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Original Article

Validation study for development of the Japan NBI Expert Team classification of colorectal lesions

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Background and Aim: The Japan narrow-band imaging (NBI) Expert Team (JNET) was organized to unify four previous magnifying NBI classifications (the Sano, Hiroshima, Showa, and Jikei classifications). The JNET working group created criteria (referred to as the NBI scale) for evaluation of vessel pattern (VP) and surface pattern (SP). We conducted a multicenter validation study of the NBI scale to develop the JNET classification of colorectal lesions.

Methods: Twenty-five expert JNET colonoscopists read 100 still NBI images with and without magnification on the web to evaluate the NBI findings and necessity of the each criterion for the final diagnosis.

Results: Surface pattern in magnifying NBI images was necessary for diagnosis of polyps in more than 60% of cases, whereas VP was required in around 90%. Univariate/multivariate analysis of candidate findings in the NBI scale identified three for type 2B (variable caliber of vessels, irregular distribution of vessels, and irregular or obscure surface pattern), and three for type 3 (loose vessel area, interruption of thick vessel, and amorphous areas of surface pattern). Evaluation of the diagnostic performance for these three findings in combination showed that the sensitivity for types 2B and 3 was highest (44.9% and 54.7%, respectively), and that the specificity for type 3 was acceptable (97.4%) when any one of the three findings was evident. We found that the macroscopic type (polypoid or non-polypoid) had a minor influence on the key diagnostic performance for types 2B and 3.

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Conclusion: Based on the present data, we reached a consensus for developing the JNET classification.

Key words: classification, magnifying endoscopy, narrow-band imaging, Japan NBI Expert Team, validation

INTRODUCTION

NARROW -BAND IMAGING (NBI) has contributed greatly to real-time optical diagnosis of colorectal polyps and gastrointestinal tumors through clearer visualization of the microvascular architecture and surface structure.[1–3] Several magnifying NBI classifications of colorectal tumors have been proposed and validated in Japan. Sano *et al.* were the first to publish a magnifying NBI classification known as the Capillary Pattern classification (Sano classification) in 2006.[4] On the basis of this classification, other magnifying NBI classifications (Hiroshima, Showa, and Jikei classifications) were proposed by several institutions. However, this led to confusion among novice endoscopists because each classification used different terminologies for similar NBI findings.[5–7]

Against this background, the Japan NBI Expert Team (JNET) was organized in 2011 to develop a universal magnifying NBI classification. The team comprised 38 members from 26 institutions throughout Japan, including the proposers of each of the existing magnifying NBI classifications.[8] It was necessary to address three key concerns for unification of these magnifying NBI classifications. First, the most reliable magnifying NBI findings corresponding to deep submucosal invasive cancer (D-SMC) were not clear because the categorization and magnifying NBI findings of invasive cancer varied among these classifications. Second, it was uncertain whether the surface pattern (SP) was needed for diagnosis of colorectal polyps, as three of the classifications (Sano, Showa, and Jikei) were based on the vessel pattern (VP), whereas the Hiroshima classification was based on both VP and SP. Third, it was uncertain how the macroscopic type of polyps (polypoid or non-polypoid) affected diagnostic performance.

The JNET working group held discussions and created common evaluation criteria, known as the NBI scale, for VP and SP based on the NBI International Colorectal Endoscopic (NICE) classification.[8–10] This scale consisted of four categories: type 1 corresponded to the most likely pathology for hyperplastic polyp/sessile serrated polyp; type 2A for low-grade intramucosal neoplasia (LGIN) including intramucosal cancer with low-grade structural atypia; type 2B for high-grade intramucosal neoplasia (HGIN)/shallow submucosal invasive cancer (S-SMC); and type 3 for D-SMC (Figure 1).[8] Furthermore, VP in the NBI scale was classified as the polypoid type or the non-polypoid type.

The main aim of the present web-based image interpretation study was to create basic data for development of the JNET classification by validating the findings used in the NBI scale, as well as the necessity of individual criterion.

METHODS

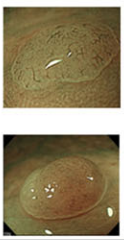
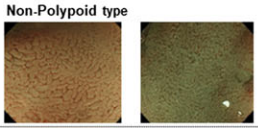
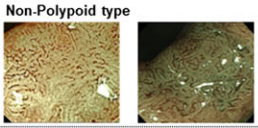
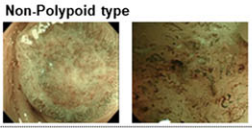
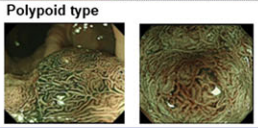
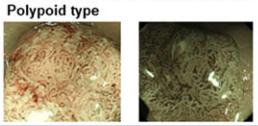
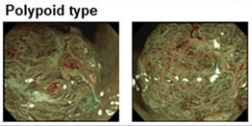
IN 2013, WE conducted a prospective multicenter validation study using web-based still NBI images read by 25 JNET colonoscopists who had more than 3 years of NBI experience. The study protocol was approved by the Institutional Review Board at Sano Hospital and Hiroshima University Hospital. This study was registered with a national clinical trial registry (UMIN 000010292).

Test images

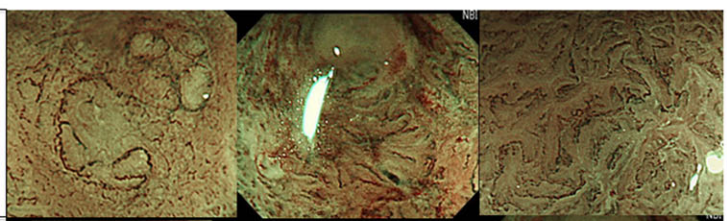
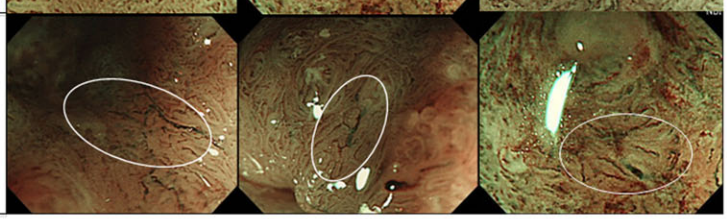
After stratifying macroscopic type and histopathology of the polyps, we randomly selected 40 pairs of images consisting of a non-magnifying and a magnifying NBI image of a subcentimeter polyp for prediction of neoplasia from the endoscopic image library stored at Sano Hospital between 2010 and 2012. Histopathology of the 40 colorectal polyps in the NBI images was neoplasia in 20 cases (polypoid: 10, non-polypoid: 10) and non-neoplasia in 20 cases (polypoid: 10, non-polypoid: 10). Sessile serrated polyp was classified as non-neoplasia because the endoscopic criteria for distinction of sessile serrated polyp from hyperplastic polyp, or a pathological gold standard for diagnosis, have not been fully established.

Similarly, 60 pairs of NBI images of each colorectal polyp of any size for prediction of D-SMC were randomly chosen from the library of endoscopic images pooled at Hiroshima University Hospital between 2010 and 2011. Histopathology of these polyps included LGIN with severe atypia in 20 cases (polypoid: 10, non-polypoid: 10), HGIN/S-SMC in 20 (polypoid: 10, non-polypoid: 10), and D-SMC in 20 (polypoid: 10, non-polypoid: 10). The 20 HGIN/S-SMC cases were further divided into eight showing low-grade structural atypia and 12 showing high-grade structural atypia. In order to evaluate the findings of pure magnifying NBI, we intentionally masked part of the area in the 60 magnifying NBI images to focus on the region of interest, so

(a)

Type 1	Type 2A	Type 2B	Type 3
	Non-Polypoid type 	Non-Polypoid type 	Non-Polypoid type 
	Polypoid type 	Polypoid type 	Polypoid type 
None, or isolated lacy vessels may be present coursing across the lesion	Regular	Has area(s) with moderately distorted vessels	Has area(s) with markedly distorted or missing vessels
• Vessels are invisible • If vessels are visible, the vessel caliber in the lesion is the same as that in the surrounding normal mucosa • Lacy vessels coursing across the lesion	• Distribution of dark brown microvessels • Uniform and regular, relatively well-ordered reticular pattern (*Note that microvessels are often distributed in a punctate pattern and the well-ordered reticular pattern is not commonly observed in depressed lesions.)	• Varied caliber/caliber change • Thick vessels/vessel dilation • Uneven and irregular distribution of vessels • Vessel meandering * Approximately ≥ 1.5 times thicker than in adenomas	• Avascular areas or loose vascular areas • Disrupted thick vessels

(b)

Scattered vessels Coarsely distributed, irregular vessels, probably corresponding to desmoplastic reaction	
Thick, linearized/ meandering atypical vessels in the tumor Vessels similar to string sign described by Terai et al, but those found at the periphery are not taken into account	

(c)

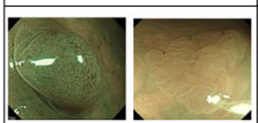
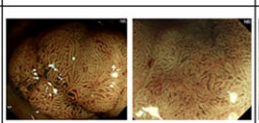
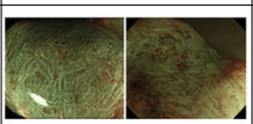
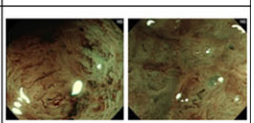
Type 1	Type 2A	Type 2B	Type 3
			
Dark or white spots of uniform size, or homogeneous absence of pattern	Regular	Irregular	Amorphous
• Regular dark or white spots • Uniformly obscure structure	• Tubular or dendritic or papillary • Regular surface pattern • Corresponding to type III or IV pit pattern	• Visible surface pattern with irregularity • Corresponding to the type Vi pit pattern	• Invisible surface pattern • Corresponding to the type Vn pit pattern

Figure 1 Narrow-band imaging scale. (a) Vessel pattern, (b) appendix in vessel pattern, (c) surface pattern.

that the diagnosis of invasion depth by the participants would be made blind to the macroscopic type.

High-definition colonoscopes with LUCERA SPECTRUM video processors (Olympus, Tokyo, Japan) were used to collect NBI images at both hospitals. System functions for NBI were set to color mode 3 and structure enhancement mode A-8. Magnifying images were basically taken by at least 60 times optical zoom colonoscopy.

Procedure

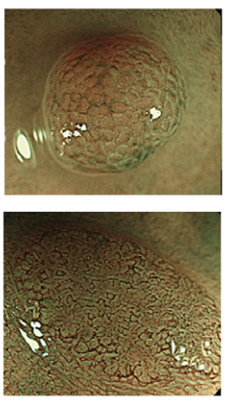
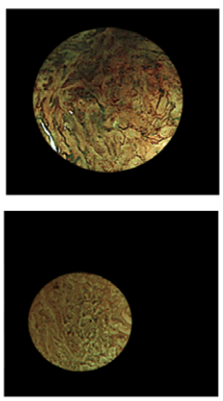
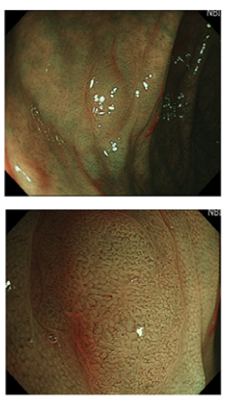
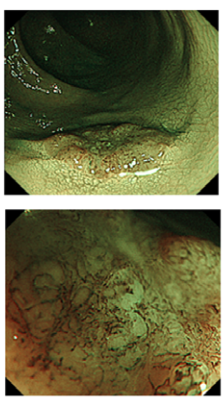
This study was divided into four phases (studies 1–4). A simple schema of each study is shown in Figure 2.

Study 1: Evaluation of 40 magnifying NBI images for differentiation of neoplasia from non-neoplasia

The 25 participants evaluated 40 still magnifying NBI images of colorectal polyps including 20 cases of neoplasia and 20 cases of non-neoplasia. The main objective of study 1 was to investigate the performance characteristics of magnifying NBI for prediction of neoplasia in terms of confidence level. The participants were asked to assign a category of VP and SP in the NBI scale (type 1, 2A, 2B, or 3) with a confidence level (high or low), the final endoscopic diagnosis (neoplasia or non-neoplasia) with a confidence level, and the necessity of each criterion for the final diagnosis (necessary or unnecessary). Necessity of each criterion was counted when the criterion gave a great contribution to the final endoscopic diagnosis. High-confidence prediction was made when participants had 90% certainty of the diagnosis.[9]

Study 2: Evaluation of 60 magnifying NBI images for differentiation of deep submucosal invasive cancer from shallow submucosal invasive cancer and intramucosal neoplasia

The main objectives of study 2 were to evaluate pure magnifying NBI findings specific to D-SMC and performance characteristics for prediction of D-SMC based on confidence level. We used 60 partially masked magnifying NBI images of colorectal polyps including 20 cases of LGIN, 20 cases of HGIN/S-SMC, and 20 cases of D-SMC. Participants were asked to assign magnifying NBI findings (multiple choice) provided from the NBI scale, a category of VP and SP in the NBI scale with a confidence level, the final endoscopic diagnosis (D-SMC or S-SMC/HGIN or LGIN) with a confidence level, and the necessity of each criterion for the final diagnosis.

Study	1	2	3	4
Endoscopic prediction	Neoplasia	D-SMC	Neoplasia	D-SMC
Main objective	Performance characteristics	Specific findings for D-SMC Performance characteristics	Advantages of magnifying NBI	Advantages of magnifying NBI
Evaluated Criteria	VP, SP	VP (+individual findings), SP	VP, SP, and Color ※	VP, SP, and Color ※
Magnifying NBI images (n)	40	60 (partially masked)	40 #	60 #
Non-magnifying NBI images (n)	0	0	40 #	60 #
Polyp pathology (n)	Neoplasia: 20 Non-neoplasia: 20	D-SMC: 20 S-SMC/HGIN: 20 LGIN: 20	Neoplasia: 40 Non-neoplasia: 40	D-SMC: 40 S-SMC/HGIN: 40 LGIN: 40
Images				

※ Color criterion was evaluated only in non-magnifying NBI images # Pairs of a non-magnifying and a magnifying NBI images for each polyp.

Figure 2 Overview of studies 1–4. NBI, narrow-band imaging; VP, vessel pattern; SP, surface pattern; D-SMC, deep submucosal invasive cancer; S-SMC, shallow submucosal invasive cancer; HGIN, high-grade intramucosal neoplasia; LGIN, low-grade intramucosal neoplasia.

Study 3: Evaluation of 40 pairs of NBI images with and without magnification for differentiation of neoplasia from non-neoplasia

We used 40 pairs of still NBI images with and without magnification in order to assess the advantages of magnifying NBI over non-magnifying NBI, in terms of performance characteristics, for prediction of neoplasia. Participants evaluated still NBI images of polyps without magnification in the first phase, followed by magnifying NBI images of the same polyps in the second phase. They assigned a category of VP, SP, color with a confidence level, final endoscopic diagnosis (neoplasia or non-neoplasia) with a confidence level, and the necessity of each criterion for the final diagnosis in both the first and second phases. The color criterion was evaluated based on the NICE classification (type 1, 2, or 3) in the first phase only, as the color of polyps in the magnifying view was difficult to compare with that of the surrounding mucosa (Figure S1). Once the participants had finished all evaluations in the first phase and proceeded to the second phase, they were not permitted to change the diagnosis they had made in the first phase.

Study 4: Evaluation of 60 pairs of NBI images with and without magnification for differentiation of deep submucosal invasive cancer from shallow submucosal invasive cancer and intramucosal neoplasia

Sixty pairs of still NBI images with and without magnification were used in order to examine the advantages of magnifying NBI over non-magnifying NBI, in terms of performance characteristics, for prediction of D-SMC. Participants assessed NBI images without magnification in the first phase, and then subsequently NBI images with magnification in the second phase, as had been done for study 3. They assigned a category of VP, SP, color with a confidence level, final endoscopic diagnosis (D-SMC or S-SMC/HGIN or LGIN) with a confidence level, and the necessity of each criterion for the final diagnosis in both the first and second phases.

As 100 images of the same polyps in studies 1 and 2 were also used in studies 3 and 4, the latter studies were conducted 4 weeks after the former studies.

Variables

Primary outcome measure

Primary outcome was to investigate the performance characteristics of NBI with and without magnification for prediction of neoplasia (studies 1, 3) and D-SMC (studies 2, 4) using a confidence level.

Secondary outcome measure

Secondary outcome had two measures: (i) proportion of the necessity of each criterion (VP, SP and color) for the final endoscopic diagnosis (all studies); and (ii) frequency of observable vessel findings defined in the NBI scale (1–10) for polypoid and non-polypoid types including (1) regular vessels, (2) spotted vessels, (3) variable caliber of vessels, (4) thick vessels, (5) irregular distribution of vessels, (6) vessel meandering, (7) loose vessel areas, (8) interruption of thick vessels, (9) scattered vessels, and (10) thick, linearized/meandering atypical vessels in the tumor (study 2).

Statistical analysis

We used McNemar's test for paired categorical variables, and chi-squared test and Fisher's exact test for unpaired categorical variables. A two-sided *P*-value of less than 0.05 was considered to indicate statistical significance.

A sample size of 996 persons achieves 80% power to detect a difference of 5% between two diagnostic tests whose sensitivities are 90% and 95%.[9,11,12] This procedure uses a two-sided McNemar's test with a significance level of 0.05 (in this setting, the prevalence of disease in the population is 50% and the proportion of discordant pairs is 15%). Following this sample size, we decided to collect 1000 images in total (500 pairs of images with and without magnification) for prediction of neoplasia and 1500 images for prediction of D-SMC (the 25 participants read 60 images).

RESULTS

Performance characteristics of NBI with magnification based on confidence level (studies 1, 2)

PERFORMANCES CHARACTERISTICS OF NBI with magnification based on confidence level for differentiation of neoplasia from non-neoplasia (study 1) and D-SMC from S-SMC/HGIN/LGIN (study 2) are shown in Table 1. Accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 89.0%, 95.3%, 81.0%, 86.7%, and 92.9%, respectively, for high-confidence prediction in study 1, 82.3%, 45.4%, 98.6%, 93.3%, and 80.3%, respectively, for high-confidence prediction in study 2.

Table 1 Performance characteristics of NBI with magnification based on confidence level in differentiating neoplasia from non-neoplasia (study 1) and D-SMC from S-SMC/HGIN/LGIN (study 2)

	Study 1			Study 2		
Prediction	Neoplasia			D-SMC		
Confidence level	HC (n = 821)	LC (n = 179)	Overall (n = 1000)	HC (n = 1093)	LC (n = 407)	Overall (n = 1500)
Performance (%)						
Accuracy	89.0	64.8	84.7	82.3	67.9	78.3
Sensitivity	95.3	52.8	92.2	45.4	29.1	40.0
Specificity	81.0	67.8	77.2	98.6	93.8	97.4
PPV	86.7	29.2	80.2	93.3	76.2	88.5
NPV	92.9	85.1	90.8	80.3	66.0	76.5

NBI, narrow-band imaging; D-SMC, deep submucosal invasive cancer; S-SMC, shallow submucosal invasive cancer; HGIN, high-grade intramucosal neoplasia; LGIN, low-grade intramucosal neoplasia; HC, high confidence; LC, low confidence; PPV, positive predictive value; NPV, negative predictive value.

Differences in performance characteristics and confidence level between NBI with and without magnification (studies 3, 4)

Differences in performance characteristics and confidence level between NBI with and without magnification for differentiation of neoplasia from non-neoplasia (study 3) and D-SMC from S-SMC/HGIN/LGIN (study 4) are shown in Table 2. In contrast to NBI without magnification, NBI with magnification showed significantly increased accuracy (81.1% *vs* 85.6%, $P < .001$) and specificity (71.6% *vs* 85.6%, $P < .001$) in study 3, and accuracy (77.9% *vs* 81.3%, $P < .001$), sensitivity (42.4% *vs* 47.4%, $P < .001$), and specificity (95.7% *vs* 98.2%, $P < .001$) in study 4. Furthermore, NBI with magnification significantly increased the proportion of high-confidence prediction in both studies (study 3, 64.3% *vs* 85.0%, $P < .001$; study 4, 41.7% *vs* 76.0%, $P < .001$).

Necessity of each criterion (VP, SP and color) for the final endoscopic diagnosis (all studies)

We assessed the proportion of the necessity of each criterion (VP, SP and color) for the final endoscopic diagnosis in all studies (Table 3). Among the criteria evaluated with magnification, the proportion of the necessity of SP was greater than 60%, whereas that of VP was approximately 90% in all studies. Color was shown to have the highest proportion of the necessity among the criteria evaluated without magnification in studies 3 and 4.

Table 2 Difference in performance characteristics and confidence level between NBI with and without magnification for differentiation of neoplasia from non-neoplasia (study 3) and D-SMC from S-SMC/HGIN/LGIN (study 4)

	Study 3			Study 4		
Prediction	Neoplasia			D-SMC		
ME (−/+)	NBI without ME (n = 1000)	NBI with ME (n = 1000)	P-value	NBI without ME (n = 1500)	NBI with ME (n = 1500)	P-value
Performance (%)						
Accuracy	81.1	85.6	<.001	77.9	81.3	<.001
Sensitivity	90.6	91.8	0.40	42.4	47.4	<.001
Specificity	71.6	79.4	<.001	95.7	98.2	<.001
PPV	76.1	81.7	<.001	83.2	92.9	<.001
NPV	88.4	90.6	0.29	76.9	78.9	0.23
HC rate (%)	64.3	85.0	<.001	41.7	76.0	<.001

NBI, narrow-band imaging; D-SMC, deep submucosal invasive cancer; S-SMC, shallow submucosal invasive cancer; HGIN, high-grade intramucosal neoplasia; LGIN, low-grade intramucosal neoplasia; ME, magnifying endoscopy; PPV, positive predictive value; NPV, negative predictive value; HC, high confidence.

Table 3 Proportion of necessity of each criterion (vessel pattern, surface pattern, and color) for final endoscopic diagnosis in all studies

	Prediction	ME	Necessity of vessel pattern (%)	Necessity of surface pattern (%)	Necessity of color (%)
Study 1 (n = 1000)	Neoplasia	(+)	91.4	66.1	–
Study 2 (n = 1500)	D-SMC	(+)	90.2	72.3	–
Study 3 (n = 1000)	Neoplasia	(−)	70.0	43.4	80.4
		(+)	93.1	71.0	–
Study 4 (n = 1500)	D-SMC	(−)	76.5	52.7	76.9
		(+)	93.3	72.9	–

D-SMC, deep submucosal invasive cancer; ME, magnifying endoscopy. Necessity of each criterion was counted when the criterion gave a great contrituion to the final endioscopic diagnosis.

Table 4 Frequency of 10 vessel findings predictive of D-SMC and S-SMC/HGIN/LGIN for polypoid and non-polypoid types (study 2)

No.	Vessel findings	Frequency in D-SMC (%)		Frequency in S-SMC/HGIN/LGIN (%)	
		Polypoid (n = 250)	Non-polypoid (n = 250)	Polypoid (n = 500)	Non-polypoid (n = 500)
1	Regular vessels	20.0†	5.2†	57.4	53.4
2	Spotted vessels	0	0.8	0.6†	11.4†
3	Variable caliber of vessels	32.4	34.8	23.6	23.8
4	Thick vessels	26.4†	16.4†	15.8	14.4
5	Irregular distribution of vessels	35.2†	44.4†	27.8	26.4
6	Vessel meandering	16.4	17.6	12.8	12.8
7	Loose vessel areas	22.0†	36.4†	1.8	2.0
8	Interruption of thick vessels	26.8	30.8	2.0	0.8
9	Scattered vessels	21.6	24.8	1.2	1.6
10	Thick, linearized/meandering atypical vessels in the tumor	10.8	8.0	0.8	0.4

†Significant difference between polypoid and non-polypoid type ($P < 0.05$).
D-SMC, deep submucosal invasive cancer; S-SMC, shallow submucosal invasive cancer; HGIN, high-grade intramucosal neoplasia; LGIN, low-grade intramucosal neoplasia.

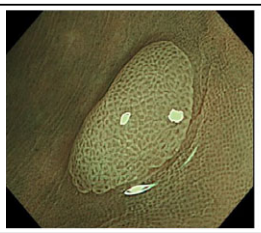
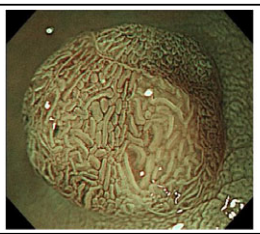
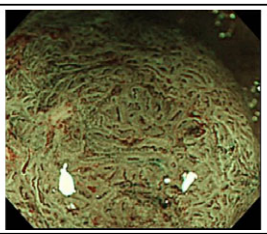
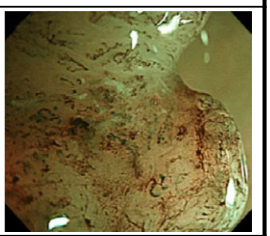
Frequency of observable vessel findings defined in the NBI scale for polypoid and non-polypoid types (study 2)

Table 4 shows the frequency of 10 vessel findings predictive of D-SMC and S-SMC/HGIN/LGIN for polypoid and non-polypoid types. The polypoid type was significantly more likely to show two findings (regular vessels and thick vessels), and less likely to show two findings (irregular distribution of vessels and loose vessel areas) than the non-polypoid type in D-SMC. The non-polypoid type was associated with a significantly higher rate of spotted vessels in S-SMC/HGIN/LGIN.

DISCUSSION

THIS PROSPECTIVE WEB -based interpretation study was the first trial conducted by the JNET for developing a universal magnifying NBI classification of colorectal lesions. We found that the proportion of the necessity of SP evaluated in magnifying NBI images by JNET was lower than that of VP, but greater than 60% for prediction of neoplasia and D-SMC. In addition, SP was confirmed to be one of the key findings in types 2B and 3, as described below. These two results led us to conclude that SP is an essential criterion, along with VP, for the JNET classification. We also identified the advantages of magnifying endoscopy for NBI diagnosis based on its diagnostic performance and the proportion of high-confidence prediction for neoplasia and D-SMC.

From the data obtained, we tried to develop the JNET classification based on the NBI scale, which consists of four categories (types 1, 2A, 2B, and 3). Some additional subset analyses were also conducted to clarify the specific magnifying NBI findings for corresponding histopathology and diagnostic performance in combination with their findings.

	Type 1	Type 2A	Type 2B	Type 3
Vessel pattern	・Invisible ※1	・Regular caliber ・Regular distribution (meshed/spiral pattern) ※2	・Variable caliber ・Irregular distribution	・Loose vessel areas ・Interruption of thick vessels
Surface pattern	・Regular dark or white spots ・Similar to surrounding normal mucosa	・Regular (tubular/branched/papillary)	・Irregular or obscure	・Amorphous areas
Most likely histology	Hyperplastic polyp/ Sessile serrated polyp	Low grade intramucosal neoplasia	High grade intramucosal neoplasia/ Shallow submucosal invasive cancer ※3	Deep submucosal invasive cancer
Endoscopic image				

*1. If visible, the caliber in the lesion is similar to surrounding normal mucosa.

*2. Microvessels are often distributed in a punctate pattern and well-ordered reticular or spiral vessels may not be observed in depressed lesions.

*3. Deep submucosal invasive cancer may be included.

Figure 3 Japan NBI Expert Team (JNET) classification. NBI, narrow-band imaging.

We used only high-confidence findings of the VP and SP in all subset analyses because they were more reliable for prediction of corresponding histopathology than low-confidence findings.

Initially, for JNET type 3 category, we needed to identify the specific magnifying NBI findings that significantly corresponded to D-SMC among five candidates in the NBI scale (loose vessel areas; interruption of thick vessels; scattered vessels; thick, linearized/meandering atypical vessels in the tumor; and amorphous areas of surface patterns) using the data from study 2. Additionally, we calculated the odds ratios of the five candidate type 3 findings for D-SMC in univariate and multivariate analyses (Table S1). Multivariate analysis found that only three type 3 findings (loose vessel area, interruption of thick vessel, and amorphous areas of surface pattern) were significantly associated with D-SMC. With regard to performance characteristics in combination with these three type 3 findings, specificity was given priority over sensitivity in order to prevent unnecessary surgery (Table S2). The presence of all three type 3 findings had the highest specificity of 99.5%, although the sensitivity reached only 23.4%. Considering that the specificity of magnifying chromoendoscopy as a gold standard method was 96.1% and the sensitivity was 86.5% for predicting D-SMC among intramucosal/submucosal cancers, the presence of any one of the three type 3 findings yielded the highest sensitivity of 54.7%, and an acceptable specificity of 97.4%.[13,14] Therefore, we decided to diagnose a lesion as JNET type 3 when any one of the three type 3 findings was present.

For the JNET type 2B category, we calculated the odds ratios of the five candidate type 2B findings in the NBI scale (variable caliber of vessels, thick vessels, irregular distribution of vessels, vessel meandering, and irregular or obscure surface pattern) in univariate and multivariate analyses based on the results of study 2 (Table S3). Corresponding histopathology of type 2B used in this anlyses was HGIN or mainly S-SMC including some D-SMC. We excluded thick vessels from the findings in the type 2B category because this was not significantly associated with the corresponding histopathology in both univariate and multivariate analyses. The diagnostic performance for type 2B places more weight on sensitivity rather than specificity for detection of HGIN and submucosal invasive cancer. As vessel meandering was marginally associated with the corresponding histopathology in univariate analysis, we calculated the diagnostic performance in combination with four type 2B findings (except for thick vessels) and three type 2B findings (except

for thick vessels and vessel meandering) (Table S4). The presence of any one of the three type 2B findings yielded the same sensitivity of 44.9% and specificity of 74.0% as that of any one of the four type 2B findings, which meant that vessel meandering could be omitted from the type 2B category. Finally, we adopted three findings: variable caliber of vessels, irregular distribution of vessels, and irregular or obscure surface pattern, as JNET type 2B, which was diagnosed when any one of these three findings was present. As described above, the sensitivity of JNET type 3 for D-SMC was 54.7%, and thus nearly half of D-SMC cases would tend to show JNET type 2B characteristics. Subsequent magnifying chromoendoscopy is recommended for all JNET type 2B lesions to differentiate between shallow and deep submucosal invasive cancers because magnifying chromoendoscopy was more sensitive and accurate than magnifying NBI for prediction of D-SMC.[14,15]

For the JNET type 1 and 2A categories, basically, the four magnifying NBI classifications had nearly the same categorization and magnifying NBI findings predictive of hyperplastic polyp and LGIN. We discussed and adopted the findings of type 1 and 2A based on the NICE classification. The VP of type 2A is a regular caliber and regular distribution with a meshed or spiral pattern, and the SP of type 2A is regular (tubular or branched or papillary pattern). We decided to diagnose JNET type 2A when any one of these three type 2A findings was present because the diagnostic performance of type 2A places more weight on sensitivity to detect neoplasia rather than specificity.

Moreover, we investigated whether the specificity of type 3 findings and the sensitivity of type 2B findings would be affected by the macroscopic type (polypoid or non-polypoid) in study 2 (Table S5). For the three type 3 findings (loose vessel area, interruption of thick vessels, and amorphous areas of surface pattern), there were no significant differences between polypoid and non-polypoid type. For the three type 2B findings (variable caliber of vessels, irregular distribution of vessels, and irregular or obscure surface pattern), the sensitivity of only one finding (irregular distribution of vessels) was significantly higher in the non-polypoid type than in the polypoid type (39% *vs* 30%). We found that the macroscopic type had only a slight influence on the key diagnostic performance based on type 2B and 3 findings, leading us to conclude that macroscopic type is not an essential factor for the JNET classification.

This study had some limitations. First, we used partially masked still images of NBI with magnification to evaluate pure NBI findings in study 2, which is an approach largely different from clinical practice. This image restriction may have worsened the diagnostic performance for prediction of D-SMC in study 2. Second, findings that were specific in differentiating sessile serrated polyp from hyperplastic polyp remained uncertain in JNET type 1. Third, we did not consider the regional expanse of NBI findings in JNET types 2B and 3 when estimating the invasion depth of colorectal cancer.

Based on the data obtained from the present study, we finally reached a consensus to develop the JNET classification through voting by the JNET using the modified Delphi method on 6 June 2014 (Figure 3).[8]

In conclusion, we have unified the four previous magnifying NBI classifications to develop the JNET classification of colorectal lesions, which will be continuously updated as new findings and endoscopy innovations are achieved. It is expected that validation studies for the JNET classification will be conducted worldwide.

AUTHOR CONTRIBUTIONS

STUDY CHAIR: SANO Y. Study coordinator: Iwatate M. Study assistants: Nakajima T, Sakamoto T, Yamaguchi Y, Tamai N, and Nakano N. Collection of test images: Tanaka S, Oka S, Hayashi N, and Iwatate M. Test images readers: Sano Y, Kudo S, Wada Y, Saito S, Saito Y, Matsuda T, Ikematsu H, Fujii T, Nakamura H, Kashida H, Tsuruta O, Kawano H, Hirata I, Yamano H, Terai T, Uraoka T, Kobayashi N, Hotta K, Sakamoto N, Takeuchi Y, Machida H, Yoshida N, Kusaka T, Horimatsu T and Fu KI. Working group for the NBI scale: Saito Y, Matsuda T, Ikematsu H, Oka S, Wada Y, Saito S, and Kawano H. Data center/Protocol advisor: Ishikawa H. Statistical analysis: Murakami Y. Supervisor: Yoshida S.

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CONFLICTS OF INTEREST

AUTHORS DECLARE NO conflicts of interest for this article.

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SUPPORTING INFORMATION

ADDITIONAL SUPPORTING INFORMATION may be found in the online version of this article at the publisher's web site.

Figure S1 Color criterion based on the NICE classification.

Table S1 Prevalence and univariate/multivariate analysis of the five candidate type 3 findings for D-SMC.

Table S2 Performance characteristics for combinations of three type 3 findings predictive of D-SMC.

Table S3 Prevalence and univariate/multivariate analysis of the five candidate type 2B findings for submucosal invasive cancer and HGIN.

Table S4 Performance characteristics for combinations of four and three type 2B findings predictive of submucosal invasive cancer and HGIN.

Table S5 Diagnostic performance of type 2B and 3 findings predictive of corresponding histopathology for polypoid and non-polypoid type.