

## Investigating endoscopic features of sessile serrated adenomas/polyps by using narrow-band imaging with optical magnification

(CME)

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**Background:** A sessile serrated adenoma/polyp (SSA/P) is a common type of colorectal polyp that possesses malignant potential. Although narrow-band imaging (NBI) can easily differentiate neoplastic lesions from hyperplastic polyps (HPs), SSA/Ps can be a challenge to distinguish from HPs.

**Objective:** To investigate specific endoscopic features of SSA/Ps by using NBI with optical magnification.

**Design:** Retrospective study.

**Setting:** Single high-volume referral center.

**Patients:** A total of 289 patients with histopathologically proven SSA/Ps or HPs obtained from colonoscopic polypectomy.

**Intervention:** Endoscopic images obtained by using NBI with optical magnification of 242 lesions (124 HPs, 118 SSA/Ps) removed between January 2010 and December 2012 were independently evaluated by 2 experienced endoscopists. Three external experienced endoscopists systematically validated the diagnostic accuracies by using 40 lesions (21 HPs and 19 SSA/Ps) removed between January and March 2013.

**Main Outcome Measurements:** Specific endoscopic features of SSA/Ps by using 5 potential characteristics: dilated and branching vessels (DBVs), irregular dark spots, a regular network pattern, a disorganized network pattern, and a dense pattern.

**Results:** Multivariate analysis demonstrated that DBV had a 2.3-fold odds ratio (95% confidence interval, 0.96-5.69) among SSA/Ps compared with HPs (sensitivity, 56%; specificity, 75%; accuracy, 65%). Interobserver and intraobserver agreement indicated almost perfect agreement for DBVs in both the evaluation and validation studies. When DBVs, proximal location, and tumor size ( $\geq 10$  mm) were combined, the positive predictive value was 92% and the area under the curve was 0.783 in the receiver-operating characteristics by using the validation group.

**Limitations:** Retrospective study.

**Conclusions:** The current study suggests that a DBV is a potentially unique endoscopic feature of a colorectal SSA/P. (Gastrointest Endosc 2015;82:108-17.)

**Abbreviations:** CI, confidence interval; CP, capillary pattern; DBV, dilated and branching vessel; HP, hyperplastic polyp; iDS, irregular dark spot; NBI, narrow-band imaging; NCCN, National Cancer Center Hospital; NICE, Narrow-Band Imaging International Colonoscopic Endoscopic; OR, odds ratio; ROC, receiver-operating characteristic; SSA/P, sessile serrated adenoma/polyp.

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Magnification colonoscopy developed by Kudo et al<sup>1,2</sup> and Fu et al<sup>3</sup> in 1993 can optically zoom up to 100 times in real time and permits pit pattern characteristics that lead to greater than 10% higher accuracy compared with nonmagnifying observation in differentiating between nonneoplastic and neoplastic colorectal lesions.<sup>1,3</sup> In addition, image-enhanced endoscopy including narrow-band imaging (NBI), autofluorescence imaging, flexible spectral imaging color enhancement, i-scan imaging, and blue laser imaging has recently been developed and is currently being used for clinical applications.<sup>4-7</sup> NBI, which became commercially available in 2006, is an innovative image-enhanced endoscopy technology that enhances the visualization of vascular and surface pattern of the polyps using short wavelength visible light that is the best absorption for hemoglobin.<sup>6,8</sup> This new endoscopic technology enables qualitative diagnosis of colorectal polyps by differentiating adenomas from hyperplastic polyps (HPs) with good accuracy.<sup>9</sup>

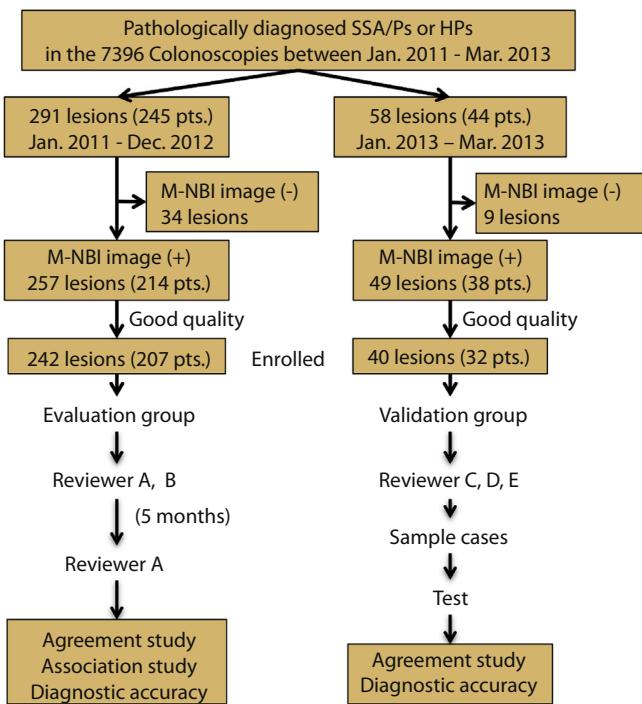
The majority of colorectal cancer arises from adenomatous polyps and serrated polyps.<sup>10,11</sup> Sessile serrated adenoma/polyps (SSA/Ps) are a relatively common type of colorectal polyp that belongs to the serrated polyps and are histologically characterized by a serrated architecture of the epithelial compartment.<sup>12-14</sup> SSA/Ps, related to the serrated neoplastic pathway, is considered to be one of the possible causes of colorectal cancer arising between scheduled and surveillance colonoscopies, so-called interval cancers, owing to its flat, nonpolypoid features that can be easily missed.<sup>11,15-17</sup> Removal of this type of precursor lesion is recommended during the screening and surveillance colonoscopy to reduce the risk of the development of colorectal cancer.<sup>18</sup>

During colonoscopic evaluation, these SSA/Ps can be challenging to distinguish from HPs because they can exhibit analogous gross surface features.<sup>19</sup> Although few studies have reported the features of SSA/Ps seen on NBI for the diagnosis, so far the findings have been obtained and described without optical magnification.<sup>20,21</sup> We hypothesized that NBI with optical magnification would be advantageous and able to better distinguish SSA/Ps from HPs. Therefore, the aim of this study was to accurately identify the specific endoscopic features of SSA/Ps by using NBI with optical magnification.

## METHODS

### Image samples

We conducted a retrospective, cross-sectional image evaluation study. The study flow chart is shown in Figure 1. From 7396 patients undergoing colonoscopy at the National Cancer Center Hospital (NCCH), Tokyo, Japan, between January 2011 and March 2013, we collected 289 patients with at least 1 or more histologically proven SSA/Ps or HPs that were removed



**Figure 1.** Study algorithm. *HPs*, hyperplastic polyps; *SSA/Ps*, sessile serrated adenoma/polyps; *pts.*, patients; *M-NBI*, magnifying narrow-band imaging.

by endoscopic resection. The lesions were assigned to 1 of 2 groups: the evaluation group including 291 lesions (245 patients) removed between January 2011 and December 2012 and the validation group including 58 lesions (44 patients) removed between January and March 2013. In the evaluation group, there were no images using NBI with optical magnification of 34 lesions, and images of 15 lesions could not be evaluated because of poor quality. Finally, 242 lesions (124 HPs, 118 SSA/Ps) in 207 patients were used for the evaluation study. Among the validation group, there were no images using NBI with optical magnification in 9 lesions, and images of 9 lesions could not be evaluated because of poor quality. Finally, 40 lesions (21 HPs, 19 SSA/Ps) in 32 patients were used for the validation study. Tubular adenomas, adenocarcinomas, mixed polyps, and traditional serrated adenomas were excluded. All images were obtained with magnifying colonoscopes (CF-H260AZI, PCF-240ZI, or PCF-260AZI; Olympus Optical Co, Tokyo, Japan) with up to 100× magnification in combination with a standard video processor system (EVIS LUCERA system; Olympus Inc, Tokyo, Japan) and NBI system (Olympus Inc). Because of the retrospective design, the indication for endoscopic resection of the HPs and SSA/Ps was dependent on the judgment of the endoscopists performing the resection. Histological diagnosis was determined based on the World Health Organization criteria by 3 GI pathologists (H.T., S.S., R.K.). In this study, a histopathological diagnosis of SSA/Ps was made when there was agreement by all 3

pathologists. In other words, the criterion standard pathology was controlled by 3 observers agreeing on the histopathological diagnosis. This study protocol was approved by the National Cancer Center Institutional Review Board, Tokyo, Japan.

## Image evaluation process

**Definition of endoscopic findings.** Before the study, 2 experienced endoscopists (M.Y. and T.S.) characterized 5 potential endoscopic features as follows (Fig. 2): (1) dilated and branching vessels (DBVs), (2) irregular dark spots (iDSs), (3) a regular meshed pattern, (4) a disorganized meshed pattern, and (5) a dense pattern. These NBI findings, except for DBVs, had already been reported in HPs and adenomatous polyps. However, known NBI findings of HPs were only isocolored or discolored mucosa and dark spots, and color change was not a magnification finding. Therefore, in this study, dark spots and other reported magnifying findings of adenomatous polyps were used. DBVs are defined as thickened capillary vessels with branching that is observed on the surface and that are different from the “meshed capillary vessels” in the Sano et al<sup>22</sup> capillary pattern (CP) classification. iDSs were defined as small dark dots inside the open crypts that are dilated at least twofold more than those surrounding them. A regular meshed pattern is defined as regular small-caliber capillaries observed in the adenomatous polyp, as in the Sano et al CP classification type II.<sup>22,23</sup> A disorganized meshed pattern is defined as an irregular and disorganized pattern in a meshlike microvascular architecture exhibiting at least 1 of the following: irregular size, complicated branching, and a disrupted irregular pattern, as Sano et al CP classification type III.<sup>23</sup> These 2 mesh patterns subclassified into regular and disorganized types indicate adenoma and adenocarcinoma, respectively. A dense pattern was defined as well-developed and rather thick vessels, indicating villous and tubulovillous adenoma.<sup>24</sup>

## Evaluation study

**Interobserver and intraobserver reliability.** Images were incorporated into a slideshow (Microsoft Power Point 2010; Microsoft, Redmond, Wash). Conventional endoscopic images were simultaneously displayed with the images obtained using NBI with optical magnification for each lesion.

The 5 endoscopic features were independently evaluated by the 2 endoscopists (M.Y. and T.S.) by using the evaluation group (242 lesions). These observers have used NBI for more than 5 years. The observers were blinded to both histopathological diagnosis and clinical information. Interobserver agreement was calculated.

All images were reevaluated by an endoscopist (M.Y.) in random order, 5 months after the interobserver agreement study, to calculate intraobserver agreement. The observer,

again, was blinded to the histopathological diagnosis and clinical information.

**Associations of NBI features with SSA/Ps.** The 5 endoscopic features evaluated by M.Y. were used to examine the associations between NBI features and SSA/Ps. Based on the magnitude of associations, we selected the candidate NBI features for improving the accuracy of diagnosis.

**Diagnostic accuracy.** By using the candidate NBI features in addition to clinicopathological characteristics, we calculated the sensitivity, specificity, and accuracy for the diagnosis of SSA/Ps. NBI features evaluated by M.Y. were used for this evaluation.

## Validation study

To confirm the diagnostic accuracy in the evaluation study, evaluation among observers outside NCCH was performed by using the validation group (40 lesions) by an experienced Japanese endoscopist (T.F.) from a different hospital and 2 experienced endoscopists from 2 different hospitals in North America (H.R.) and South America (A.P.). They all have used and are experienced with the NBI system in usual clinical practice for more than 5 years. Furthermore, the Japanese observer in the evaluation study has been using NBI since its development, and the 2 observers outside NCCH have been well trained in NCCH.

**Interobserver reliability.** After orientation with a short PowerPoint presentation of the 5 endoscopic features and 10 sample cases, the reviewers independently assessed the 40 lesions for the absence or presence of the 5 endoscopic features as done in the evaluation step. The observers were blinded to both histopathological diagnosis and clinical information. Interobserver agreement among the 3 reviewers was calculated.

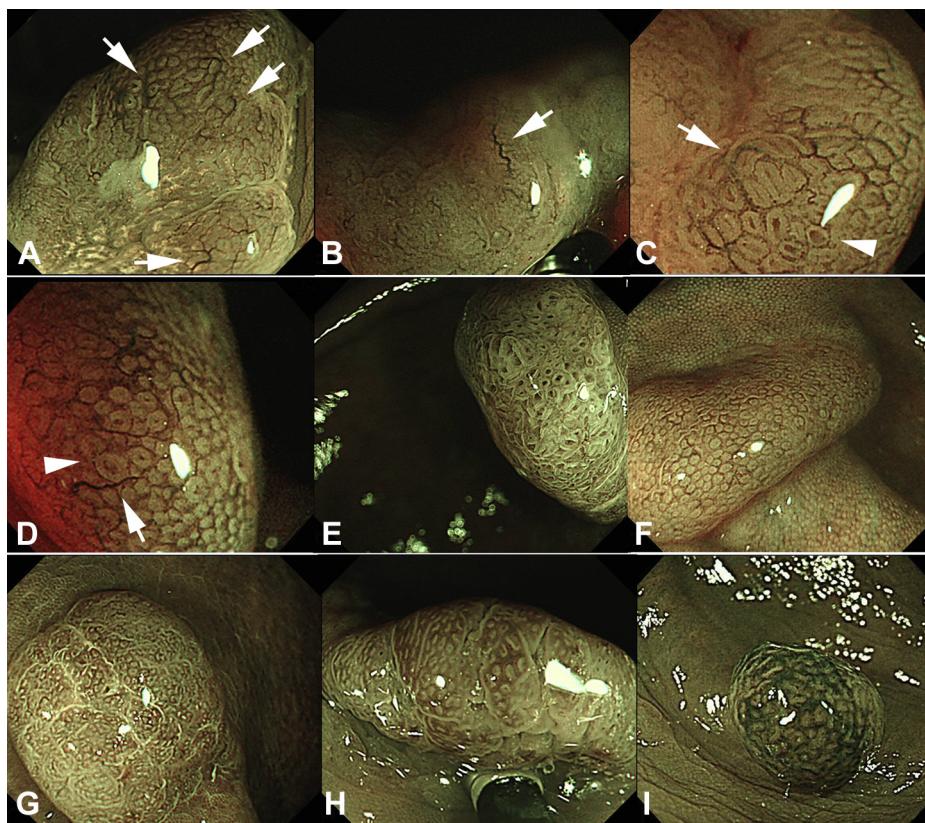
**Diagnostic accuracy.** The sensitivity, specificity, and accuracy of the combination of DBVs and location and size of SSA/Ps were calculated according to the data by an observer (T.F.).

## Statistical analysis

The baseline characteristics of the HPs and SSA/Ps were compared by using the Fisher exact test for binary data and the Mann–Whitney *U* test for count data.

The primary purpose of this study was to examine the associations of the NBI features with SSA/Ps. A logistic regression model was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs). Univariate- and multivariate-adjusted ORs were estimated. The multivariate logistic regression model included the following variables: DBVs, iDSs, regular meshed pattern, disorganized meshed pattern, dense pattern, sex, lesion location, and lesion size.

The secondary purpose was to examine the performance of NBI findings in predicting a diagnosis and validating the performance by using independent polyps that were not in the evaluation study. The performance



**Figure 2.** Magnifying narrow-band imaging of sessile serrated adenomas/polyps (SSA/Ps) illustrating the 5 representative features of capillary pattern in this study. **A, B,** Dilated and branching vessels (DBVs) (arrows). **C, D,** DBVs (arrows) and irregular dark spots (iDSs) (arrowhead). **E,** Prominent iDS image. **F,** Regular meshed capillary pattern. **G,** Disorganized meshed capillary pattern. **H, I,** Dense pattern.

was evaluated by estimating the sensitivity, specificity, and accuracy with their 95% CIs, which were defined as the proportion of SSA/Ps diagnosed by NBI among actual SSA/Ps, the proportion of HPs diagnosed by NBI among actual HPs, and the proportion of accurately diagnosed polyps, respectively.

For interobserver and intraobserver agreement studies,  $\kappa$  statistics and 95% CIs were estimated. Fleiss  $\kappa$  statistics were estimated for interobserver agreement among the 3 reviewers in the validation study. We used the arbitrary interpretation of Landis and Koch: 0, poor agreement; 0.00-0.20, slight agreement; 0.21-0.40, fair agreement; 0.41-0.60, moderate agreement; 0.61-0.80, substantial agreement; and 0.80-1.00, almost perfect agreement.<sup>25</sup>

The statistical analyses were performed by using SPSS, version 17.0 (SPSS Inc, Chicago, Ill).  $P$  values  $<.05$  were considered statistically significant.

## RESULTS

### Characteristics of the HPs and SSA/Ps

The clinicopathological characteristics and prevalence of the 5 endoscopic features of the subjects are shown in Table 1. In the evaluation group, 178 patients (86%) had

1 polyp, 26 patients (13%) had 2 polyps, and 3 patients (1%) had 3 or more polyps. In the validation group, 25 patients (78%) had 1 polyp, 6 patients (19%) had 2 polyps, and 1 patient (3%) had 3 polyps.

A significantly higher prevalence of women, proximal location, and larger lesion size was observed in SSA/Ps compared with HPs in the evaluation group. On multivariate analysis including the clinicopathological features, ORs (95% CIs) were 0.8 (0.3-1.9) for age (younger than 60 years of age), 2.2 (0.9-5.6) for sex (female), 18.3 (7.2-46.2) for location (proximal colon), 26.6 (10.6-66.4) for lesion size ( $\geq 10$  mm), and 4.3 (1.8-10.2) for morphology (0-Is type), indicating that location, lesion size, and morphology were the predictive indicators of SSA/Ps compared with HPs in the baseline characteristics in this sample.

### Evaluation study

**Interobserver and intraobserver variability of the NBI findings.** Interobserver agreement of each of the NBI findings indicated substantial agreement for DBVs, iDSs, and a dense pattern ( $\kappa = 0.69, 0.65$ , and  $0.66$ , respectively), and slight agreement for regular and disorganized meshed CPs ( $\kappa = 0.24$  and  $0.22$ , respectively). Intraobserver agreement indicated almost perfect agreement for DBVs and a dense pattern ( $\kappa = 0.90$  and  $0.82$ ,

**TABLE 1. Characteristics of patients with HPs and SSA/Ps of the colorectum**

	Evaluation group		P value	Validation group		P value
	HPs	SSA/Ps		HPs	SSA/Ps	
No. of the lesions (pts.)	124 (102)	118 (105)		21 (16)	19 (16)	
Age, y*	63 (23-84)	64 (34-87)	.3857	69.5 (48-83)	59 (39-85)	.2411
Female, no. (%)	18 (18)	49 (47)	<.001	7 (44)	7 (44)	1.00
Location, %						
Proximal colon†	30 (24)	98 (83)	Ref.	6 (29)	15 (79)	Ref.
Distal colon‡	49 (40)	17 (14)	<.001	7 (33)	2 (10)	.020
RS and rectum	45 (36)	3 (3)	<.001	8 (38)	2 (10)	.018
Tumor size, mm*	5 (3-20)	12 (3-50)	<.001	6 (3-15)	8 (4-25)	.029
Morphology, %						
0-IIa type	86 (69)	71 (60)	.1410	16 (76)	13 (68)	.7271
0-Ia type	38 (31)	47 (40)		5 (24)	6 (32)	
M-NBI findings, %§						
DBVs	30 (24)	77 (65)	<.001	7 (33)	15 (79)	.005
iDSs	36 (29)	53 (45)	.011	4 (19)	8 (42)	.017
Meshed capillary pattern, %						
Regular	18 (15)	13 (11)	.4471	0	0	
Disorganized	10 (8)	11 (9)	.8209	0	0	
Dense	6 (5)	3 (3)	.5007	3 (14)	0	.9423

HPs, Hyperplastic polyps; SSA/Ps, sessile serrated adenoma/polyps; Pts., patients; RS, rectosigmoid colon; M-NBI, magnifying narrow-band imaging; DBVs, dilated and branching vessels; iDSs, irregular dark spots.

\*Mean (range).

†Proximal colon includes cecum-transverse colon.

‡Distal colon includes descending sigmoid colon.

§Data show a representative observer.

**TABLE 2. Proportion of individual NBI features for SSA/Ps stratified by size, location, and sex**

Feature	Lesion size, mm, no. (%)			Location, no. (%)		Sex, no. (%)	
	<6	6-9	≥10	Proximal	Distal	Female	Male
Total no.*	6	23	89	98	20	56	62
DBVs	5 (83)	10 (43)	64 (72)	69 (70)	10 (50)	38 (68)	41 (66)
iDSs	2 (33)	9 (39)	38 (43)	42 (43)	7 (35)	23 (41)	26 (42)
Meshed capillary pattern							
Regular	30 (50)	11 (48)	11 (12)	22 (22)	3 (15)	15 (27)	10 (16)
Disorganized	1 (17)	3 (13)	4 (4)	8 (8)	0	6 (11)	2 (3)
Dense pattern	0	1 (4)	3 (3)	2 (2)	2 (10)	1 (2)	3 (5)
DBVs and iDSs	2 (33)	3 (13)	33 (37)	34 (35)	4 (20)	18 (32)	20 (32)
DBVs or iDSs	5 (83)	16 (70)	69 (78)	77 (79)	13 (65)	43 (77)	47 (76)

NBI, Narrow-band imaging; SSA/Ps, sessile serrated adenoma/polyps; Proximal, proximal colon (cecum-transverse colon); Distal, distal colon (descending colon-rectosigmoid colon) and rectum; DBVs, dilated and blanching vessels; iDSs, irregular dark spots.

\*Total number of lesions.

respectively), substantial agreement for iDSs and a regular meshed CP ( $\kappa = 0.77$  and  $0.62$ , respectively), and moderate agreement for a disorganized meshed CP ( $\kappa = 0.54$ ).

**Subgroup analysis by size, location, and sex.** The proportion of each NBI finding for SSA/Ps stratified by lesion size, location, and sex are shown in Table 2. DBVs

were constantly observed irrespective of size, location, and sex. Diminutive (<6 mm) and small (6-9 mm) polyps were more likely to have a regular network pattern than lesions 10 mm or larger. There were no remarkable differences in iDSs, the disorganized network pattern, and the dense pattern.

**TABLE 3. Association between NBI findings and SSA/Ps (N = 24w)**

	HPs, no. (%)	SSA/Ps, no. (%)	<b>Univariate analysis</b>	<b>Multivariate analysis</b>
			OR (95% CI)	OR (95% CI)
Female	18 (18)	49 (47)	4.99 (2.72-9.17)	2.05 (0.83-5.05)
Size (>10 mm)	14 (11)	89 (75)	24.1 (12.0-48.4)	21.0 (8.48-51.8)
Location (proximal)*	30 (24)	98 (83)	15.4 (8.16-28.9)	11.1 (4.59-27.1)
DBVs	30 (24)	77 (65)	5.88 (3.36-10.3)	2.33 (0.96-5.69)
iDSs	36 (29)	53 (45)	1.99 (1.17-3.39)	1.27 (0.53-3.01)
Meshed capillary pattern				
Regular	18 (15)	13 (11)	0.73 (0.34-1.56)	1.52 (0.51-4.54)
Disorganized	10 (8)	11 (9)	1.17 (0.48-2.87)	2.02 (0.52-7.93)
Dense pattern	6 (5)	3 (3)	0.51 (0.13-2.10)	2.19 (0.31-15.6)

NBI, Narrow-band imaging; SSA/Ps, sessile serrated adenoma/polyps; OR, odds ratio; CI, confidence interval; DBVs, dilated and blanching vessels; iDSs, irregular dark spots.

\*Proximal colon.

**TABLE 4. Diagnostic accuracy of the NBI findings for SSA/Ps (N = 242)**

	<b>Sensitivity, % OR (95% CI)</b>	<b>Specificity, % OR (95% CI)</b>	<b>Accuracy, % OR (95% CI)</b>
DBV	65 (56.3-73.6)	76 (67.6-82.5)	71 (64.6-76.0)
iDS	45 (36.2-53.9)	71 (62.4-78.2)	58 (52.0-64.3)
Meshed capillary pattern			
Regular	11 (6.6-17.9)	85 (78.2-90.6)	49 (42.9-55.4)
Disorganized	9 (5.3-15.9)	92 (85.8-95.6)	52 (45.4-57.9)
Dense pattern	3 (0.9-7.2)	96 (89.9-97.8)	50 (43.8-56.3)

NBI, Narrow-band imaging; SSA/Ps, sessile serrated adenoma/polyps; OR, odds ratio; CI, confidence interval; DBVs, dilated and blanching vessels; iDSs, irregular dark spots.

### Association between NBI findings and SSA/Ps.

Among 242 lesions, DBVs were observed in 24% of HPs and 65% of SSA/Ps ( $P < .001$ ). iDSs were observed in 29% of HPs and 45% of SSA/Ps ( $P = .011$ ). A regular network pattern was found in 15% of HPs and 11% of SSA/Ps ( $P = .44$ ). A disorganized network pattern was observed in 8% of HPs and 9% of SSA/Ps ( $P = .82$ ). A dense pattern was observed in 5% of HPs and 3% of SSA/Ps ( $P = .50$ ) (Table 1). Multivariate analysis estimated that DBVs were the diagnostic indicator for SSA/Ps compared with HPs. In contrast, other findings including iDSs were not implemented as definitive markers of SSA/Ps (Table 3).

When the DBVs and iDSs were used in combination, the OR (95% CI) by univariate analysis were 3.87 (2.00-7.48). With the combination of the DBVs or iDSs, the OR (95% CI) by univariate analysis was 4.39 (2.53-7.62).

**Diagnostic accuracy of the NBI findings for SSA/Ps.** The diagnostic accuracy of the individual NBI findings is summarized in Table 4.

iDSs are considered to reflect a dilated pit orifice that is one of the histopathological diagnostic features of SSA/Ps. When the DBVs and iDSs were used in combination, the sensitivity (95% CI), specificity (95% CI), and diagnostic accuracy (95% CI) were 35% (26.8%-43.7%), 88% (81%-92.5%), and 62% (55.7%-67.9%), respectively. With the combination

of the DBVs or iDSs, the sensitivity (95% CI), specificity (95% CI), and diagnostic accuracy (95% CI) were 75% (66.9%-82.3%), 59% (50.1%-67.1%), and 67% (60.8%-72.6%), respectively.

The diagnostic accuracy of combined DBVs and/or location and/or tumor size and/or morphology is shown in Table 5. When DBVs, proximal location (right side of the colon), and tumor size ( $\geq 10$  mm) were combined, the positive predictive value exceeded 90%.

Based on this result, we calculated a receiver-operating characteristic (ROC) curve by using the evaluation group (Fig. 3A). When the 3 factors acquired 1 point, respectively, the area under the ROC curve was 0.9025. When a total of 2 points was defined as the cutoff value, the sensitivity was 79% and the specificity was 87%, indicating best cutoff point.

### Validation study

**Interobserver variability in the NBI findings by different experienced endoscopists.** Interobserver agreement for the diagnosis of SSA/Ps indicated substantial agreement for DBVs ( $\kappa = 0.72$ ) and moderate agreement for iDSs ( $\kappa = 0.43$ ), but only poor or fair agreement in other findings.

**Diagnostic accuracy of combined predictors of SSA/Ps.** Sensitivity (95% CI), specificity (95% CI), and accuracy (95% CI) of DBVs were 79% (56.7%-91.5%), 67% (45.4%-82.8%), and 73% (57.2%-83.9%), respectively,

**TABLE 5. Diagnostic accuracy of combined possible predictors of SSAs/Ps (N = 242)**

	<b>Sensitivity, % (no.)*</b>	<b>Specificity, % (no.)†</b>	<b>Accuracy, % (no.)‡</b>	<b>PPV, % (no.)§</b>	<b>NPV, % (no.)  </b>
DBVs and Rt	57 (67)	90 (111)	74 (178)	84 (67/80)	65 (111/162)
DBVs and Fe	31 (36)	96 (119)	64 (155)	88 (36/41)	59 (119/201)
DBVs and size	53 (62)	95 (118)	74 (180)	91 (62/68)	68 (118/174)
DBVs and ls	26 (31)	92 (114)	60 (145)	76 (31/41)	57 (114/201)
DBVs and Rt and size	46 (54)	97 (120)	72 (174)	93 (54/58)	65 (120/184)

SSA/Ps, sessile serrated adenoma/polyps; PPV, positive predictive value; NPV, negative predictive value; DBVs, dilated and blanching vessels; Rt, proximal colon (cecum-transverse colon); Fe, female; size, tumor size  $\geq 10$  mm.

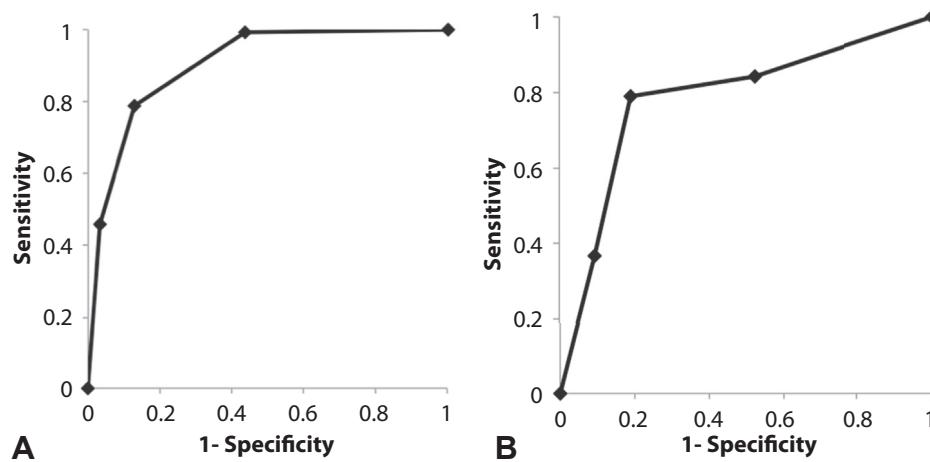
\*The sensitivity value shows SSA/Ps with the factors.

†The specificity value shows HP without the factors.

‡The accuracy value shows SSA/Ps with the factors and HPs without the factors.

§The PPV value shows SSA/Ps with the factors/all lesions with the factors.

||The NPV value shows HP with the factors/all lesions without the factors.



**Figure 3.** Receiver-operating characteristic curve for endoscopic diagnosis of serrated adenomas/polyps. **A**, Evaluation set. **B**, Validation set. The area under the curve was 0.903 in **A** and 0.783 in **B** for the combined use of dilated and branching vessels, location, and tumor size. The best cutoff point was 2 points.

whereas for iDSs, they were 42% (23.1%-63.7%), 81% (60.0%-92.3%), and 63% (47.0%-75.8%), respectively. The regular and disorganized meshed CPs and dense pattern were not observed in SSA/Ps. When the DBVs and iDSs were used in combination, the sensitivity (95% CI), specificity (95% CI), diagnostic accuracy (95% CI), and OR (95% CI) by univariate analysis were 26% (11.8%-48.8%), 95% (77.3%-99.2%), 63% (47.0%-75.8%), and 7.14 (0.75-68.0), respectively. With the combination of the DBVs and iDSs, they were 95% (75.4%-99.1%), 52% (32.4%-71.7%), 73% (57.2%-83.9%), and 19.8 (2.22-176.6), respectively.

To confirm the best cutoff point in the evaluation study, we calculated the ROC curve using the validation group (Fig. 3B). When the 3 factors were acquired one point, respectively, the area under the ROC curve was 0.7832. The best cutoff point was confirmed as 2 points, with sensitivity of 79% and specificity of 81%.

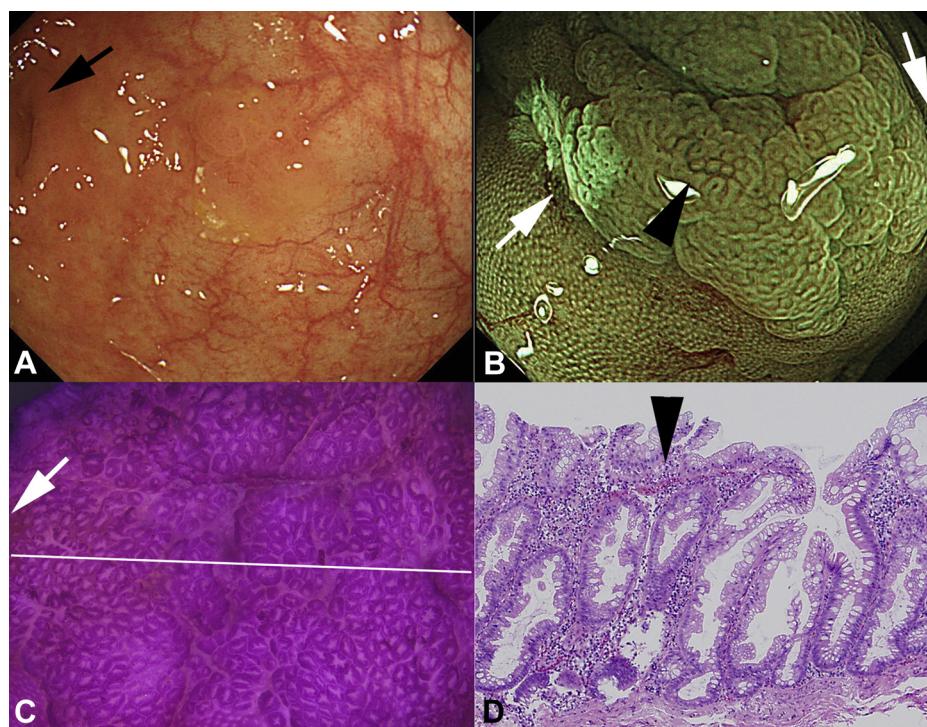
**Histological evaluation of the DBV.** We compared endoscopic images and the histological appearance of

the DBVs in SSA/Ps as a representative case, illustrated in Figure 4. A thickened capillary vessel that runs between serrated glands near the surface was observed as the area where DBVs were endoscopically detected.

## DISCUSSION

This study demonstrates that DBVs, a NBI finding on optical magnification, can be a unique feature of SSA/Ps. This specific finding can be interpreted not only by Japanese endoscopists but also by endoscopists from different regions around the world.

Two recent studies reported the NBI features of SSA/Ps.<sup>20,21</sup> Hazewinkel et al<sup>20</sup> evaluated NBI features of 150 polyps including 50 SSA/Ps, 50 HPs, and 50 adenomas with 5 experts. They found that a cloudlike surface, indistinctive borders, irregular shape, and dark spots were potential predictive NBI features of SSA/Ps compared with HPs. However, the reported sensitivities of SSA/Ps was 66%, 65%, 78%, and 58%, respectively, which were not



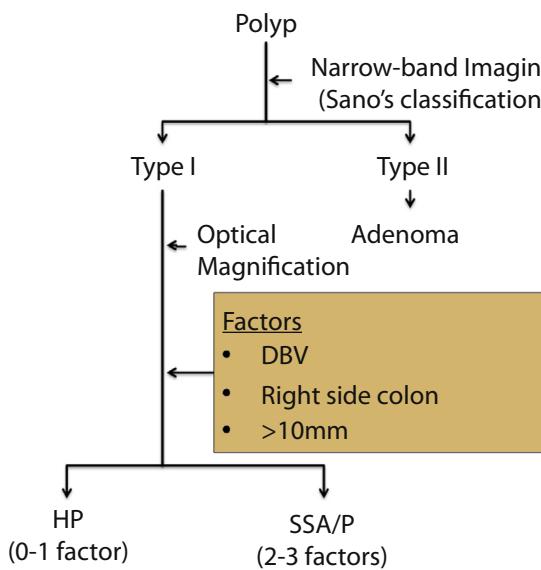
**Figure 4.** Comparison of endoscopic appearance and histological features of a serrated adenomas/polyp. **A**, A flat elevated type lesion, 7 mm in size, in the cecum (appendiceal orifice, black arrow). **B**, Narrow-band imaging with optical magnification revealed dilated and branching vessels (arrowhead) on the surface (markings at the bilateral side of the dilated and branching vessels, white arrows). **C**, Stereomicroscopic view revealed an asteroid-shape pit pattern with irregular dilation. We cut the specimen through the markings (marking, white arrow; cut line, white line). **D**, Histological feature of the lesion (H&E, orig. mag.  $\times 40$ ). At the part where the DBVs were endoscopically observed, a thickened capillary vessel can be observed at the lamina propria mucosae (arrowhead).

acceptably high. Kumar et al reported unimpressive results by using the Narrow-Band Imaging International Colono-scopy Endoscopic (NICE) classification of serrated lesions from a large prospective study using NBI without optical magnification.<sup>21,26</sup> They found that by using the NICE classification, approximately one-third of diminutive SSA/Ps (< 6 mm) could be assessed by using NBI with high confidence, but incorrectly, as HPs. Therefore, NBI for the diagnosis of SSA/Ps was not perfect, and the clinical importance of how to diagnose these clinically significant small and diminutive serrated polyps still remains challenging.

Previously, some studies noted that telangiectasia observed on the surface of the serrated polyps was termed as isolated lacy vessels,<sup>9</sup> superficial telangiectasia,<sup>27</sup> tiny microvessels, and irregular spiral vessels.<sup>20,28</sup> However, histological evidence of telangiectasia and the association between the vessels and SSA/Ps are not well defined yet. This study differs clearly from previous studies because of the use of optical magnification. By using optical magnification, our finding of DBVs tends to be associated with SSA/Ps and was observed even in any lesion, irrespective of size, location, or sex. SSA/Ps are also known to occur less frequently in the distal colon. Interestingly, based on the subgroup analysis by using lesion location of the distal colon, multivariate analysis revealed that DBVs were a significant predictive factor adjusted for sex and lesion size

(OR 7.2; 95% CI, 1.27-40.6). Although the CI was wide due to the limited sample size, this result suggested that the presence of DBVs is useful to diagnose SSA/Ps in daily practice.

Based on the PIVI (Preservation and Incorporation of Valuable Endoscopic Innovations) statement, endoscopists can “resect and discard” or “diagnose and observe” the diminutive polyps when they diagnose the lesion as an HP with high confidence, especially in the sigmoid colon and rectum.<sup>29</sup> However, the polyps may include SSA/Ps. The results of this study can be useful to achieve greater confidence to distinguish SSA/Ps from HPs in clinical practice. When endoscopists detect a lesion having features of an HP with high confidence, if the lesion has 2 or more of the following factors, (1) DBVs, (2) proximal location, and (3) lesion size ( $\geq 10$  mm), the lesion is probably an SSA/P, and it can then be managed by the “resect and submit” strategy because the surveillance interval is different from that of HPs.<sup>12</sup> If the lesion has only 1 or no factor, the lesion is probably an HP, and it can then be managed by the “resect and discard” or “diagnose and observe” strategy (Fig. 5). We know that SSA/Ps in the sigmoid colon and rectum are rare. However, by using the study results, even in the sigmoid colon and rectum, SSA/Ps can be diagnosed as 10 mm or larger with DBV findings, which



**Figure 5.** Diagnostic flow chart to diagnose sessile serrated adenomas/polyps (SSA/Ps) in clinical practice from this study. If the polyp has 2 or 3 factors, it is probably an SSA/P and if 0 or 1 factor, a probable hyperplastic polyp (HP). DBV, dilated and branching vessel.

is useful and very convenient in accordance with PIVI statement.

Increasing the number of endoscopic features will increase interobserver variability and decrease the sensitivity. In this study, we used DBVs as the only NBI feature of pattern recognition for the diagnosis of SSA/Ps, and the DBV feature had substantial agreement. In addition, the other 2 findings in the pattern recognition are clinical features of the lesion, proximal location, and tumor size, with less interobserver variability. Therefore, we think that the combined use of these 3 findings for the diagnosis SSA/Ps is useful in clinical practice.

However, the sensitivity of DBVs for SSA/Ps was not acceptably high (65%). Therefore, a combination of other possible predictive features is needed to help in the endoscopic diagnosis of SSA/Ps. When combining DBVs, proximal location, and tumor size ( $\geq 10$  mm), although the sensitivity was still low, the specificity and positive predictive value attained were sufficient to endoscopically diagnose SSA/Ps. Given the results of ROC curve, resect and discard or simple observation are possible strategies for polyps that satisfy less than 2 of the 3 combination factors. We can have more confidence in diagnosing HPs and can eliminate preforming biopsies.

The iDSs may reflect a crypt dilation that is one of the major histological features of SSA/Ps. However, iDSs were not associated with SSA/Ps on multivariate analysis. A proposed possible reason was that histological changes are often observed lower in the crypts of SSA/Ps. Another reason is that, given the specificity (71%), approximately 30% of HPs may demonstrate the crypt dilation on the surface. The dilation of pits in SSA/P was reported as a type II

open pit pattern in magnifying chromoendoscopy and oval lumen in endocytoscopy.<sup>30,31</sup> Given the reported higher sensitivity than that of iDSs, chromoendoscopy is needed to accurately assess for the pits pattern features.

Although SSA/Ps can be histologically distinguished from HPs, the interobserver agreement is reported to be inferior.<sup>32</sup> Because the pathologists did not know the results of this study and the observer did not know the pathological diagnosis, in the event there was a misclassification, it would be a nondifferential misclassification. Therefore, any misclassification of SSA/Ps would be expected to bias toward null association of DBVs with SSA/Ps.

Based on the study by Kumar et al,<sup>21</sup> using the NICE classification by NBI, features of the SSA/Ps were between those of HPs and adenomas, and large lesions ( $\geq 10$  mm) were more likely to resemble adenomas. Eighty-one percent (17/21) of the large lesions were reported to have all 3 NBI features of adenomas, according to the NICE classification. However, the impact of discriminating SSA/Ps from adenomas is negligible. In our study, only 17% (15/89) of the lesions 10 mm or larger had the meshed capillary pattern, indicating adenomas. Although the recommended surveillance interval is the same for SSA/Ps and adenomas, another study is needed to know the role of NBI to optically differentiate between SSA/Ps and adenomas.

Increasing detection is a significant problem with SSA/Ps that may otherwise be missed. Because about 60% of the SSA/Ps had a flat morphology (0-IIa in the Paris classification) (Table 1), good bowel preparation is important to detect them. In addition, there was a remarkable distribution in the proximal colon, and a mucous cap is a well-known endoscopic feature of SSA/Ps.<sup>27</sup> Therefore, to increase detection of SSA/Ps, it is important to actively search for flat lesions and mucous caps in the proximal colon.

One of the realities of optical biopsy criteria in clinical practice is that there is interobserver variability and frankly a great deal of difficulty in remembering/translating pit and vascular patterns seen in polyps. Based on the substantial agreement of experienced endoscopists regarding DBVs, we think that image training under experienced physicians is important to accurately distinguish SSA/Ps from HPs and adenomas and to decrease interobserver variability among less experienced endoscopists.

This study was limited by its retrospective design, resulting in selection bias and excluding data on tubular adenomas. However, we use consecutive lesions and validated the data by observers outside NCCH by using other samples from the evaluation study. The interobserver agreement for DBVs was substantial, but poor in other findings due to the brief training. It is known that a greater learning curve is required to reduce interobserver variability and improve observer accuracy. Therefore, longer and extensive training will be necessary to increase interobserver agreement in a future validation study. Finally, due to the limited sample size, our findings should be carefully

interpreted. Further studies are needed to identify the specific features of SSA/Ps. One advantage of this study is the use of magnifying endoscopy. Observation with magnification has a greater than 10% higher accuracy of a qualitative diagnosis than conventional endoscopy,<sup>3</sup> and NBI with optical magnification is more practical, convenient, and time saving than magnification with chromoendoscopy.<sup>33</sup> Magnifying colonoscopes are not yet commonly available in the most parts of the world. Recently, however, endoscopes with a near focus function are also available outside Japan (Olympus CF-HQ190 series). Thus, we believe that DBVs will be a useful endoscopic finding to aid real-time diagnosis of these lesions across the world. We are now planning confirmation of the results of this study by a prospective multicenter validation study with a large number.

In conclusion, this study demonstrated that DBVs may be a unique endoscopic feature of SSA/Ps. By using DBVs in addition to known clinicopathological features, the accuracy of diagnosis of SSA/Ps may be improved.

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