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Chromoendoscopy Using the Non-extension Sign as a Marker Is Comparable to Endoscopic Ultrasonography in Terms of Diagnostic Performance for Evaluating the Invasion Depth of Early Colorectal Cancer

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Abstract

Background: No reports have compared diagnostic performance between non-extension sign（NES）-based chromoendoscopy（CE）and endoscopic ultrasonography（EUS），magnifying endoscopy with narrow-band imaging（M-NBI），or magnifying chromoendoscopy（M-CE）for invasion depth evaluation for T1b cancer（submucosal invasion depth ≥ 1000 μm）. This study compared NES-based CE with EUS, M-NBI, and M-CE for evaluating invasion depth in early colorectal cancer.

Methods: We retrospectively analyzed 45 patients with early colorectal cancer who underwent endoscopic or surgical resection. Invasion depth was evaluated using CE with NES as a marker, M-NBI, M-CE, and EUS in preoperative examination. The primary aim was to compare CE using the NES as a marker with EUS in evaluating invasion depth of T1b.

Results: CE had a accuracy of 75.6%, sensitivity of 78.1%, and specificity of 69.2% for T1b cancer invasion depth, while the corresponding figures were 71.1%, 78.1%, and 53.9% for EUS. Thus, CE showed comparable sensitivity to EUS but had higher specificity and accuracy without significant differences.

Conclusions: CE using the NES as a marker demonstrated comparable diagnostic performance to EUS for invasion depth evaluation, suggesting its potential as an excellent and cost-effective modality for early colorectal cancer.

Key words: Non-extension sign, early colorectal cancer, submucosal invasion, endoscopic ultrasonography, chromoendoscopy

Introduction

In recent years, the widespread use of minimally invasive treatments, such as endoscopic submucosal dissection（ESD），has led to aggressive endoscopic therapy for early colorectal cancer [1),2)]. However, due to the risk of lymph node metastasis in approximately 10% of patients with T1（submucosal invasion）cancer [3)], assessing curability based on histopathological diagnosis after endoscopic resection and considering the indication for additional surgical resection is crucial. The accurate pretreatment diagnosis of invasion depth plays a vital role in achieving endoscopic resection for cancer curation.

Different endoscopic modalities, including chromoendoscopy（CE），magnifying endoscopy with narrow-band imaging（M-NBI），magnifying chromoendoscopy（M-CE）using crystal violet staining,

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and endoscopic ultrasonography (EUS), are used for diagnosing the invasion depth of early colorectal cancer. While M-NBI is the best modality for visualizing the surface structure of tumors, CE and EUS are more effective in assessing lesions that invade submucosal tissues while preserving the surface structure.

Conventional CE has been deemed less useful for evaluating invasion depth because of its low sensitivity and the lack of sufficiently defined findings suggestive of T1b (submucosal invasion depth ≥ 1000 μm) cancer [4]. However, Hisabe et al. recently reported that non-extension sign (NES) was an effective marker with a sensitivity of 66.0%, a specificity of 95.8%, and an accuracy of 86.3% for diagnosing the invasion depth of T1b cancer when used as a marker of T1b cancer in CE [5]. The specificity was significantly higher for NES-based CE than for M-CE, and the incidence of lymphovascular invasion was also significantly higher in the NES-positive group than in the NES-negative group. They stated that surgery should be considered in patients with a positive NES. The NES is a simple marker for evaluating the difference in the extensibility of tumors and their surrounding mucosa instead of the surface properties of tumors. Cancer invasion into the deep submucosal layer causes a desmoplastic reaction, which locally increases the thickness and rigidity of tumors. Thus, when the colon wall is fully extended by endoscopic insufflation, findings such as convergence of mucosal folds around a tumor, trapezoid elevation of a tumor, and linear rigidity against a background circular arc at a tumor site are observed. These phenomena are referred to as the NES [5]. Therefore, NES can be objectively judged only on an entirely extended colon wall with sufficient air insufflation.

Meanwhile, EUS is the only modality that allows direct diagnostic evaluation of invasion depth on the vertical sectional view. However, it is not widely used in real-world practice due to difficulty visualizing definite lesions and challenges in differentiating submucosal fibrosis, lymphoid follicles, and cancer invasion that hamper histological characterization on EUS images. Additionally, it imposes an economic and physical burden on patients [6]. Furthermore, the accuracy of EUS for diagnosing invasion depth varies considerably among institutions (67%–90%) [7-9].

There have been no comparative studies on the diagnostic performance of CE using the NES as a marker and EUS for evaluating T1b cancer invasion depth. Additionally, no reports have compared CE using the NES as a marker with M-NBI or M-CE in terms of diagnostic performance for evaluating the invasion depth of T1b cancer. Hence, the primary objective of this study was to compare the diagnostic performance of CE using the NES as a marker and EUS for evaluating the invasion depth of early colorectal cancer. The secondary objective was to compare CE using the NES as a marker with M-NBI and M-CE regarding diagnostic performance for evaluating the invasion depth of T1b cancer.

Methods

Study design

This was a retrospective, single-center, observational study.

Patient selection

This study selected and analyzed patients with early colorectal cancer who met the following inclusion and exclusion criteria. The inclusion criteria were as follows: (1) patients with early colorectal cancer who underwent endoscopic or surgical resection at Fukuoka University Chikushi Hospital between January 2010 and April 2020 whose resected specimens were available for detailed histopathological examination and (2) patients in whom the modalities of CE using the NES as a marker, M-NBI, M-CE using crystal violet staining, and EUS were performed for diagnosing invasion depth during preoperative examination. The exclusion criteria were as follows: (1) patients in whom any of the modalities was difficult to perform and (2) patients whose lesions were difficult to visualize by EUS. The study protocol was approved by the ethics committee of Fukuoka University Chikushi Hospital (Approval No: C20-10-001).

Endoscopy procedures

A total colonoscopy was performed first. When the targeted lesions were suspected of early colorectal cancer, the following modalities were utilized to diagnose invasion depth. CE using the NES as a marker, followed by M-NBI, and then M-CE using crystal violet staining. When these modalities led to a suspicion of T1b cancer, EUS was performed for suspicious lesions.

All endoscopic diagnostic examinations were implemented with a magnifying colonoscope (PCF-Q240ZI, CF-H260AZI, PCF-Q260AZI, CF-HQ290ZI, or PCF-H290ZI, Olympus Co., Tokyo, Japan). EUS was conducted with a 20-MHz small diameter probe (UM-DP20-25R, Olympus Co., Tokyo, Japan).

The macroscopic classification was performed according to the Japanese Society for Cancer of the Colon and Rectum guidelines [10].

Analysis of endoscopic findings

All endoscopic findings were retrospectively analyzed by 2 endoscopist reviewers (K.O. and K.T.), each with at least 5 years of colonoscopy experience. We randomized a list of early CRC patients that only contained the patient allocation number and date of endoscopy and reviewed all endoscopic images. CE, M-CE, M-NBI and EUS images were evaluated at the same time. The reviewers were blinded to the histopathological diagnosis, and the final evaluation of endoscopic findings was decided by the consensus agreement of the 2 reviewers.

Diagnosis of invasion depth by CE using the NES as a marker

The tumor surface was thoroughly rinsed using water with added defoaming agent. An antispasmodic agent was administered to block intestinal peristalsis. Subsequently, indigo carmine (0.1%) was sprayed and a large amount of air was insufflated to strongly extend the colon wall. Under these conditions, the lesions were observed in the front and oblique or tangential directions. When any of the following three findings were observed, the lesions were considered as positive for the NES and diagnosed as T1b cancer. Those with a negative NES were diagnosed with Tis cancer/T1a cancer [5), 11), 12)].

1. Rigidity against a background circular arc: Normal mucosa appears like an arc when the colon wall is strongly extended. However, in cancer invading the submucosal layer, tumors and their surrounding areas do not extend; consequently, the affected mucosa appears linear instead of having an arc-like appearance (Fig. 1A).
2. Trapezoid elevation: When the colon wall is sufficiently extended by air, the mucosa in non-tumor areas is fully extended. In contrast, because tumors invading the submucosal layer are rigid and thick, the tumor site protrudes in a trapezoidal shape (Fig. 1B).
3. Converging mucosal folds: Three or more folds converge from the surrounding mucosa towards the tumor, and the tips of the folds protrude at the tumor site (Fig. 1C). Mucosal folds that converge at one point are regarded as an ulcer scar and, therefore, not judged to be converging mucosal folds.

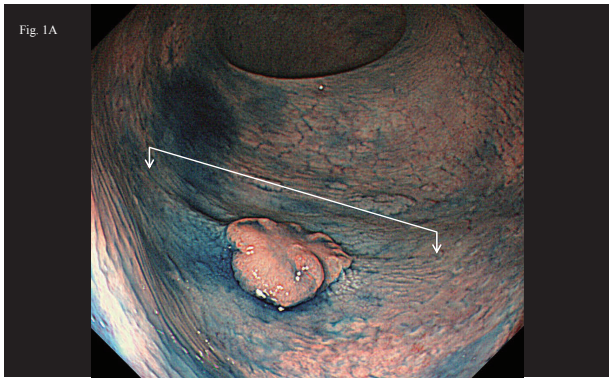

Fig. 1A. Chromoendoscopic images. Rigidity against a background circular arc (arrow). When the colon wall is strongly extended by air, normal mucosa appears arc-like. However, tumors and their surrounding areas do not extend; consequently, the affected mucosa appears linear.

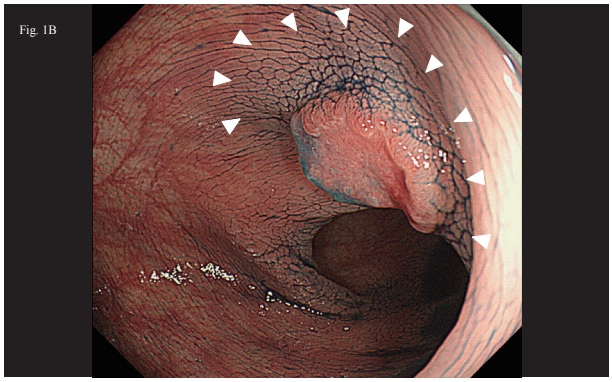

Fig. 1B. Chromoendoscopic images. Trapezoid elevation on chromoendoscopic images (arrowhead). When the colon wall is strongly extended by air, the mucosa in non-tumor areas is fully extended. In contrast, because tumors invading the submucosal layer are rigid and thick, the tumor site protrudes in a trapezoidal shape.

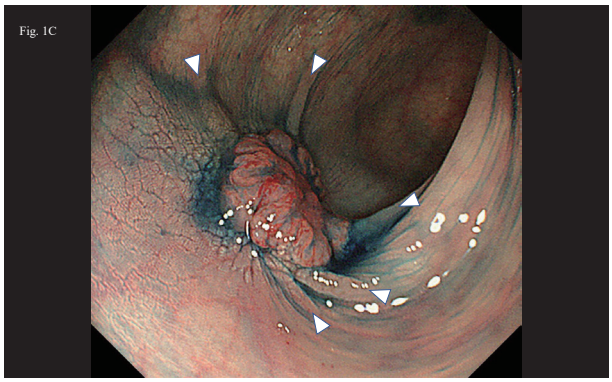

Fig. 1C. Chromoendoscopic images. Converging mucosal folds (arrowhead). When the colon wall is strongly extended by air, three or more folds converge from the surrounding mucosa toward the tumor and the tips of the folds protrude at the tumor site.

Diagnosis of invasion depth by M-NBI

Type 3 lesions of the Japan NBI Expert Team (JNET) classification, defined by the following vessel and surface patterns, were diagnosed as T1b cancer (Fig. 2). Those other than the above-described lesions were diagnosed as Tis cancer/T1a cancer [13].

1. Vessel pattern: Loose vessel areas, interruption of thick vessels
2. Surface pattern: Amorphous areas

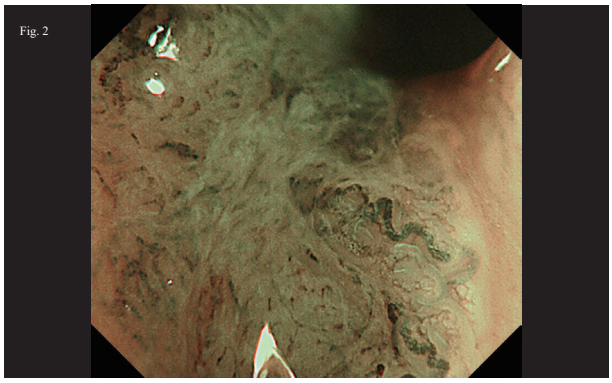

Fig. 2. Image of magnifying endoscopy with narrow-band imaging. The surface pattern is amorphous. Disrupted large blood vessels and hypovascular areas are observed.

Diagnosis of invasion depth by M-CE using crystal violet staining

The tumor surface was stained with crystal violet (0.05%). Pit patterns were classified according to the Kudo–Tsuruta classification. V_I high-grade and V_N lesions, diagnosed as T1b cancer, are described below. Those other than the above-described lesions were diagnosed as Tis cancer/cT1a cancer [14)-16)].

1. V_I high-grade: The narrowed pit lumen, a rough pit margin, unclear plot outline, unclear staining characteristics of the areas between pits, and scratch sign (Fig. 3A).
2. V_N: Loss or decrease of pits with an amorphous structure (Fig. 3B).

Diagnosis of invasion depth by EUS

The normal colon wall is visualized as a 5-layer structure by EUS. The first and second layers correspond to the mucosal layer, the third layer to the submucosal layer, the fourth layer to the proper muscular layer, and the fifth layer to the subserosal layer or serosa. EUS visualizes colorectal cancer as a hypoechoic area. Lesions with narrowing or laceration of the third layer (submucosal layer) due to tumors were diagnosed as T1b cancer (Fig. 4). Lesions other than the ones described above were diagnosed as Tis cancer/T1a cancer [17].

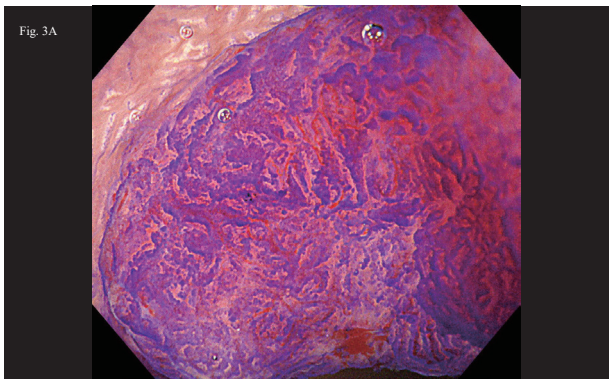

Fig. 3A. Magnifying chromoendoscopic images. V_I high-grade (classification of pit pattern). The pit exhibits a rough margin and unclear outline. The lumen of the pit is narrowed, and the intervening mucosa is poorly stained.

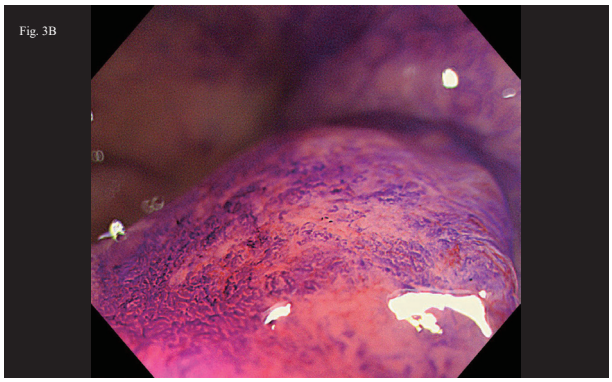

Fig. 3B. Magnifying chromoendoscopic images. V_N (classification of pit pattern). The pit is highly destroyed, and a localized amorphous structure is observed.

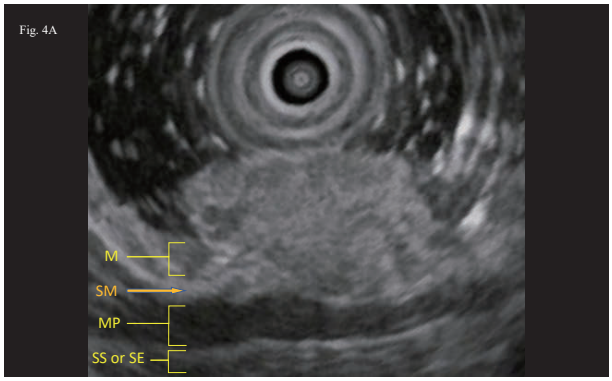

Fig. 4A. Endoscopic ultrasonographic observation. The third layer (submucosal layer) is narrowed and lacerated due to the tumor; the fourth layer (proper muscular layer) is preserved. M, mucosa; SM, submucosa; MP, muscularis propria; SS, subserosa; SE, serosa.

Endpoints

The primary endpoint was to compare diagnostic performance (sensitivity, specificity, and accuracy) for evaluating the invasion depth of T1b cancer between CE using the NES as a marker and EUS. The secondary

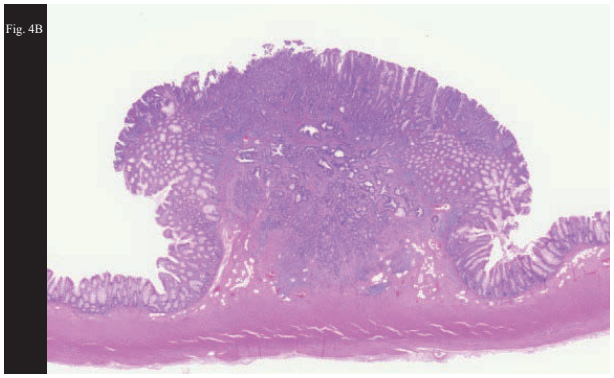

Fig. 4B. Histopathological findings (hematoxylin-eosin staining). The tumor invades as a mass just above the proper muscular layer. T1b (4800 μm).

endpoints were to determine the additive effect of EUS for correctly diagnosing patients in whom the invasion depth of T1b cancer was misdiagnosed by CE, to compare the diagnostic performance (sensitivity, specificity, and accuracy) of CE and magnifying endoscopy (M-NBI and M-CE) in evaluating the invasion depth of T1b cancer, and to determine the additive effect of magnifying endoscopy (M-NBI and M-CE) for correctly diagnosing patients in whom the invasion depth of T1b cancer was misdiagnosed by CE.

Statistical analysis

McNemar's test was performed to compare the proportions of categorical variables between two paired groups. A *P* value of less than 0.05 was considered to indicate a statistically significant difference. SPSS 16.0 for Windows (SPSS Inc, Chicago, USA) was used for statistical analyses.

Results

Clinicopathological characteristics

A total of 521 patients with early colorectal cancer were treated at our hospital between January 2010 and April 2020. After excluding 470 patients who did not undergo EUS, 51 patients remained. After further exclusion of three patients whose lesions were difficult to evaluate by the NES and three patients whose lesions were difficult to visualize by EUS, 45 patients were included and analyzed in this study. Table 1 shows the characteristics of patients with early colorectal cancer who were analyzed in this study. The mean age±standard deviation was 68.4±10.2 years, and the male-to-female ratio was 31:14. The mean diameter of the lesions was 18.3±8.3 mm. The lesion sites

Table 1. Clinicopathological characteristics of patients and lesions (n=45)

Age (y)	
mean±SD	68.4±10.2
Sex	
Male	31
Female	14
Size of lesion (mm)	
mean ±SD	18.3±8.3
Location of lesion	
Cecum	1 (2.2%)
Ascending colon	6 (13.3%)
Transverse colon	6 (13.3%)
Descending colon	2 (4.4%)
Sigmoid colon	10 (22.2%)
Rectum	20 (44.4%)
Macroscopic types*	
0-Is	11 (24.4%)
0-Isp	11 (24.4%)
0-IIa	20 (44.4%)
0-IIb	1 (2.2%)
0-IIc	2 (4.4%)
Depth of invasion	
Tis	5 (11.1%)
T1a	12 (26.7%)
T1b	28 (62.2%)

SD, standard deviation; Tis, intramucosal cancer; T1a, submucosal invasion depth<1000μm;
T1b, submucosal invasion depth≥1000μm.
*Paris classification

were the cecum for 1 lesion, the ascending colon for 6 lesions, the transverse colon for 6 lesions, the descending colon for 2 lesions, the sigmoid colon for 10 lesions, and the rectum for 20 lesions. The macroscopic types were 0-Is type for 11 lesions, 0-Isp type for 11 lesions, 0-IIa type for 20 lesions, 0-IIb type for 1 lesion, and 0-IIc type for 2 lesions. The histological findings were Tis cancer for 5 lesions, T1a cancer for 12 lesions, and T1b cancer for 28 lesions.

Primary endpoint

For the diagnostic performance of evaluating the invasion depth of T1b cancer, the accuracy, sensitivity, and specificity were 75.6%, 78.1%, and 69.2% for CE and 71.1%, 78.1%, and 53.9% for EUS, respectively (Table 2). The sensitivity of CE was comparable to that of EUS. The specificity and accuracy of CE were higher than those of EUS, although no significant differences were observed.

Table 2. Diagnostic Performance of CE and EUS for Early Colorectal Cancers

	Accuracy (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
CE	75.6 * (62.2-88.9)	78.1 (62.5-90.6)	69.2* (46.2-92.3)
EUS	71.1 (57.8-84.4)	78.1 (62.6-90.6)	53.9 (23.1-76.9)

CE; chromoendoscopy, EUS; endoscopic ultrasonography.
*p> .05 for CE vs EUS, McNemar's test.

Table 3. Diagnostic Performance of CE, M-NBI and M-CE for Early Colorectal Cancers

	Accuracy (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
CE	75.6* (62.2-88.9)	78.1* (62.5-90.6)	69.2 (46.2-92.3)
M-NBI	53.3 (37.8-68.9)	46.9 (31.3-62.5)	69.2 (46.2-92.3)
M-CE	60.0 (44.4-73.3)	62.5 (46.9-81.2)	53.9 (23.1-84.6)

CE; chromoendoscopy, M-NBI; magnifying endoscopy with narrow-band imaging, M-CE; magnifying endoscopy with chromoendoscopy.
*p< .05 for C-WLI vs M-NBI, McNemar's test.

Secondary endpoints

In terms of diagnosis of the invasion depth of T1b cancer, four patients were diagnosed as having T1b cancer by CE but were found to have Tis cancer/T1a cancer by pathological examination. In these patients misdiagnosed as having deep invasive cancer, EUS showed no additive effect for obtaining a correct diagnosis. Additionally, seven patients were diagnosed as having Tis cancer/T1a cancer by CE but found to have T1b cancer by pathological examination. One of these patients misdiagnosed as having less invasive cancer was correctly diagnosed by EUS.

In terms of diagnostic performance of magnifying endoscopy for evaluating the invasion depth of T1b cancer, the accuracy, sensitivity, and specificity were 53.3%, 46.9%, and 69.2% for M-NBI and 60.0%, 62.5%, and 53.9% for M-CE, respectively (Table 3). The accuracy, sensitivity, and specificity of CE tended to be higher than those of magnifying endoscopy (M-NBI and M-CE), although no significant differences were observed. The sensitivity of CE was significantly higher than that of M-NBI.

One of the four patients misdiagnosed as having deep invasive cancer by CE was correctly diagnosed by M-NBI, whereas M-CE did not yield a correct diagnosis in any of the diagnostic tools. Among the seven patients misdiagnosed as having less invasive cancer by CE, accurate diagnoses were obtained in one patient by M-NBI and two patients by M-CE.

Discussion

This study presents novel findings indicating that CE using the NES as a marker exhibits diagnostic performance comparable to that of EUS. No prior reports have compared the diagnostic performance of CE using the NES as a marker with either EUS or magnifying endoscopy.

In this study, the sensitivity of CE using the NES as a marker was comparable to that of EUS in terms of the diagnosis of the invasion depth of T1b cancer. The accuracy and specificity of CE were higher than those of EUS, although no significant differences were observed. These findings suggest that EUS may not be necessary if CE using the NES as a marker is performed. Based on the histopathological examination results, the lower specificity of EUS was attributable to the fact that lymphoid follicles and fibrosis in the submucosal layer had been diagnosed as cancer invasion by EUS.

Among the patients misdiagnosed by CE using the NES as a marker, only one patient misdiagnosed as having less invasive cancer by CE was correctly diagnosed by EUS. Consequently, EUS did not significantly contribute to mitigating unnecessary surgical interventions, which remains a critical objective in accurately determining the depth of invasion.

The NES manifests as rigidity against a background circular arc, trapezoid elevation, or converging mucosal folds. It is a marker for evaluating invasion depth based on the morphology of the mucosa around a tumor instead of the surface properties of tumors, such as pattern, irregularity, hemorrhage, and tension. To accurately

evaluate the NES, the tumors should be observed from a slightly distant location after fully extending the intestinal tract wall by endoscopic insufflation. In gastric cancer, the diagnosis of invasion depth based on the NES has been reported to be associated with a high false negative rate unless lesions are observed in the oblique or tangential direction [18]. In the context of colorectal cancer, maintaining a safe distance from tumors is often difficult, primarily due to many tumors exhibiting considerable height and the anatomical complexities associated with the large intestine; these complexities include an increased number of curvatures and larger folds compared to the stomach.

Using a 20-MHz high-frequency ultrasound small-diameter probe is known to cause deep attenuation in tumors with a thickness of 11 mm or more [19]. In patients with such tumors, magnifying endoscopy, by which a diagnosis is made based on the surface structure, was considered advantageous for diagnosing invasion depth. Hisabe et al. reported that CE using the NES as a marker was useful for diagnosing the invasion depth of T1b cancer (sensitivity: 66%; specificity: 95.8%; accuracy: 86.3%) and that its specificity was significantly higher than that of M-CE [5]. In addition, because of its high positive predictive value (88.0%), they stated that surgery could be considered without performing additional M-CE in patients with an NES. In this study, the specificity and accuracy of CE using the NES as a marker were lower than those reported by Hisabe et al. This was attributable to the fact that this study included patients only suspected of having T1b cancer diagnosed by CE and magnifying endoscopy.

Although there were no statistically significant differences, the diagnostic parameters (sensitivity, specificity, and accuracy) of CE using the NES as a marker tended to be higher than those of magnifying endoscopy techniques (M-NBI and M-CE). This suggests that CE may potentially be more valuable for diagnostic purposes than magnifying endoscopy. However, one patient who was misdiagnosed as having deep invasive cancer by CE using the NES as a marker was correctly diagnosed with M-NBI. Thus, magnifying endoscopy was found to exert a rather small additive effect.

Although EUS is the only modality that allows observation of the vertical cross-section of tumors for diagnosing the invasion depth of early colorectal cancer, its diagnostic performance does not have additive effects on the diagnostic performance of CE using the NES as a marker. Thus, it appeared unlikely that EUS had benefits that exceeded those of CE using the NES as a marker, even in terms of medical costs and examination time. The findings of this study suggest that CE using the NES, which does not require any specialized equipment such as magnifying endoscopes, image enhancement endoscopes, or ultrasound devices, may offer notable advantages in terms of medical economics and examination time.

The limitations of this study include the single-center retrospective study design. Multicenter prospective studies need to be conducted in the future to verify the results of this study. In addition, the data of this study may have been affected by a selection bias because only lesions observed with all four diagnostic modalities were included in the analyses. Thus, prospective studies, including consecutive patients, need to be conducted to verify the results of this study. As the images were evaluated by the same physicians, the diagnostic results may have been affected by the carrying-over effect. However, we emphasize that, even with the carrying-over effect taken into consideration, EUS and other modalities did not exert any additive effect on the diagnostic performance of CE using the NES as a marker for evaluating invasion depth. Considering the above-described limitations, it is necessary to design multicenter prospective studies including a large number of consecutive patients to compare the diagnostic performance of each modality.

In conclusion, this study demonstrated that CE using the new NES as a marker was comparable to EUS in terms of diagnostic performance and suggested that CE might be an excellent diagnostic modality for early colorectal cancer, even from medical and economic perspectives.

Acknowledgments

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