

[ORIGINAL ARTICLE]

The Differential Diagnosis of Colorectal Polyps Using Colon Capsule Endoscopy

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Abstract:

Objective Although colorectal polyps (CPs) can be observed with colon capsule endoscopy (CCE), it is difficult to determine the type of polyp using CCE. The objective of this study was to differentiate adenomatous polyps (APs) from hyperplastic polyps (HPs) with CCE.

Methods In this single-center retrospective study, an analysis was conducted on the same CPs with both CCE and colonoscopy (CS) and histopathologically diagnosed as AP or HP. The color difference (ΔE) between the polyp surface and the surrounding mucosa was calculated using the CIE1976 $L^*a^*b^*$ color space method on white light (WL), flexible spectral imaging color enhancement (FICE), and blue mode (BM) CP images. We investigated the ability of the ratio of the color differences ($\Delta E'$) to differentiate between APs and HPs.

Results The size of all 51 polyps (34 APs, 17 HPs) was 7.5 ± 4.6 mm with CCE and 7.3 ± 4.2 mm with CS, and this difference was not significant ($p=0.28$). The FICE $\Delta E'$ of APs was 3.3 ± 1.8 , which was significantly higher than the FICE $\Delta E'$ of HPs (1.3 ± 0.6 ; $p < 0.001$). A receiver operating characteristic analysis showed that FICE $\Delta E'$ was useful for differentiating between APs and HPs, with an area under the curve of 0.928 (95% confidence interval, 0.843-1). The sensitivity was 91.2%, and the specificity was 88.2% with a cut-off value of 1.758.

Conclusion Using FICE on CCE images of CPs and applying the CIELAB color space method, we were able to differentiate between APs and HPs with high accuracy. This method has the potential to reduce unnecessary CS procedures.

Key words: colon capsule endoscopy, colorectal polyp, adenomatous polyp, hyperplastic polyp, flexible spectral imaging color enhancement

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Introduction

The incidence of colorectal cancer is increasing worldwide (1, 2); however, secondary prevention by the early detection and treatment of colorectal polyps (CPs) provides the possibility of a complete cure (3-5). Colonoscopy (CS) is a very effective method for identifying and removing CPs.

However, it is an invasive procedure that can cause pain in some patients, and the complications associated with CS may include perforation and bleeding. The first generation of colon capsule endoscopy (CCE) (PillCam Colon; Given Imaging, Yoqneam, Israel) procedures appeared in 2006, offering a pain-free, noninvasive examination (6). Technological advances led to a second generation of CCE in 2009; this technology is reportedly associated with high CP detec-

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tion rates of approximately 84-94% with polyps ≥ 6 mm and 88-92% with polyps ≥ 10 mm (7-9).

If a CP detected with CCE is identified as a neoplastic lesion (NL), CS should be performed to remove it. However, if the polyp is a non-neoplastic lesion (NN), it will not require endoscopic resection (ER), and unnecessary CS should be avoided. Thus far, it has not been possible to differentiate between NLs and NNs with CCE (10, 11). Therefore, CS is generally performed even for NNs that do not require ER.

Second-generation CCE is equipped with flexible spectral imaging color enhancement (FICE) and blue mode (BM), which are digital image processing technologies that use the RAPID software program (Given Imaging, Yoqneam, Israel, V.7.0) (12). FICE creates a new and flexible spectral image by approximating spectral reflectance from the white light (WL) image of an object and selecting and reconstructing red, green, and blue (RGB) wavelengths that emphasize the object (13-15). The BM superimposes the color coefficient shift of light in the short-wavelength range (490-430 nm) on a WL image (16). Imagawa et al. reported that using FICE in small bowel capsule endoscopy (SBCE) achieved greater visibility of angioectasia, erosion/ulceration, and tumors than WL (17). Similarly, Sato et al. reported that the detection rate of small bowel lesions increased when using FICE (18). Improved visibility of blood vessels and the demarcation of lesion borders has been reported when using BM in SBCE (19). However, there have been no reports on whether or not CCE can differentiate between different types of polyps.

The present study investigated whether or not the CIE 1976 $L^*a^*b^*$ (CIELAB) color space method (20, 21) could be used to differentiate between adenomatous polyps (APs) and hyperplastic polyps (HPs) in WL, FICE, and BM images of CPs obtained using CCE.

Materials and Methods

Patients

This was a retrospective single-center study. From April 2014 to December 2018, we recruited consecutive patients in whom CCE identified a CP of ≥ 6 mm and who underwent CS for ER within 1 month after CCE. The Ethics Committee of Osaka Medical College approved this study.

Study protocol

The analysis was performed on lesions that were identified as CCE and confirmed to be the same polyps resected during CS and that had been histopathologically diagnosed as AP or HP by ER or a biopsy. The size and morphology of each polyp in CS and CCE images were compared. In addition, the color difference between the polyp surface and the surrounding mucosa was calculated from WL, FICE, and BM images using the CIELAB color space method to determine whether or not this approach could be used to differentiate between APs and HPs.

If the following criteria were met, the lesion was judged to be the same in CCE and CS: 1) the polyps diagnosed with CCE and CS were in the same or adjacent segments (with the large intestine divided into four segments: cecum to ascending colon, transverse colon, descending colon to sigmoid colon, and rectum); 2) the error in the size of the polyps evaluated by CCE and CS was $\pm 50\%$ or less; and 3) the interpreter determined that the lesion was the same polyp identified with CCE and CS.

CCE and CS procedures

The examinations were performed via second-generation CCE (PillCam[®] COLON2; Covidien Japan, Tokyo, Japan). The CCE pretreatment protocol followed that of a previous report (9). The CCE system consists of a capsule, a data recorder (DR3), and a computer equipped with the RAPID software program (9). The CCE system has cameras with a viewing angle of 172° at both ends, enabling the acquisition of almost 360° images. It is also able to perform polyp size estimation (PSE), which can measure the size of the lesion (22). Thus, the sizes of the CPs that were found were measured using PSE. The location of the lesion was estimated based on the landmarks captured by CCE (cecum, hepatic flexure, splenic flexure, and rectum) and on the trajectory of the capsule, as displayed in the RAPID software program (23). The macroscopic type of CPs was divided into protruded and superficial types using the Paris endoscopic classification (24). The CCE diagnosis was performed by two practitioners (KN, SN), each with experience in at least 20 cases.

A PCF-H290I or PCF-Q260AZI (Olympus, Tokyo, Japan) was used for the CS procedure. The CP observed with CCE was carefully identified with CS to perform ER (cold snare polypectomy or endoscopic mucosal resection) or a biopsy. With CS, the size of the CP was measured using biopsy forceps or a ruler. CS was performed by 4 practitioners (KN, SN, YH, KK), including the 2 practitioners (KN, SN) who performed CCE diagnosis, each with experience in at least 1,000 cases.

Calculation of the color differences

The CIELAB color space is the most widely used method for measuring and ordering object color (20, 21). The color coordinates are: L^* for the lightness from black (0) to white (100), a^* from green (-) to red (+), and b^* from blue (-) to yellow (+) (Fig. 1). In this study, the color difference between the polyp surface (p) and the normal mucosa (b) in the CCE image of a CP was calculated for WL, FICE, and BM. The normal mucosa was detected from the mucosa surrounding the polyp and did not include residues, bubbles, or blood vessels in WL images. The color difference was the distance between two points in the $L^*a^*b^*$ color space calculated using the formula

$$\Delta E_{pb} = \sqrt{(L^p - L^b)^2 + (a^p - a^b)^2 + (b^p - b^b)^2} \quad (18).$$

In brief, 1) corresponding regions (polyp surface and surrounding mucosa, 64 pixels each) were selected in the Adobe Photoshop Elements 15 software program (Adobe Systems, San Jose, USA) (Fig. 2); 2) the median RGB value was then determined; 3) the $L^*a^*b^*$ value was calculated from the mean RGB value; and 4) the $L^*a^*b^*$ value was used to calculate ΔE . We examined the color differences in the CCE images of AP and HP separately (Fig. 3). Furthermore, the ratio of the color differences in the FICE and WL images was defined as $FICE\Delta E/WL\Delta E$ ($FICE\Delta E'$).

The utility of the $FICE\Delta E'$ value to differentiate between APs and HPs was then examined via a receiver operating characteristic (ROC) analysis.

Statistical analyses

Wilcoxon's signed-rank test was used to compare CP sizes. The paired *t*-test was used to compare ΔE and $\Delta E'$.

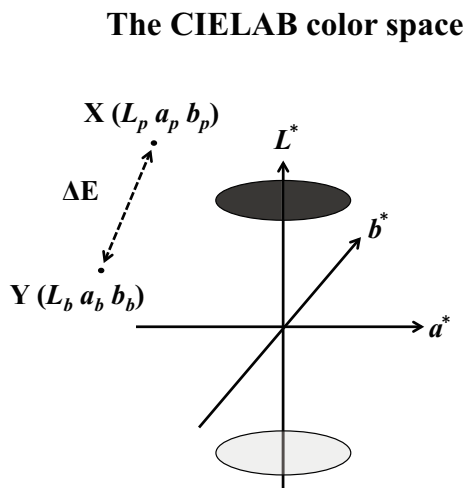


Figure 1. CIE 1976 $L^*a^*b^*$ (CIELAB) color space. The color coordinates are: L^* for the lightness from black (0) to white (100), a^* from green (-) to red (+), and b^* from blue (-) to yellow (+). (X) is the polyp surface; (Y) is the surrounding mucosa. The color difference (ΔE) was the distance between two points calculated using the formula $\Delta E_{pb} = \sqrt{(L^p - L^b)^2 + (a^p - a^b)^2 + (b^p - b^b)^2}$.

Fisher's exact test was used to compare the morphological diagnoses with CS and CCE. The statistical significance level was set as $p < 0.05$.

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

Results

Of the 49 patients who underwent CCE at our hospital, polyps ≥ 6 mm in size were observed in 19. Of these, 18 patients underwent CS for therapeutic purposes. From these examinations, 53 lesions were judged to be the same as those identified with CCE. The 18 patients included 11 men and 7 women with a median age of 71 (35-87) years old (Table 1). The histopathological diagnoses were 34 cases of AP, 17 of HP, 1 sessile serrated adenoma/polyp (SSA/P), and 1 traditional serrated adenoma (TSA). We analyzed 51 lesions, excluding SSA/P and TSA. The polyps were located from the cecum to the ascending colon in 12 cases, in the transverse colon in 10 cases, from the descending to the sigmoid colon in 24 cases, and in the rectum in 5 cases by CS.

The overall polyp size was 7.5 ± 4.6 mm on CCE and 7.3 ± 4.2 mm on CS, and this difference was not significant (Table 2). There was no marked difference between the CCE and CS measurements when the polyps were separated into APs and HPs. Macroscopically, CPs were identified as protruded in 42 cases and superficial in 9 cases with CCE and as protruded in 39 cases and superficial in 12 cases with CS (including lateral spreading tumors; LSTs), with a diagnostic agreement of 92.2% (47/51 cases). Of the discrepancies, three cases were diagnosed as protruded on CCE but superficial on CS, and one case was diagnosed as superficial on CCE but protruded on CS.

The comparison of color differences in CCE images

Among the 34 APs, the $FICE\Delta E$ (39.2 ± 19.3) was significantly higher than the $WL\Delta E$ (14.9 ± 10.4) ($p < 0.001$), as was the $BM\Delta E$ (23.3 ± 15.4) ($p < 0.001$) (Fig. 4). In contrast,

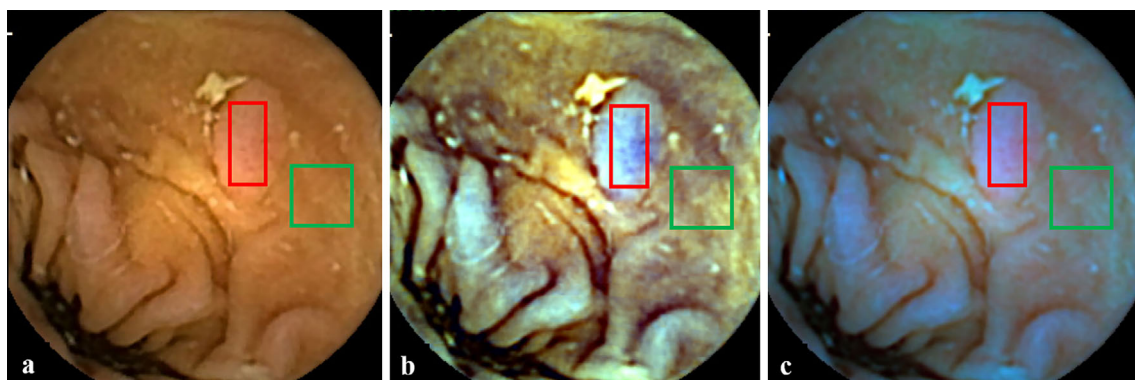


Figure 2. Selection of points for assessing the color differences in colon capsule endoscopy (CCE) images. Red square areas consisting of 64 (8×8) pixels show the polyp surface. Green square areas show the surrounding mucosa. (a) White light (WL), (b) flexible spectral imaging color enhancement (FICE), and (c) blue mode (BM).

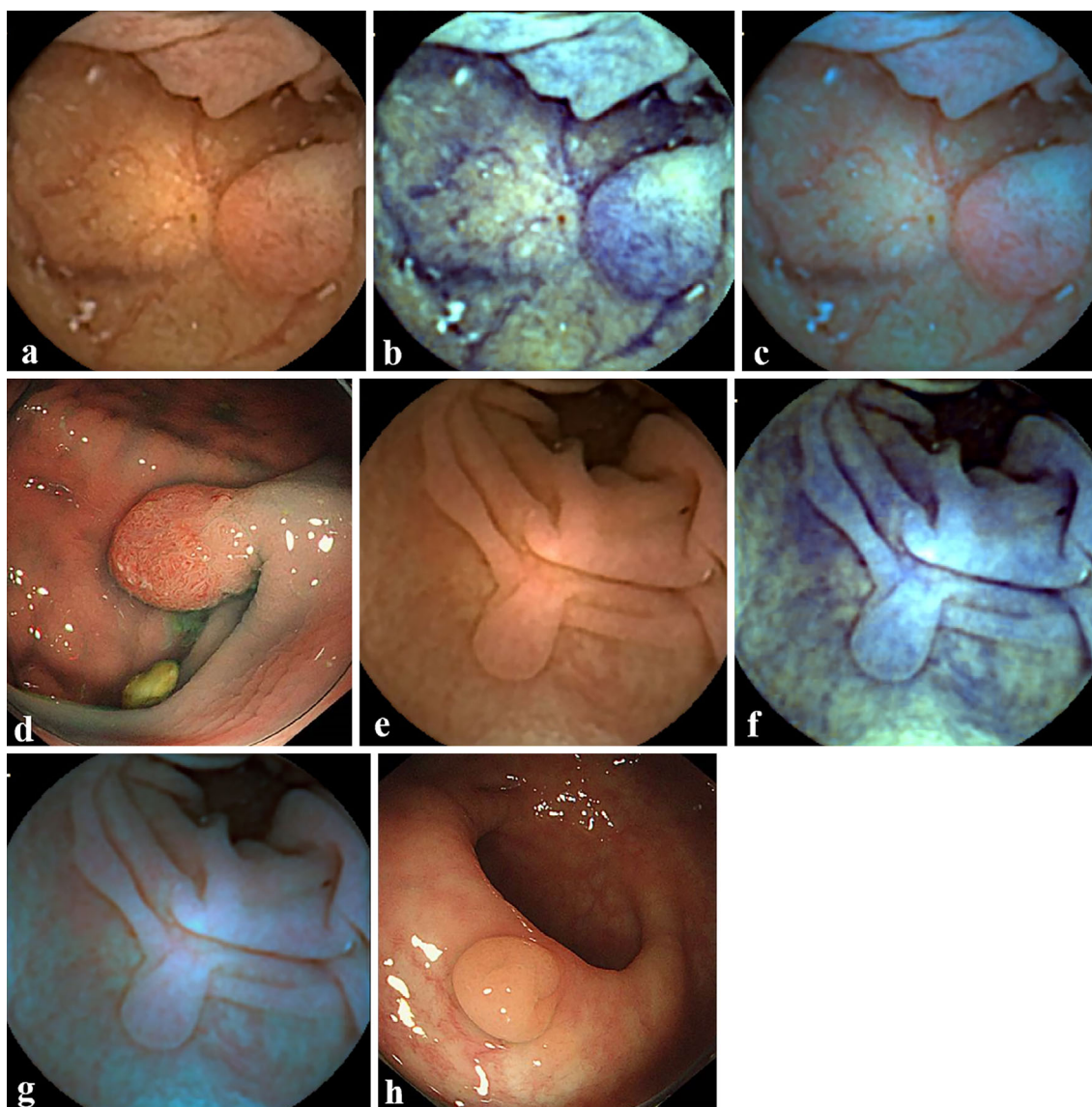


Figure 3. WL, FICE, and BM colon polyp images with colon capsule endoscopy (CCE) and WL images with CS. (a-d) The same adenomatous polyp, (e-h) the same hyperplastic polyp. (a, e) CCE WL images, (b, f) CCE FICE images, (c, g) CCE BM images, and (d, h) CS WL images.

among the 17 HPs, the FICE $\Delta E'$ (12.8 ± 10.4) and BM $\Delta E'$ (13.1 ± 11.9) were not significantly different from the WL $\Delta E'$ (10.7 ± 6.8) ($p=0.44$ and $p=0.45$, respectively) (Fig. 4).

Differentiation of adenoma and hyperplastic polyps using $\Delta E'$

We attempted to differentiate APs and HPs using $\Delta E'$ from the CCE images. The FICE $\Delta E'$ of the APs (3.3 ± 1.8) was significantly higher than that of the HPs (1.3 ± 0.6 ; $p < 0.001$) (Table 3). In contrast, the BM $\Delta E'$ of the APs (1.6 ± 0.5) was not significantly different from that of the HPs (1.2 ± 0.6 ; $p=0.23$).

In the ROC analysis, the FICE $\Delta E'$ was shown to be useful for differentiating between APs and HPs, with an area under the curve of 0.928 (95% confidence interval, 0.843-1) (Fig. 5). The optimal cut-off value for differentiation was 1.758. This cut-off value had 91.2% sensitivity and 88.2%

specificity.

Influence of the factors relevant to anemia on the calculation of the FICE $\Delta E'$

Of the 18 patients, 3 had mild anemia and had 8 polyps. Fifteen patients without anemia had 43 polyps. The FICE $\Delta E'$ of patients with anemia was 3.1 ± 1.0 , which was not significantly different from the FICE $\Delta E'$ of patients without anemia (2.5 ± 1.9 ; $p=0.195$). Regarding gender differences, the FICE $\Delta E'$ of the 11 men was 2.7 ± 2.0 , which was not significantly different from the FICE $\Delta E'$ of the 7 women (2.5 ± 1.5 ; $p=0.756$).

Discussion

This study demonstrated that APs and HPs can be differentiated with high accuracy using FICE on CCE to perform

Table 1. Baseline Characteristics of the Patients and Polyps.

Characteristic	Value
Number of patients	18
Sex (male/female)	11/7
Age, years	71 (63-79)
Number of polyps	51
Polyp location (Cecum-A/C:T/C:D/C-S/C:rectum)	12:10:24:5
Pathological diagnosis (Adenomatous polyp, hyperplastic polyp), n(%)	34:17 (66.7:33.3)

A/C: ascending colon, T/C: transverse colon, D/C: descending colon, S/C: sigmoid colon

Table 2. Size and Macroscopic Type of Polyps with CCE and CS.

	CCE	CS	p value
Size (mm)			
overall	7.5±4.6	7.3±4.2	0.275
Adenomatous polyps	8.5±4.6	8.1±4.1	0.135
Hyperplastic polyps	5.5±4.0	5.6±3.8	0.986
Macroscopic type (Protruded:Superficial)	42:9	39:12	0.292

CCE: colon capsule endoscopy, CS: colonoscopy

a CIELAB color difference analysis. This study is the first to differentiate between APs and HPs on CCE. As it is not possible to determine the type of polyp with CCE, there is no choice but to perform CS when a CP is identified (11). However, although there is a risk of malignancy with APs due to the adenoma-carcinoma sequence (25, 26), HPs are unlikely to become malignant (27). Therefore, if a polyp observed using CCE is shown to be an HP, CS is generally unnecessary unless the polyp is relatively large. In the present study, good differentiation was made possible by calculating the FICEΔE' from CCE images, with a sensitivity of 91.2% and specificity of 88.2%. This method may be of great clinical significance for reducing unnecessary CS procedures.

A diagnosis using CCE should first be performed conventionally with WL images. With CCE, the most important thing is not to miss colorectal cancer. If a lesion is suspected of being colorectal cancer, CS must be performed, regardless of the size of the lesion. Differentiation using color differences is at most an auxiliary diagnosis, and its significance lies in identifying cases where CS is not necessary. The present study examined APs and HPs and did not include colorectal cancer. Because colorectal cancer appears redder than APs (28), we expect the FICEΔE' of colorectal cancer to be equal to or greater than that of APs. NLs that are ≥6 mm are more often cancerous than those that are <6 mm, and ER is recommended (29-31). Although the frequency of cancer with lesions <6 mm is extremely low, at 0.03-0.3% (31, 32), ER may be performed to prevent progression to cancer, depending on the patient's age, overall condition, and comorbidities (33, 34). HPs, which are NNs,

are flat, white elevations frequently found in the rectum and sigmoid colon. Lesions with a diameter <6 mm are unlikely to become tumors in the future, and the recommendation is to watch and wait (33-35). Recently, SSA/Ps have attracted attention because they are thought to be precursors of MSI-positive colorectal cancer (36). SSA/Ps occur predominantly in the right colon and have a malignant transformation rate of 3.0-15% (37, 38). Lesions ≥10 mm are indicated for ER (39-41). Because SSA/Ps are flat and have a faded color; they can be difficult to differentiate from HPs using endoscopic findings with WL CS (42). While we did not examine any such lesions, they may be difficult to differentiate from HPs even when using the FICEΔE' determined from CCE. Therefore, a comprehensive assessment that includes several factors, such as the location and size, must be performed to determine whether or not therapy is indicated.

For all of these reasons, if a lesion is <6 mm and the FICEΔE' ≤1.76 and the location in the rectum or sigmoid colon, it can be considered HP, and a watch-and-wait approach can be applied. If a lesion is 6-9 mm and the FICEΔE' ≤1.76, CS may not be required immediately, as the lesion may be an HP. However, the patient should undergo CCE or CS after one year or more.

Few reports have compared the macroscopic type of polyps with CCE and CS (9). Although the macroscopic type matched in most cases in the present study, there was disagreement in 7.8% (4/51) of cases. Three cases were diagnosed as protruded with CCE but as superficial with CS. This may be because observations using CCE are performed while immersed in fluid, and if the intestinal tract is insufficiently dilated, lesions may be more likely to appear protruded. Furthermore, one lesion was diagnosed as superficial with CCE but as protruded with CS. In this case, the polyp was not observed entirely on CCE, which made it difficult to assess its elevation. General differences in the observation conditions of CCE and CS may have led to differences in the macroscopic type.

CIELAB is a colorimetric system that numerically replaces colors with a color space close to what humans perceive (20, 21). It is useful for comparing visibility in endoscopy. We found that, when using CIELAB color differences in CS, linked-color imaging was useful for identifying CP,

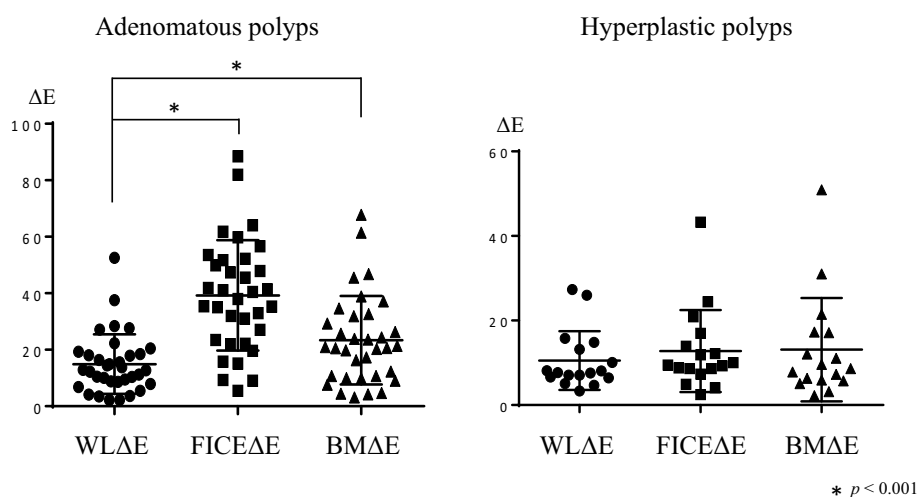


Figure 4. Color differences in the colon capsule endoscopy (CCE) images of APs and HPs. The FICE ΔE and BM ΔE were significantly higher than the WL ΔE in AP images ($p < 0.001$). In contrast, the FICE ΔE and BM ΔE were not significantly different from the WL ΔE in HP images ($p = 0.44$ and $p = 0.45$, respectively). WL: white light, FICE: flexible spectral imaging color enhancement, BM: blue mode, ΔE : color differences

Table 3. The Ratio of the Color Differences in the CCE Images of Adenomatous and Hyperplastic Polyps.

	Adenomatous polyps	Hyperplastic polyps	p value
FICE $\Delta E'$	3.3 \pm 1.8	1.3 \pm 0.6	<0.001
BM $\Delta E'$	1.6 \pm 0.5	1.2 \pm 0.6	0.227

CCE: colon capsule endoscopy, FICE: flexible spectral imaging color enhancement, BM: blue mode, $\Delta E'$: the ratio of the color differences

and blue-laser imaging was useful when observing magnified images (21). Furthermore, it was reported that, when using this method with SBCE, FICE was effective in improving the detection rate of small bowel lesions (18). In the present study, we showed that using the CIELAB color difference in FICE images from CCE to calculate the $\Delta E'$ and determine a cut-off value enabled the differentiation of APs from HPs with high sensitivity and specificity. While it was previously reported that using narrow-band imaging improves the ability to differentiate between AP and HP with CS (41-43), this is the first report on CCE. Sato et al. reported that visibility is improved to a greater degree with FICE than with BM, especially for vascular lesions, such as angioectasia, to emphasize the redness of the lesions (18). As APs appear redder than HPs, FICE $\Delta E'$ but not BM $\Delta E'$ can differentiate between APs and HPs with high accuracy. The FICE used in the present study was installed in the CCE system (Covidien Japan), and no new specialized equipment was required. Therefore, this method can be widely applied and is expected to be of great use.

Several limitations associated with the present study warrant mention. First, we only examined APs and HPs, excluding malignant tumors, SSA/Ps, and other lesions. Nevertheless, the value of differentiating with FICE $\Delta E'$ is its ability to reduce unnecessary CS. We believe that it is highly likely

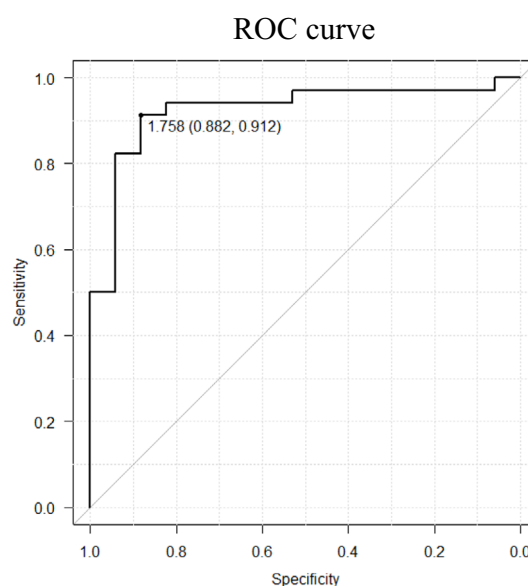


Figure 5. Receiver operating characteristic (ROC) curve for FICE $\Delta E'$ in the CCE images of adenomatous vs. hyperplastic polyps. The area under the curve (AUC) was 0.928 (95% confidence interval 0.843-1). The optimal cut-off value that allows for the differentiation of these polyps was 1.758. This cut-off value had 91.2% sensitivity and 88.2% specificity.

that there is no need to rush to perform CS for polyps that have a FICE $\Delta E' \leq 1.758$ and are <10 mm. Second, even if APs and HPs can be differentiated with high sensitivity and specificity using FICE $\Delta E'$, a histopathological diagnosis by a biopsy is not possible with CCE; thus, a definitive diagnosis cannot be made. Third, while we examined cases in which the polyps observed with CCE were confirmed with CS, there was no guarantee that these were the same polyps. In the present study, we only examined polyps that were in

the same location or adjacent areas with CCE and CS, that did not differ in size, and that were confirmed by an interpreter to be the same polyp. We therefore believe they were almost always the same polyps. Fourth, this was a retrospective, single-center study, and the sample size was small. A prospective multicenter trial in a larger population should be performed to confirm the clinical usefulness of this method.

In conclusion, APs and HPs can be differentiated with high accuracy by using FICE on CCE images and applying a CIELAB color difference analysis. This method has the potential to reduce unnecessary CS procedures. To clarify the clinical usefulness of this method, a multicenter trial would be worth performing in a future study.

The authors state that they have no Conflict of Interest (COI).

Kei Nakazawa and Sadaharu Nouda contributed equally to this work.

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