severity of inflammation in ulcerative colitis. The study has been well designed and written.

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