Diagnostic accuracy of narrow-band imaging and pit pattern analysis significantly improved for less experienced endoscopists following expanded training program

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Abbreviations: narrow-band imaging, NBI; no endoscopy experience group, NEE; less experienced endoscopist group, LEE; highly experienced endoscopist group, HEE; kappa, κ; conventional colonoscopy, CC; low-magnification NBI, NBI-L; high-magnification NBI, NBI-H; low-magnification chromoendoscopy, CE-L; high-magnification chromoendoscopy, CE-H

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DISCLOSURE

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CONFLICT OF INTEREST

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ABSTRACT

Background: Previous reports assessing diagnostic skill using narrow-band imaging (NBI) and pit pattern analysis for colorectal polyps involved only highly experienced endoscopists.

Objective: Evaluate diagnostic skill of less experienced endoscopists (LEE group) for differentiation of diminutive colorectal polyps using NBI and pit pattern analysis with and without magnification following expanded training program.

Design: Prospective study.

Patients and Setting: Forty-four colorectal polyps (27 adenomas and 17 hyperplastic polyps) ≤5mm identified and analyzed in 32 patients using conventional colonoscopy as well as non-magnification and magnification NBI and chromoendoscopy followed by endoscopic removal for histopathological analysis.

Interventions: 220 endoscopic images distributed in randomized orderings once before and once after training to residents with no prior endoscopy experience (NEE group) and LEE group who had performed colonoscopies >5 years, but never used NBI; and once to highly experienced endoscopists (HEE group) who had routinely used NBI >5 years. Magnification NBI and chromoendoscopy images assessed using Sano and Kudo classification systems, respectively.

Main Outcome Measurements: Diagnostic accuracy and interobserver agreement for each endoscopic modality in each group.

Results: Diagnostic accuracy was significantly higher and kappa (κ) values improved in LEE group for NBI with high-magnification (NBI-H) following expanded training. Diagnostic accuracy and κ values using NBI-H were highest among endoscopic techniques for LEE group following such training and HEE group (accuracy 90% vs. 93%; κ=0.79 vs. κ=0.85, respectively).

Limitations: Study involved only polyps ≤5mm.

Conclusions: Using NBI-H increased differential diagnostic skill of LEE group after expanded training so that it was equivalent to HEE group.

(250 words)

INTRODUCTION

It is widely accepted that adenomatous polyps are precursors of colorectal cancer and performing polypectomies on such lesions can reduce the risk of subsequent colorectal cancer by up to 80% for a period that may exceed 10 years.[1] In addition, adenomas are a major factor in guidelines that have been developed for recommended colonoscopy surveillance intervals following polypectomies because they are a powerful predictor for future colorectal cancer risk.[1-3] Small colorectal adenomas as well as advanced adenomas[4] are precursors of colorectal cancer and multiple genetic alterations have been implicated in the adenoma-carcinoma sequence.[5]

Endoscopic differentiation of small adenomas from non-adenomatous polyps is important because endoscopists should avoid performing any unnecessary procedure including polypectomies that can sometimes cause related complications such as

bleeding and perforation.[6,7] The diagnostic accuracy of conventional colonoscopy for such colorectal polyps, however, has previously been reported to be unsatisfactory.[8,9] In contrast, chromoendoscopy with indigo-carmine dye spraying has been shown to be an effective procedure for detecting and evaluating colorectal polyps[10-15] despite having several disadvantages including a longer procedure time and the additional cost for dye spaying.

Narrow-band imaging (NBI) is an innovative optical technology providing a unique image that emphasizes the morphological and structural character of lesions as well as their surface capillary patterns.[16-25] It has been reported that this modality is a new non-dye tool for differentiation of neoplastic from non-neoplastic polyps with a diagnostic accuracy including pit pattern analysis equivalent to chromoendoscopy.[17-21] Such reports have been based on studies involving only highly experienced endoscopists, however, with few published articles concerned with the learning curve for NBI being dependent on an individual endoscopist's experience and ability. The aim of this study was to determine, therefore, whether expanded training in the effective use of NBI and pit pattern analysis with and without magnification would improve the diagnostic skill of less experienced endoscopists in the differentiation of diminutive colorectal polyps.

METHODS

Patients

Patients scheduled for a total colonoscopy at Okayama University Hospital and Sumitomo Besshi Hospital between September and October 2008 were invited to participate in this study. Informed consent was obtained from all patients before their

examinations. Patients with inflammatory bowel disease, familial adenomatous polyposis, an international normalized ratio greater than 2.0 or a platelet count less than 50,000/mm^3 were excluded from this study.

Colonoscopy and Polyp Assessment Protocol

Bowel preparation consisted of patients drinking 2-3 liters of polyethylene glycol solution in the morning before their procedures.[13] Total colonoscopies were prospectively performed using a video endoscopic system (EVIS, Lucera Spectrum; Olympus Co., Tokyo, Japan) with CF-H260AZI or PCF-Q240ZI magnification colonoscopes (Olympus) by two highly experienced endoscopists (RH, TU) each of whom had previously performed over 1,000 colonoscopies annually.

When a lesion was detected by conventional colonoscopy examination, surface mucus was washed away with lukewarm water and endoscopic images were taken in the following order: conventional colonoscopy (CC), low-magnification NBI (NBI-L), high-magnification NBI (NBI-H), low-magnification chromoendoscopy (CE-L) and high-magnification chromoendoscopy (CE-H). A standard optical filter was used for both conventional colonoscopy and chromoendoscopy with chromoendocopic images taken after 0.2% indigo-carmine dye was sprayed on the lesion surface. The enhanced surface structure function of the video image processor at the level A5 setting was used in taking all endoscopic images.[23] Location, size and macroscopic type of each lesion were recorded with size measured using open forceps. Lesions were classified macroscopically based on the criteria of the Paris classification of superficial gastrointestinal lesions.[26] A biopsy, polypectomy or endoscopic mucosal resection was then performed and the resulting specimen was analyzed histopathologically.

Image Evaluator Categories

A total of 12 doctors with different levels of endoscopic experience were asked to independently evaluate endoscopic images. The doctors were separated into three groups: four residents with no prior endoscopy experience (NEE group); four less experienced endoscopists each of whom had performed colonoscopies for more than five years, but had never previously used NBI (LEE group); and four highly experienced endoscopists each of whom had routinely used magnification colonoscopy with NBI for more than five years (HEE group).

Assessment of Endoscopic Images

The best quality endoscopic images were selected for each modality and stored digitally in JPEG format. All images were distributed in randomized orderings to each group of evaluators. For the NEE and LEE groups, the same images were distributed in randomized orderings once before and once after those group members participated in an intensive one-hour interactive training program on white light endoscopy, NBI and chromendoscopy including Sano NBI classification[20,21] and Kudo pit pattern classification[27,28] using an atlas of endoscopic images of polyps produced by an independent group of highly experienced endoscopists. Although completely unaware of the histopathological results, every participant correctly diagnosed polyps as either neoplasms or non-neoplasms using 1) chromoendoscopy based on Kudo pit pattern classification with types III (including IIIʟ and IIIs), IV and V (including Vɪ and Vɴ) pit patterns considered to be neoplasms and types I and II pit patterns regarded as non-neoplasms[27,28]; 2) NBI-L that revealed a brownish area determined to be neoplastic in nature; and 3) NBI-H together with the Sano classification of meshed capillary vessel pattern in which types II and III were considered as being neoplastic while type I without meshed capillaries was non-neoplastic (Figures 1, 2).[20-21] Patient information

such as age, gender and clinical diagnosis was not disclosed to any of the evaluators and discussions were not permitted among the doctors individually or in groups.

Statistical Analysis

Diagnostic accuracy of each endoscopic modality was assessed in reference to histopathological results. Estimates of diagnostic accuracy were calculated based on the average diagnostic accuracy for each group of doctors as well as each diagnostic modality. The upper and lower 95% confidence interval (CI) limits were calculated using a normal model that consisted of symmetric CIs with limits at a distance from the estimate equal to the product of 1.96 times the standard error. Interobserver agreement in diagnosing colorectal lesions in each group and by each modality was determined by calculation of the kappa statistic (κ) and its 95% CI using the Fleiss method. Diagnostic accuracies before training and after training in the NEE and LEE groups were compared with the McNemar test. As for differences in diagnostic accuracies after training among the NEE, LEE and HEE groups, those findings were analyzed using Fisher's exact test. Multiple statistical testing of outcome data was conducted in this study, therefore, a Bonferroni correction was applied and differences with a *p* value <0.025 were considered significant as the correction. A κ value <0.4 was regarded as poor agreement, a κ value of 0.41–0.60 was considered to be fair agreement, a κ value of 0.61–0.80 represented good agreement and a κ value >0.80 was determined to be excellent agreement. Statistical analyses were conducted using version 7.0 of the JMP statistical software package (SAS Institute, Cary, NC, USA) and a Microsoft Excel 2007® spreadsheet (Microsoft, Renton, WA, USA).

RESULTS

Clinicopathological Features of Colorectal Lesions

Seventy-two consecutive patients were enrolled in this study for prospective endoscopic evaluation. A total of 44 lesions ≤5mm were identified and analyzed in 32 patients (Table 1). Mean patient age was 61.2 (standard deviation [SD], 12.3) years and the male/female ratio was 2.2:1. Bowel preparation was considered adequate in all examinations and complete colonoscopy was performed to the cecum in every case. There were no complications during any procedure. Of the 44 lesions, 37 lesions were macroscopically classified as type 0-Is, 6 lesions as type 0-IIa and 1 lesion as type 0-IIc. Mean lesion size was 3.4mm (1.1). As for location, 22 (50%) polyps were found in the right colon (cecum, ascending and transverse colon), 14 (32%) in the left colon (descending and sigmoid colon) and eight (18%) in the rectum**.** Histopathological assessments included 27 (61%) adenomas and 17 (39%) hyperplasic polyps. A total of 220 images of the 44 lesions were collected as each lesion was photographed during CC, NBI-L, NBI-H, CE-L and CE-H.

Diagnostic Accuracy of NBI and Pit Pattern Analysis

Table 2 indicates diagnostic accuracy for each endoscopic modality. In the NEE group, diagnostic accuracies using CC, NBI-L and NBI-H significantly improved after the training program (CC, $p<0.001$; NBI-L, $p=0.006$ and NBI-H, $p=<0.001$), but the NEE group's diagnostic accuracies were still significantly lower in all modalities except CC compared to the HEE group (CC, $p=0.049$; NBI-L, $p=0.0023$; NBI-H, $p<0.001$; CE-L, $p<0.001$; and CE-H, $p<0.001$). Diagnostic accuracies in the LEE group for NBI-L, NBI-H and CE-H also improved significantly following the training program ($p=0.001$, $p<0.001$ and $p=0.001$, respectively). In contrast to the NEE group's results, however, subsequent diagnostic accuracies of the LEE group were not significantly

different from diagnostic accuracies of the HEE group with respect to the CC, NBI-L, NBI-H, CE-L and CE-H modalities ($p=1.0$, $p=0.60$, $p=0.57$, $p=0.031$ and $p=0.48$, respectively).

Assessment of Interobserver Agreement Based on Endoscopic Experience

Interobserver agreements in the HEE group for NBI-H were >0.80 representing excellent agreement and >0.60 for NBI-L, CE-L and CE-H representing good agreement (κ value; CC: 0.5, NBI-L 0.62, NBI-H: 0.85, CE-L: 0.69, CE-H 0.7). Meanwhile, κ values for NBI-H in the LEE group improved to "good agreement" after the training program while the κ values for NBI-L, CE-L and CE-H in the LEE group improved to "fair agreement" after the training program (κ value before training vs. after training: NBI-H, 0.46 vs. 0.79; NBI-L, 0.31 vs. 0.54; CE-L, 0.32 vs. 0.44; and CE-H, 0.33 vs. 0.59). In contrast, however, none of the κ values for any of the modalities in the NEE group improved beyond "poor agreement" after the training program (CC, -0.068 vs. 0.24; NBI-L, 0.059 vs. 0.25; NBI-H, 0.16 vs. 0.39; CE-L, 0.28 vs. 0.23; and CE-H, 0.12 vs. 0.18) (Figure 3).

In comparing diagnostic accuracy for each modality in the NEE group after the training program, the LEE group after the training program and the HEE group, NBI-H had the highest accuracy rate among all three groups (Table 2). Similarly, the κ value for NBI-H was significantly higher in the NEE group after the training program, the LEE group after the training program and the HEE group compared to the other endoscopic diagnostic modalities (Figure 3).

DISCUSSION

Endoscopic diagnostic tools and technology are expected to be accurate and provide

reliably reproducible agreement as well as being easy to use, readily available and relatively inexpensive, but sufficient skill on the part of the endoscopist is still required for proper diagnosis. Our prospective study demonstrated significant improvement in the LEE group in diagnostic accuracy when using NBI and CE after undergoing limited, but intensive training. The improved diagnostic accuracy of the LEE group was equivalent to the HEE group in terms of differential diagnosis using NBI-L, NBI-H and CE-H. In addition, both higher diagnostic accuracy (>80%) and good interobserver agreement (κ value >0.6) for diminutive colorectal polyps were achieved by the LEE group when using NBI-H, following the training program.

The fact that the diagnostic accuracy and κ value of NBI-H were the highest among all the endoscopic techniques analyzed in this study for both the NEE and LEE groups following the expanded training program as well as for the HEE group leads us to suggest that NBI-H is more accurate and provides a higher level of reproducible agreement than the other diagnostic tools in differentiating diminutive neoplastic from non-neoplastic colorectal polyps. Chiu et al. earlier validated that diagnostic accuracy of NBI-H was equivalent to CE-H.[29] Their study reported that diagnostic accuracies for two experienced endoscopists ranged from 91% to 92% using CE-H and from 87% to 90% for NBI-H. In our study, the diagnostic accuracy of the HEE group was 85% (95% CI 79%-89%) using CE-H and 93% (95% CI 88%-96%) with NBI-H although the difference between the two modalities was not significant. Earlier reports analyzing the diagnostic accuracy rate based on polyp size indicated that differentiation using CE-H was more difficult for diminutive colorectal polyps <6mm in size.[6-7]

Our results indicated that it was possible to significantly improve the diagnostic skill for differentiating diminutive colorectal polyps using NBI-L, NBI-H, CE-L and CE-H in

the LEE group following the limited, but intensive one-hour interactive training program. We believe that of the various endoscopic modalities, the use by the LEE group of NBI-H subsequently became both statistically equivalent to that of the HEE group in terms of diagnostic accuracy and closest to reaching "excellent agreement" compared with the other modalities in terms of κ value for two possible reasons. The first concerns the smaller size of the polyps examined in this study because diagnostic accuracy of diminutive colorectal polyps using CE-H has been reported to be lower than for polyps >5mm.[6-9] It is conceivable that differentiation of diminutive colorectal polyps could have been similarly effected somehow reducing the diagnostic accuracy of CE-H while not affecting the diagnostic accuracy of NBI-H by the LEE group. Secondly, the possibility exists that members of the LEE group were able to recognize whether or not there were meshed capillary vessels on the surface of the mucosa easier than they could identify the pit patterns of diminutive colorectal polyps.

In the Rogart et al. report on the NBI learning curve[30], diagnostic accuracy using NBI-L significantly improved as the experience level of endoscopists increased with the diagnosis of approximately 130 lesions necessary for basic competency. Their findings indicated that educational sessions conducted prior to the assessment of lesions in combination with continual feedback regarding the accuracy of endoscopic diagnoses compared with histopathological results every two weeks for half-a-year were important factors in achieving a satisfactory learning curve. It has also been reported that use of the Kudo pit pattern classification required a longer learning curve with experience from diagnosing at least 200 lesions needed to become competent.[6,7,31] In contrast, our study demonstrated that an expanded one-hour intensive interactive training program conducted by a highly experienced endoscopist enabled the LEE group members in

particular to accelerate their learning curve. In addition, the Sano classification with NBI-H appears to have had a shorter learning curve compared with using NBI-L or the Kudo pit pattern classification in the diagnostic differentiation of diminutive colorectal polyps.

Besides having a higher differential diagnosis accuracy and being easier to improve the necessary diagnostic skill for accurately differentiating diminutive colorectal polyps, NBI has a couple of other clinical advantages. First, the conventional endoscopic view can be switched almost instantaneously to the NBI view by pressing a single electronic button on the control handle of the colonoscope and, second, NBI does not require any dye or staining solution to detect and differentiate neoplastic lesions from non-neoplastic lesions.

In recent years, advancements in the quality of endoscopic images available from high-definition endoscopy and chromoendoscopy have considerably enhanced polyp detection. Although the risk of neoplasia in diminutive polyps is <50% and the risk of high-grade dysplasia is <2%,[7,32,33] diminutive colorectal neoplasms as well as advanced neoplasms are among the precursors of colorectal cancer and multiple genetic alterations have been implicated in the adenoma-carcinoma sequence.[4] It also has been reported that lesions ≤5mm make up more than 80% of the colorectal polyps subjected to histopathological assessment.[33] Besides the primary consideration of reducing the risk of future colorectal cancer, the endoscopic differentiation of diminutive neoplastic polyps from non-neoplastic polyps is essential because endoscopists should avoid performing any unnecessary procedures including polypectomies on non-neoplastic polyps and this will also substantially reduce the number of colorectal polyps requiring histopathological assessment.

There has been considerable interest recently in sessile serrated adenoma (SSA) and serrated adenoma (SA) polyps that also have increasingly been associated with an apparent increased risk of malignant transformation.[34] SSAs endoscopically appear as hyperplastic polyps, but there have not been any published reports as yet applying the Kudo pit pattern analysis to such SSA polyps. In the general population, the prevalence of SSAs has been estimated to range from only 1–7% of all polyps and it has further been shown that most such SSA polyps can exceed 10mm in size,[35] but we did not detect any SSAs or SAs in this study. Although it was recently reported that SSAs could be differentiated from hyperplastic polyps by combining NBI and autofluorescence imaging, the report in question had several limitations including the total number of SSAs being relatively small and the lack of any comparison between those two modalities and pit pattern analysis.[36] In addition, their actual prevalence is difficult to assess as pathologists have been unable to reach a consensus on the diagnosis of either hyperplastic polyps or SSAs.[37,38] Further studies will be required, therefore, to clarify the endoscopic features and conduct histopathological and molecular-based analyses of SSAs and SAs.

The primary limitation of our study is that it involved only a small number of polyps. The power of the trial compared to the observed difference was lower because the observed difference was smaller than in the alternative hypothesis used in planning this study. The sample size that was set, however, was not much different from the sample size used in other similar studies. Another limitation is that this study was conducted using endoscopic images. During a "real-time" evaluation, an endoscopist can usually view a detected lesion using multiple angles and light modalities at variable distances, but we digitally stored all the endoscopic images taken during each examination,

selected the best image from each of the five endoscopic observation modalities and then randomized the distribution order of the images for diagnosis. This process was intended to decrease the likelihood of observational bias occurring and strengthen the reliability of our results because separate findings based on NBI images and chromoendoscopic images might otherwise have been influenced by the other and made objective evaluation of the individual diagnostic modalities difficult. A third limitation was the relatively short interval between the intensive training program and the follow-up reviews by the NEE and LEE groups. The participants in both groups reviewed all the images for the second time within 24 hours of the training program so as to avoid any possible bias resulting from a feedback learning effect such as self-training. It has previously been reported that feedback received during the development of a diagnostic skill is effective.[39]

In conclusion, NBI particularly high-magnification NBI was shown to be a promising tool for diagnostic differentiation of diminutive colorectal neoplastic from non-neoplastic polyps. Expanded training of the LEE group members improved their overall diagnostic ability so that it was equivalent in certain key respects to that of the participating HEE group.

FIGURE LEGENDS

Figure 1 – Examples of colorectal neoplastic polyps viewed by different endoscopic modalities in this study. (A) Conventional colonoscopy view. (B) Low-magnification NBI showed a brownish area. (C) High-magnification NBI revealed meshed capillary vessels indicative of Sano classification type II. (D) Low-magnification chromoendoscopy using 0.2% indigo-carmine dye spraying clearly revealed demarcated

margins and surface structure. (E) High-magnification chromoendoscopy clearly indicated Kudo classification type III∟.

Figure 2 – Examples of colorectal non-neoplastic polyps viewed by different endoscopic modalities in this study. (A) Conventional colonoscopy view. (B) Low-magnification NBI showed a non-brownish area. (C) High-magnification NBI in which meshed capillary vessels were not visible or only faintly visible indicative of Sano classification type I. (D) Low-magnification chromoendoscopy using 0.2% indigo-carmine dye spraying clearly revealed demarcated margins and surface structure. (E) High-magnification chromoendoscopy clearly indicated Kudo classification type II.

Figure 3 – Comparison of 95% Confidence Interval of κ Value for Each Endoscopic Diagnostic Endoscopic Modality According to Endoscopy Experience
Each bar represents the range of 95% confidence interval of κ value.; NEE, no endoscopy experience group; LEE, less experienced endoscopist group; HEE, highly experienced endoscopist group; Before, before participating in an intensive one-hour interactive training program; After, after participating in an intensive one-hour interactive training program; CC, conventional colonoscopy; NBI-L, low-magnification NBI; NBI-H, high-magnification NBI; CE-L, low-magnification chromoendoscopy; CE-H, high-magnification chromoendoscopy.

CAPSULE SUMMARY
What is already known on this topic
- Both narrow-band imaging (NBI) and pit pattern analysis have been reported to be effective modalities in differentiating neoplastic lesions from non-neoplastic

lesions.

- Diagnostic accuracy and interobserver agreement of experienced colonoscopists using NBI is equivalent to chromoendoscopy.

- Such reports were based on studies involving only highly experienced colonoscopists, however, with few published articles concerned with NBI and pit pattern analysis learning curve dependency on experience and ability of individual colonoscopists.

What this study adds to our knowledge

- Expanded interactive training in effective use of NBI both with and without magnification as well as pit pattern analysis improved diagnostic accuracy and interobserver agreement of less experienced colonoscopists in differentiating diminutive colorectal polyps.

- Using NBI with high-magnification increased the differential diagnostic skill of less experienced colonoscopists, who underwent such training, to a level equivalent to that of highly experienced colonoscopists.

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Table 1 – Patient Characteristics and Histopathological Features

Patients/Lesions	**32/44**
Gender (Male/Female)	**22/10**
Age, Years (Mean[SD])	**61.2(12.3)**
Macroscopic Type	
0-Is	**37**
0-IIa	**6**
0-IIc	**1**
Size, mm (Mean[SD])	**3.4(1.1)**
Location (Right/Left/Rectum)	**22/14/8**
Histopathology	
Tubular Adenoma	**27**
Hyperplastic Polyp	**17**

SD, Standard Deviation   **Right: Cecum, Ascending Colon and Transverse Colon**

Left; Descending Colon and Sigmoid Colon

Table 2 - Effectiveness of Training Program on Diagnostic Accuracy

Modality	NEE			LEE			HEE	
	Before Accuracy (95% CI)	After Accuracy (95% CI)	*p* Value*	Before Accuracy (95% CI)	After Accuracy (95% CI)	*p* Value*	Accuracy (95% CI)	*p* Value**
CC	0.43 (0.35-0.50)	0.64 (0.57-0.71)	*p*<0.001	0.72 (0.65-0.78)	0.74 (0.67-0.80)	NS	0.74 (0.68-0.80)	NS
NBI-L	0.53 (0.46-0.61)	0.66 (0.59-0.73)	*p*=0.006	0.65 (0.58-0.72)	0.78 (0.72-0.84)	*p*=0.001	0.81 (0.75-0.87)	NS
NBI-H	0.63 (0.56-0.70)	0.74 (0.68-0.80)	*p*<0.001	0.73 (0.66-0.79)	0.90 (0.85-0.94)	*p*<0.001	0.93 (0.88-0.96)	NS
CE-L	0.68 (0.60-0.74)	0.67 (0.60-0.74)	NS	0.68 (0.60-0.74)	0.76 (0.69-0.82)	NS	0.85 (0.79-0.90)	NS
CE-H	0.63 (0.56-0.70)	0.66 (0.59-0.73)	NS	0.67 (0.60-0.74)	0.81 (0.75-0.87)	*p*=0.001	0.85 (0.79-0.89)	NS

**p* Values Determined by McNemar Test Comparing Before and After

***p* Values Determined by Fisher's Exact Test Comparing LEE After Training and HEE

NEE, No Endoscopy Experience Group; LEE, Less Experienced Endoscopist Group; HEE, Highly Experienced Endoscopist Group

Before, Before Training; After, After Training

CC, Conventional Colonoscopy; NBI-L, Low-Magnification NBI; NBI-H, High-Magnification NBI;

CE-L, Low-Magnification Chromoendoscopy; CE-H, High- Magnification Chromoendoscopy
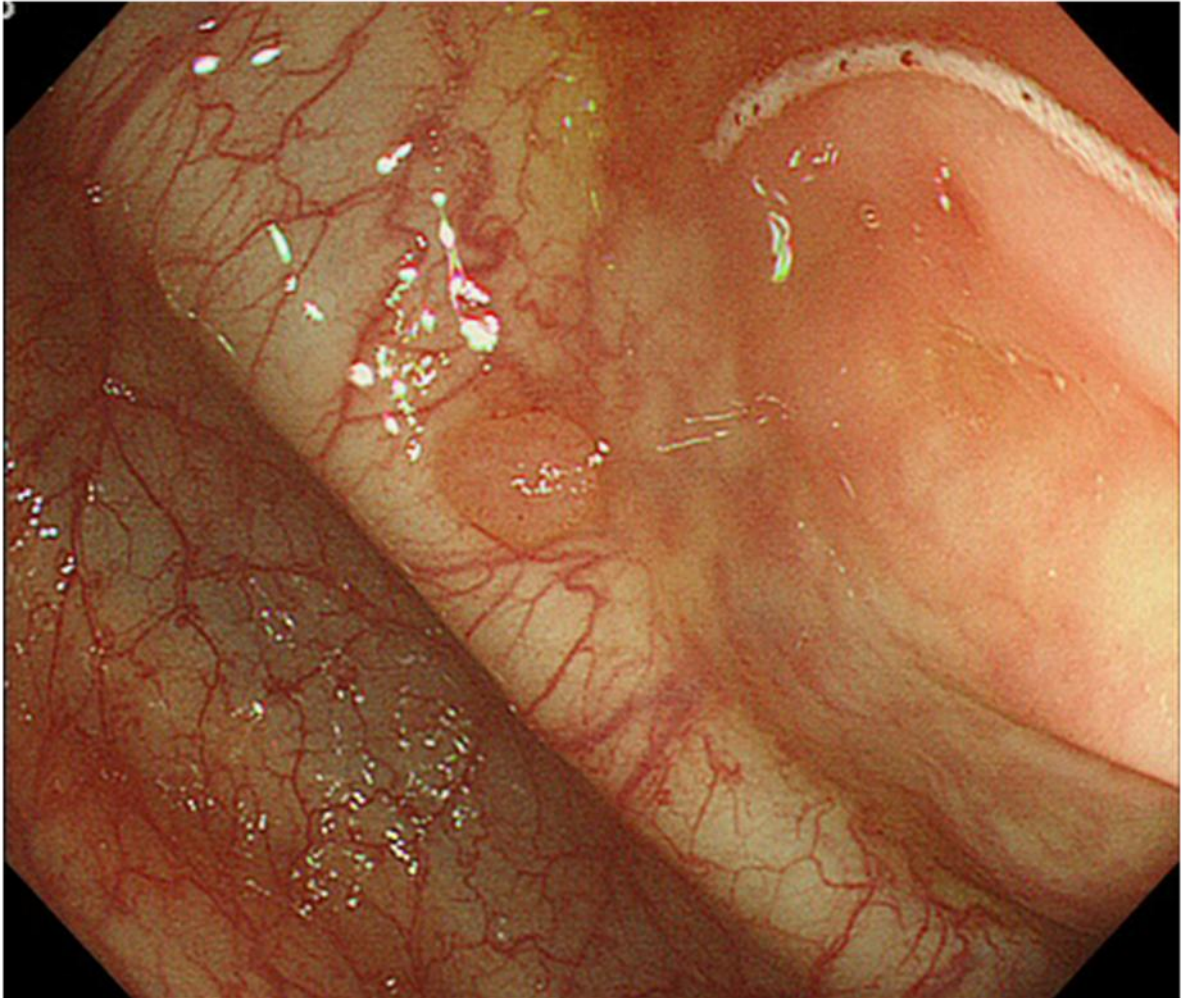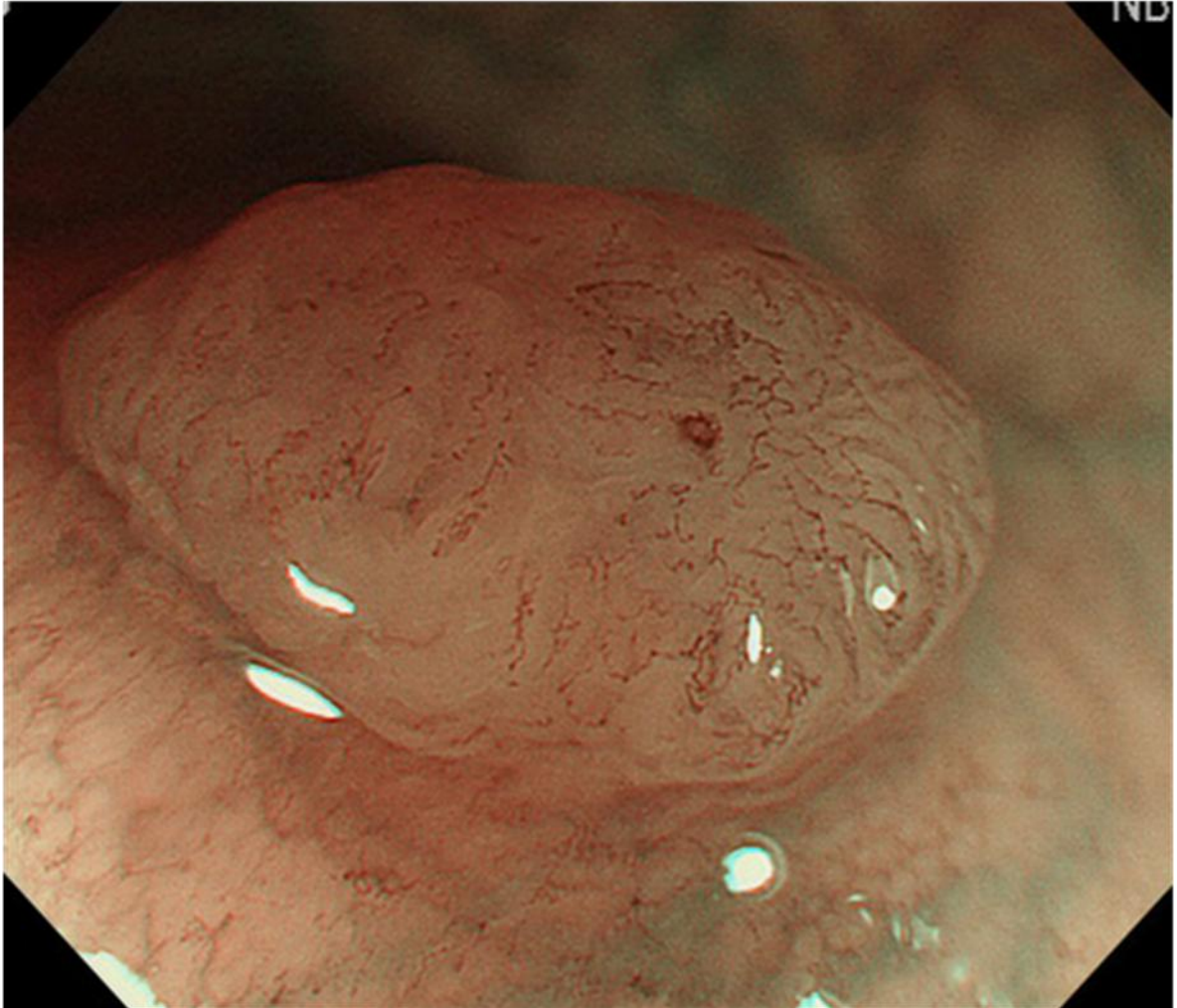
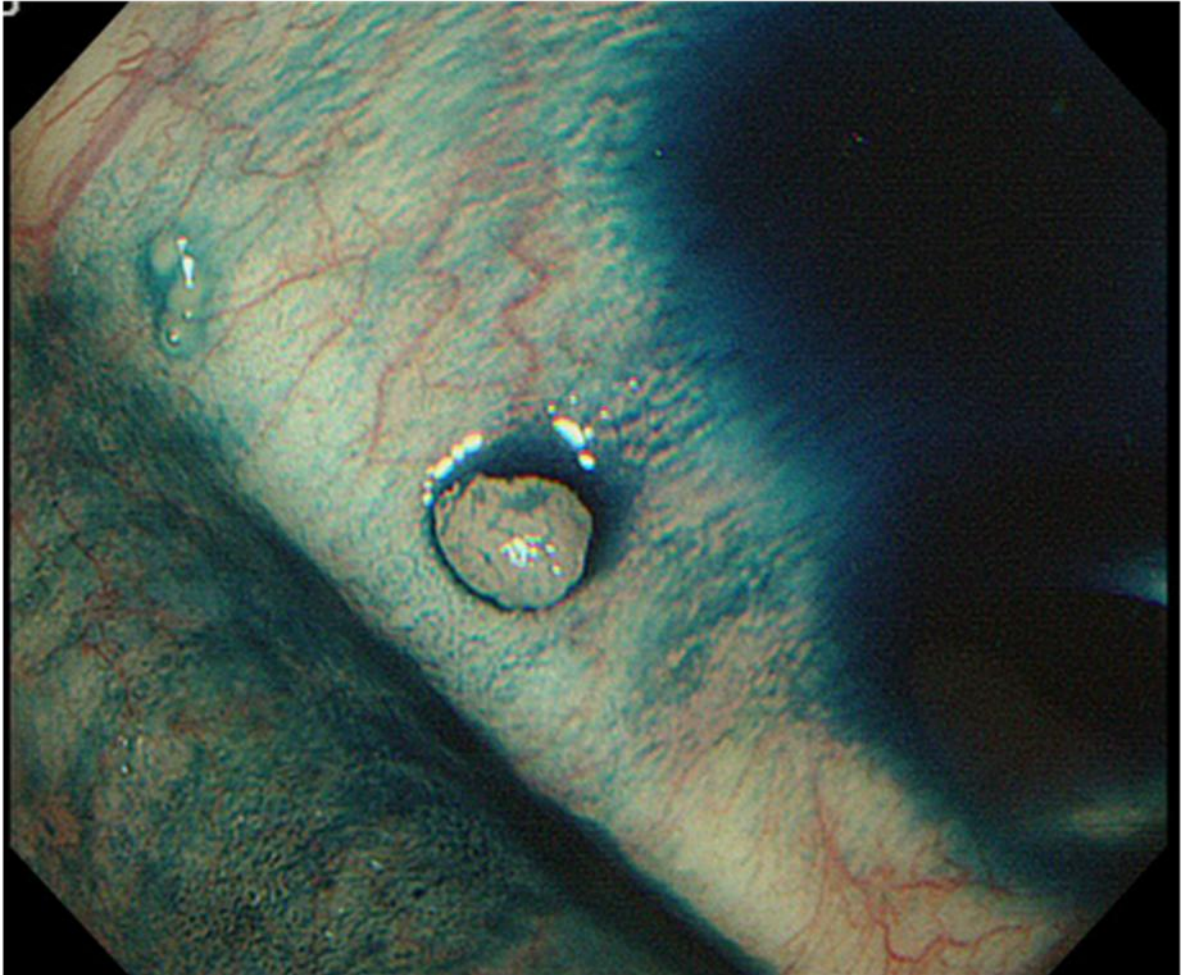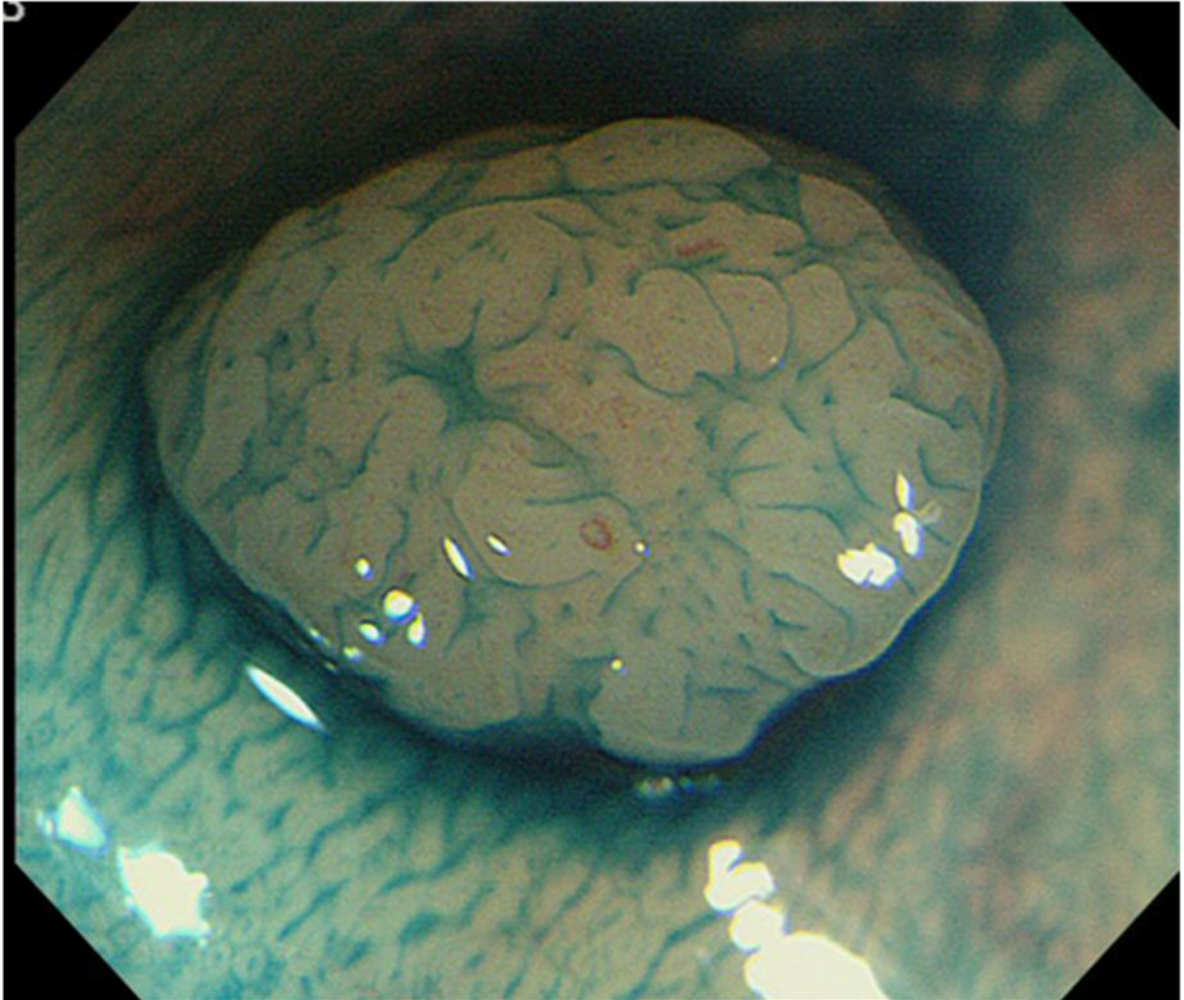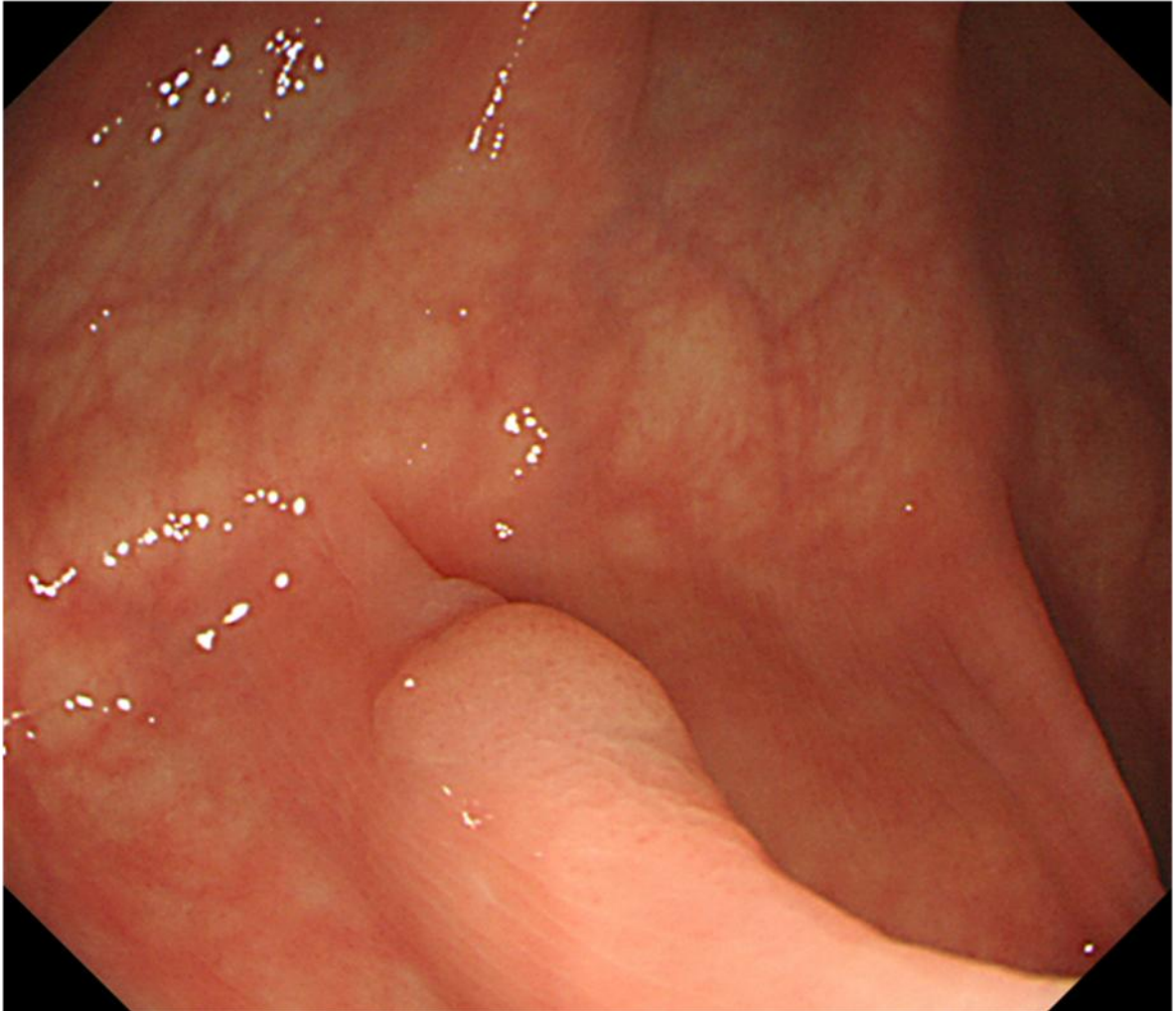NS, Not Significant

Figure1-A
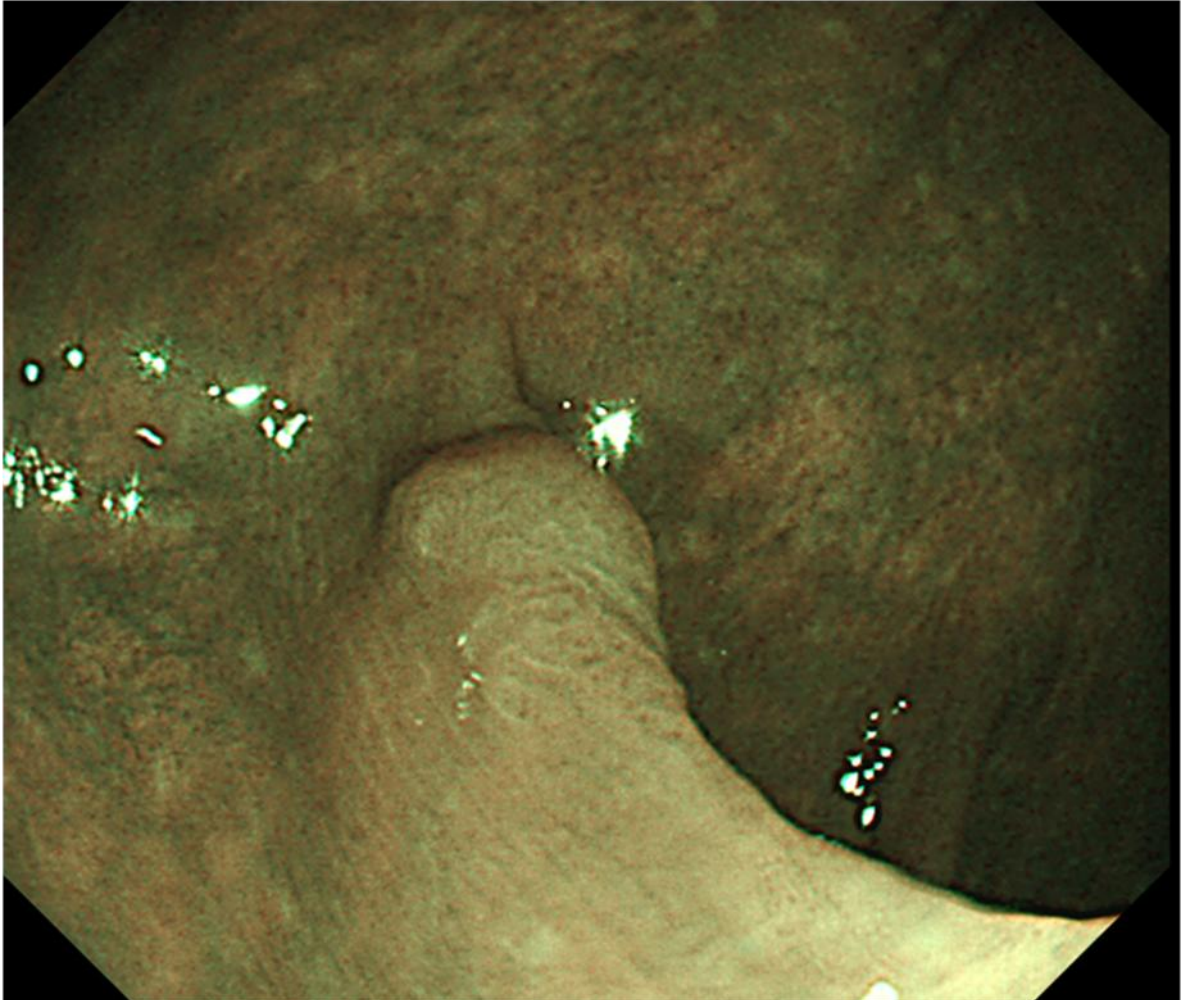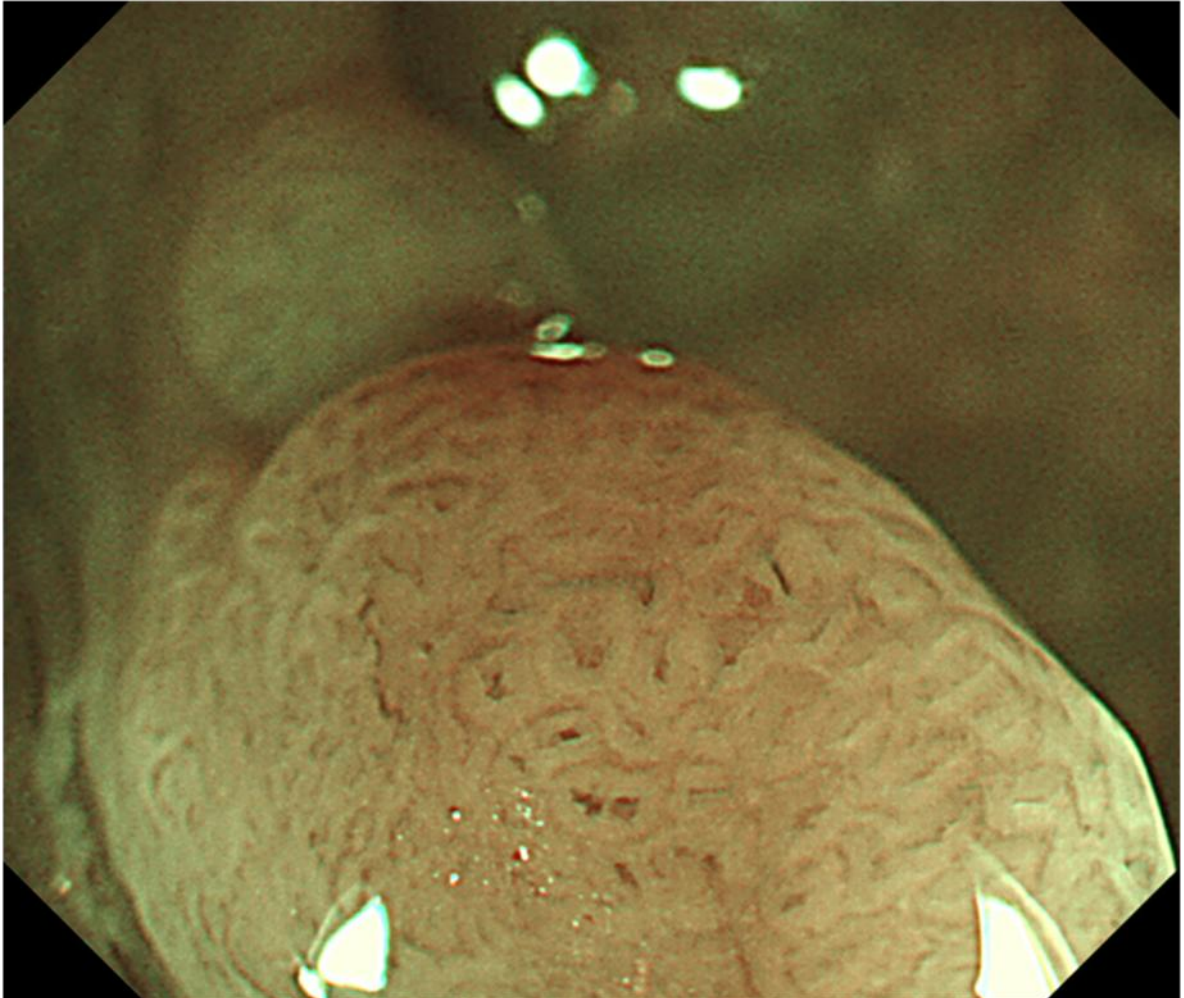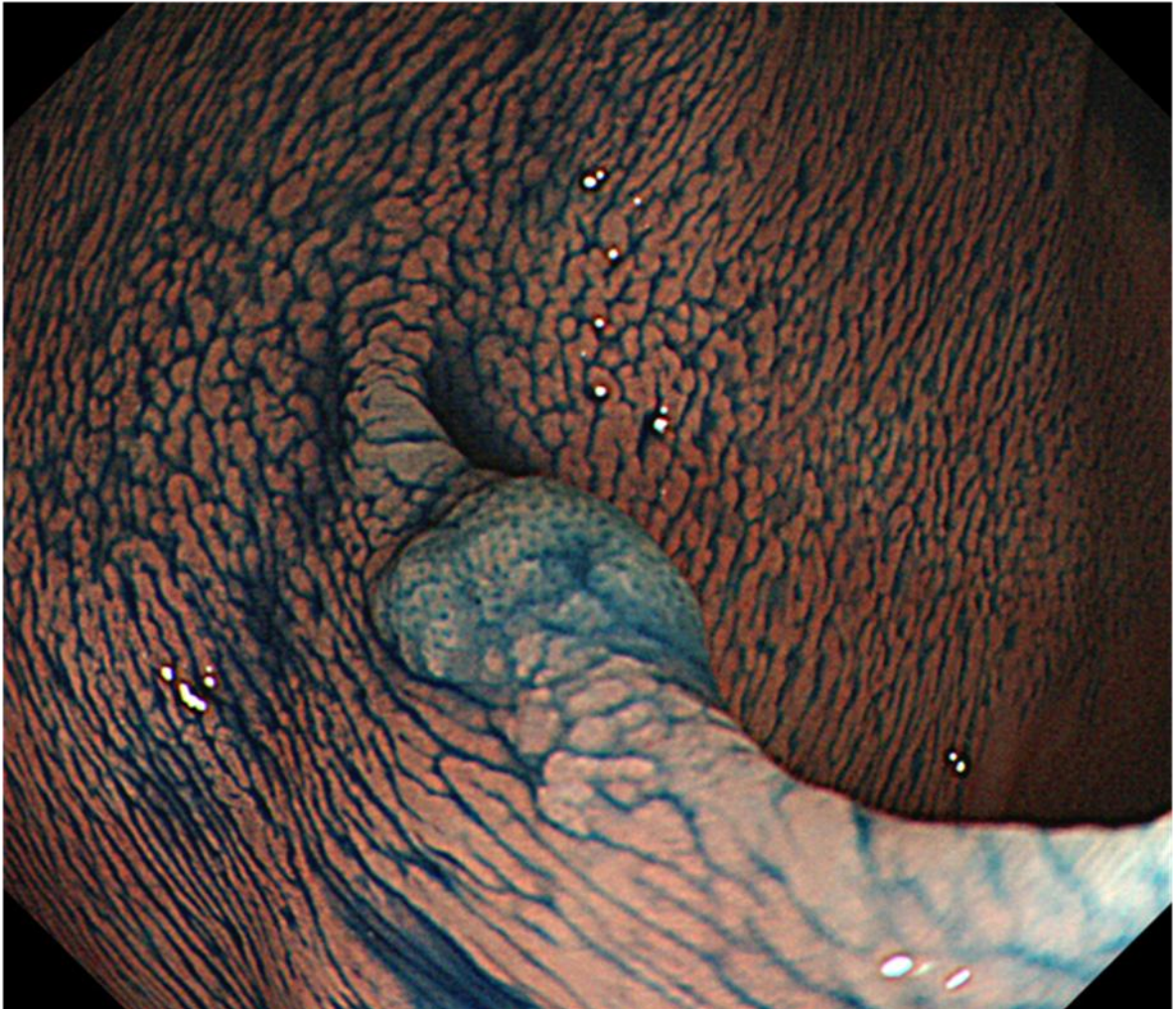
Figure1-B

Figure1-C

Figure1-D

Figure1-E

Figure2-A

Figure2-B

Figure2-C

Figure2-D

Figure2-E

Figure 3