An International Study on the Diagnostic Accuracy of the Japan Narrow-Band Imaging Expert Team Classification for Colorectal Polyps Observed with Blue Laser Imaging

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Abstract

Background: The Japan narrow-band imaging Expert Team (JNET) classification of colorectal polyps based on magnifying endoscopy is used in Japan, but not worldwide. The objective of this study was to clarify differences of diagnostic accuracy between JNET users in Japan and non-JNET users in other countries. ***Methods:*** A total of 185 colorectal tumors were assessed. Six endoscopists (3 each from Japan and Taiwan) participated in the study. The Japanese endoscopists normally used the JNET classification and the Taiwanese endoscopists normally used the narrow-band imaging International Colorectal Endoscopic classification for diagnosis of colorectal tumors. After receiving a lecture on the JNET classification, they all observed one blue laser imaging magnified image per lesion and performed diagnosis based on the JNET classification. ***Results:*** Diagnostic ability was equivalent for Type 1, Type 2A, and Type 2B. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value of Type 3 for deep submucosal invasive carcinoma was, respectively, 44.4, 98.3, 57.1, and 97.2% in Group J and 70.0, 94.7, 40.4, and 98.4% in Group T. The PPV for diagnosis of Type 3 with a high confidence was significantly higher in Group J than in Group T (81.8% [55.4–94.6] vs. 44.4% [33.6–50.9], $p < 0.05$). ***Conclusions:*** The PPV for Type 3 differed between the 2 groups, suggesting the need to become familiar with differentiation between Type 2B and Type 3.

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Introduction

Colorectal cancer is respectively the 3rd and 2nd most frequent carcinoma in men and women worldwide [1], and it is increasing in Japan and Asia [2]. It is accepted

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that Colorectal cancer develops from a preexisting adenoma. Endoscopic resection is considered desirable for all adenomatous polyps [3, 4], while endoscopic treatment is unnecessary for hyperplastic polyps (HP) and surgery is indicated for deep submucosal invasive carcinoma (dSM: T1b; ≥1,000 μm). Accordingly, endoscopic diagnosis of the histology and depth of invasion is important when selecting a treatment strategy for colorectal tumors.

Image-enhanced endoscopy (IEE), such as narrow-band imaging (NBI) or blue laser imaging (BLI), is widely used for endoscopic diagnosis of the histology and depth of invasion of colorectal tumors. For the international diagnostic method, NBI International Colorectal Endoscopic (NICE) classification proposed by the Colon Tumor NBI International Group in 2012 is widely accepted [5]. Differentiation among HP, adenoma, and dSM is possible by using this classification, allowing decisions to be made about the necessity for endoscopic treatment or surgery [5, 6]. Evaluation can be done without magnification by the NICE classification, and it is widely used in Western and Asian countries because of its simplicity and convenience.

However, no study on differentiation of high grade dysplasia (HGD)/shallow submucosal invasive carcinoma (sSM: T1a; <1,000 μm) by the NICE classification has been reported [7, 8]. Since the risk of lymph node metastasis is extremely low with HGD and sSM [9, 10], these lesions are indicated for endoscopic treatment. However, reliable en bloc resection is required for accurate histological diagnosis and to reduce the risk of recurrence [10, 11]. Endoscopic submucosal dissection (ESD) has recently become an important treatment for colorectal tumors, allowing reliable en bloc resection of large lesions for which endoscopic en bloc resection was difficult in the past. Accordingly, distinguishing between LGD, HGD, and sSM has become more important with regard to the selection of endoscopic treatment.

In Japan, NBI magnifying endoscopic classification was developed for diagnosing the depth of invasion of colorectal tumors, and the effectiveness of this method has been demonstrated [12–15]. However, several different classifications were proposed, leading to problems such as multiple terms for the same or similar findings, differences in describing the surface pattern, and differences of features between protruding and flat lesions. In June 2016, the Japan NBI Expert Team (JNET) proposed a unified magnifying NBI classification of colorectal tumors, the JNET classification [16], and investigation of its clinical usefulness is currently underway [8, 17, 18].

Differentiation among LGD, HGD, and sSM by the JNET classification may become important because less invasive endoscopic treatment is becoming more widespread internationally. The diagnostic performance of the JNET classification has not been compared internationally, but this is essential to facilitate the adoption of the classification outside Japan. Therefore, we investigated differences of diagnostic accuracy between Japanese endoscopists using the JNET classification and Taiwanese endoscopists using the NICE classification.

Materials and Methods

Patients
A total of 185 lesions, comprising 90 lesions (71 patients) from Nagoya University Hospital and 95 lesions (74 patients) from Chang Gung Memorial Hospital, were examined by BLI with magnification between May 2016 and October 2016, and the histopathological diagnosis was confirmed after endoscopic resection or surgery. Images were selected by doctors who were not involved in this study. The Ethics Committees of Nagoya University Hospital and Chang Gung Memorial Hospital approved this study and it was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000024747).

Endoscopic Examination
Patients ingested 1–2 L of polyethylene glycol solution on the morning of or night before the examination. An EC-L590ZW/M, L or EC-L600ZP magnifying endoscope was used with an LL-4450 processor. Any polyps detected were observed by using BLI magnification before endoscopic resection. Histopathological diagnosis was performed according to World Health Organization criteria [19].

JNET Classification
In the JNET classification, colorectal tumors are classified into 4 categories (Type 1, Type 2A, Type 2B, and Type 3) based on the vessel pattern and surface features. Type 1 includes HP and sessile serrated polyp (SSP), Type 2A is LGD, Type 2B includes HGD and sSM, and Type 3 is dSM (Fig. 1).

Study Participants, Learning, and Testing
The participants were 3 Japanese endoscopists and 3 Taiwanese endoscopists (Group J and Group T, respectively). The Japanese endoscopists had all evaluated colorectal tumors using the JNET classification in more than 1,000 patients. On the other hand, the Taiwanese endoscopists routinely used the NICE classification for non-magnifying endoscopic diagnosis and had little experience with magnifying endoscopy. All participants received a lecture on the JNET classification just before performing the study. Then the region of each lesion with the deepest invasion was presented in one BLI magnifying endoscopic image, and the 6 participants performed diagnosis of all images by using the JNET classification. They also allotted a level of confidence (high or low) for each diagnosis.

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	Type 1	Type 2A	Type 2B	Type 3
Vessel pattern	Not visible[1]	Regular caliber Regular distribution[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 or sessile serrated polyp	Low grade intramucosal neoplasia	High grade intramucosal neoplasia or shallow submucosal invasive carcinoma[3]	Deep submucosal invasive carcinoma
Examples on this study				
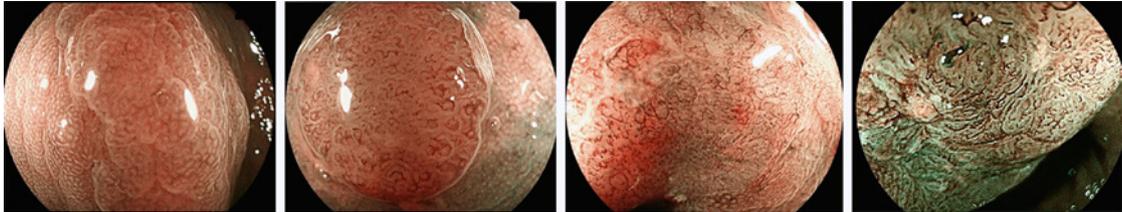
Fig. 1. The JNET classification. [1] If visible, the caliber in the lesion is similar to surrounding normal mucosa. [2] Micro-vessels are often distributed in a punctate pattern and well-ordered reticular or spiral vessels may not be observed in depressed lesions. [3] Deep submucosal invasive cancer may be included. JNET, Japan NBI Expert Team.

Table 1. Clinical characteristics of the 185 colorectal polyps

	Total	Japan	Taiwan	*p* value
Number of polyps	185	90	95	–
Number of patients	145	71	74	–
Polyp size, mm, mean ± SD	11.0±10.9	14.4±12.7	7.7±7.5	<0.05*
Location (right colon/left colon/rectum)	80/68/37	41/33/16	39/35/21	ns
Morphology (protruding/flat)	73/112	47/43	26/69	<0.05**
Histopathologic findings (HP-SSP/LGD/HGD-sSM/dSM)	57/96/23/9	18/48/17/7	39/48/6/2	<0.05**

* Student *t* test.
** Chi-square test.
Right colon, cecum, ascending colon, and transverse colon.
Left colon, descending colon and sigmoid colon.
HP, hyperplastic polyp; SSP, sessile serrated polyp; LGD, low grade dysplasia; HGD, high grade dysplasia; sSM, shallow submucosal invasive carcinoma; dSM, deeply submucosal invasive carcinoma; ns, non significant.

Statistical Analysis

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for each JNET classification type and were compared between the 2 groups. The diagnostic ability of the JNET classification was compared between Group J and Group T by using the χ^2 test and Student *t* test, with $p < 0.05$ being considered to indicate statistical significance. All data were analyzed by using SPSS software (version 24).

Results

A total of 185 lesions (Japan: 90, Taiwan: 95) were assessed (Tables 1, 2), including HP/SSP ($n = 57$), LGD ($n = 96$), HGD and sSM ($n = 23$), and dSM ($n = 9$). Inflammatory polyps, traditional serrated adenomas, and juvenile polyps were excluded because evaluation of these lesions

Table 2. Clinical characteristics of each histopathologic diagnosis

	HP/SSP	LGD	HGD-sSM	dSM
Number of polyps	57	96	23	9
Polyp size, mm, mean ± SD	5.8±4.3	8.0±4.7	26.8±11.5	34.9±15.8
Location (right colon/left colon/rectum)	26/20/11	42/40/14	9/7/7	3/1/5
Morphology (protruding/flat)	9/48	50/46	8/15	6/3

Right colon: cecum, ascending colon, and transverse colon.
Left colon: descending colon and sigmoid colon.
HP, hyperplastic polyp; SSP, sessile serrated polyp; LGD, low grade dysplasia; HGD, high grade dysplasia; sSM, shallow submucosal invasive carcinoma; dSM, deeply submucosal invasive carcinoma.

Table 3. Relationship between the JNET classification and histopathological findings of colorectal lesions

	Number	Histopathological findings			
		HP/SSP	LGD	HGD-sSM	dSM
Group J ALL					
Type 1	178	143	34		1
Type 2A	282	24	225	27	6
Type 2B	79	4	29	38	8
Type 3	16			4	12
Group J HC					
Type 1	157	136	21		
Type 2A	244	15	202	25	2
Type 2B	49	1	12	29	7
Type 3	11			2	9
Group T ALL					
Type 1	173	140	33		
Type 2A	263	25	219	17	2
Type 2B	72	4	33	29	6
Type 3	47	2	3	23	19
Group T HC					
Type 1	150	130	20		
Type 2A	229	13	198	17	1
Type 2B	38	2	13	20	3
Type 3	36		1	19	16

HC, high confidence; SSP, sessile serrated polyp; JNET, Japan NBI Expert Team; HP, hyperplastic polyps; LGD, low grade dysplasia; HGD, high grade dysplasia; sSM, shallow submucosal invasive carcinoma; dSM, deeply submucosal invasive carcinoma.

is difficult using the JNET classification. There were significant differences of size and morphology between the lesions collected in Japan and Taiwan ($p < 0.05$), with the polyps selected in Japan being significantly larger based on the histopathological findings. In addition, SSPs were significantly larger than HPs and SSPs were significantly

more likely to be found in the right colon. Many HPs and SSPs were flat, unlike the LGDs, HGDs, and SM carcinomas.

The endoscopic diagnoses of Groups J and T and the corresponding histological findings are shown in Table 3. The sensitivity, specificity, PPV, and NPV for each JNET classification type are listed in Table 4. The PPV for Type 1 was high in both groups (Group J vs. Group T: 80.3% [75.9–84.0] vs. 80.9% [76.3–84.7], $p = 0.89$), and the PPV for Type 2A was also high in both groups (79.8% [76.2–83.0] vs. 83.3% [79.6–86.7], $p = 0.30$). In contrast, the PPV for Type 2B was low in both groups (48.8% [40.0–56.9] vs. 40.3% [31.1–49.5], $p = 0.30$), even when the confidence level was high (59.2% [47.4–69.7] vs. 52.6% [38.7–68.9], $p = 0.54$). The PPV for Type 3 was higher in Group J than Group T (57.1% [38.7–73.3] vs. 40.4% [30.6–47.9], $p = 0.20$), and the PPV for Type 3 with a high confidence level was significantly higher in Group J than Group T (81.8% [55.4–94.6] vs. 44.4% [33.6–50.9], $p < 0.05$).

Lesions misdiagnosed as Type 3 are shown in Table 5. Some cases of HP and LGD were misdiagnosed as Type 3, although no significant difference was noted.

Discussion/Conclusion

Development of ESD for colorectal tumors has allowed the en bloc resection of large lesions that were difficult to manage in the past [20]. The risk of local recurrence is low after complete en bloc resection by ESD. To promote less invasive management, lesions as adenoma and carcinoma with a low risk of lymph node metastasis should be treated endoscopically. Since the risk of lymph node metastasis is low for HGD and sSM, these lesions are appropriate for endoscopic treatment [9–11]. The method of endoscopic treatment is decided from the tumor morphology, tumor size [20, 21], and other endoscopic features including the IEE findings and pit pattern [8, 22]. Especially for carcinoma, careful evaluation of the depth of invasion is necessary to decide whether treatment should involve endoscopic en bloc resection or surgery. For accurate diagnosis before treatment, pit pattern diagnosis is considered to be the most reliable method [8, 22–24], but time-consuming preparation and spraying of an indigocarmine or crystal violet is required. There are also other disadvantages, such as interference with resection of the lesion and staining of the surrounding region by the dye. In contrast, IEE magnifying endoscopy can be performed

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Table 4. Performance for each JNET classification type

	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Group J ALL				
Type 1	83.7 (79.0–87.4)	90.9 (88.8–92.6)	80.3 (75.9–84.0)	92.6 (90.5–94.0)
Type 2A	78.1 (74.6–81.6)	78.7 (74.9–82.0)	79.8 (76.2–83.0)	76.9 (73.3–80.2)
Type 2B	55.1 (45.2–64.3)	91.8 (90.4–93.1)	48.8 (40.0–56.9)	93.5 (92.1–94.8)
Type 3	44.4 (30.1–57.0)	98.3 (97.6–98.9)	57.1 (38.7–73.3)	97.2 (96.5–97.8)
Group J HC				
Type 1	89.5 (85.2–92.7)	93.2 (91.1–94.8)	86.6 (82.5–89.7)	94.7 (92.6–96.3)
Type 2A	86.0 (82.4–89.0)	81.4 (77.7–84.5)	82.8 (79.4–85.7)	84.8 (80.9–88.0)
Type 2B	51.8 (41.5–61.0)	95.1 (93.6–96.3)	59.2 (47.4–69.7)	93.4 (92.0–94.7)
Type 3	50.0 (33.8–57.8)	99.5 (98.9–99.9)	81.8 (55.4–94.6)	98.0 (97.4–98.3)
Group T ALL				
Type 1	81.9 (77.2–85.7)	91.4 (89.3–93.1)	80.9 (76.3–84.7)	91.9 (89.8–93.6)
Type 2A	76.0 (72.7–79.0)	83.5 (79.9–86.7)	83.3 (79.6–86.7)	76.4 (73.0–79.3)
Type 2B	42.0 (32.5–51.6)	91.2 (89.8–92.5)	40.3 (31.1–49.5)	91.7 (90.4–93.1)
Type 3	70.4 (53.3–83.4)	94.7 (93.8–95.4)	40.4 (30.6–47.9)	98.4 (97.5–99.1)
Group T HC				
Type 1	92.4 (88.5–95.2)	94.8 (92.9–96.1)	89.3 (85.5–92.0)	96.4 (94.5–97.7)
Type 2A	85.3 (81.9–88.2)	86.0 (82.4–89.0)	86.5 (83.0–89.4)	84.8 (81.3–87.8)
Type 2B	35.7 (26.3–44.7)	95.5 (94.1–96.7)	52.6 (38.7–65.9)	91.3 (90.1–92.5)
Type 3	80.0 (60.5–91.6)	95.4 (94.5–95.9)	44.4 (33.6–50.9)	99.0 (98.1–99.6)

PPV, positive predictive value; NPV, negative predictive value; HC, high confidence; JNET, Japan NBI Expert Team.

Table 5. Characteristics of lesions misdiagnosed as Type 3

	Group J	Group T	*p* value
Number of misdiagnoses	4	28	–
Total number of polyps misdiagnosed	3	17	–
Polyp size, mm, mean ± SD	31.7±23.4	23.4±12.0	ns*
Location (right colon/left colon/rectum)	1/0/2	7/6/4	ns*
Morphology (protruding/flat)	0/3	4/13	ns**
Histopathologic findings (HP/SSP/Ad/M-sSM)	0/0/0/3	1/1/2/13	ns**

* Student *t* test.
** Chi-square test.
Right colon, cecum, ascending colon, and transverse colon.
Left colon, descending colon and sigmoid colon.
HP, hyperplastic polyp; SSP, sessile serrated polyp; LGD, low grade dysplasia; HGD, high grade dysplasia; sSM, shallow submucosal invasive carcinoma; dSM, deeply submucosal invasive carcinoma; ns, non significant.

much more easily and also has the advantage of not affecting resection.

In this study, the PPV for Type 3 was different between Group J and Group T, especially for diagnosis with high confidence. The low PPV for Type 3 indicates that HGD and sSM not requiring surgery were overdiagnosed as dSM. This may have been due to difficulty in judging small irregular blood vessels and surface structures without magnifying endoscopy (Fig. 2). Since endoscopists who use the NICE classification do not typically focus on the thickness and distribution of small vessels, they need to gain experience in diagnosing Type 2B.
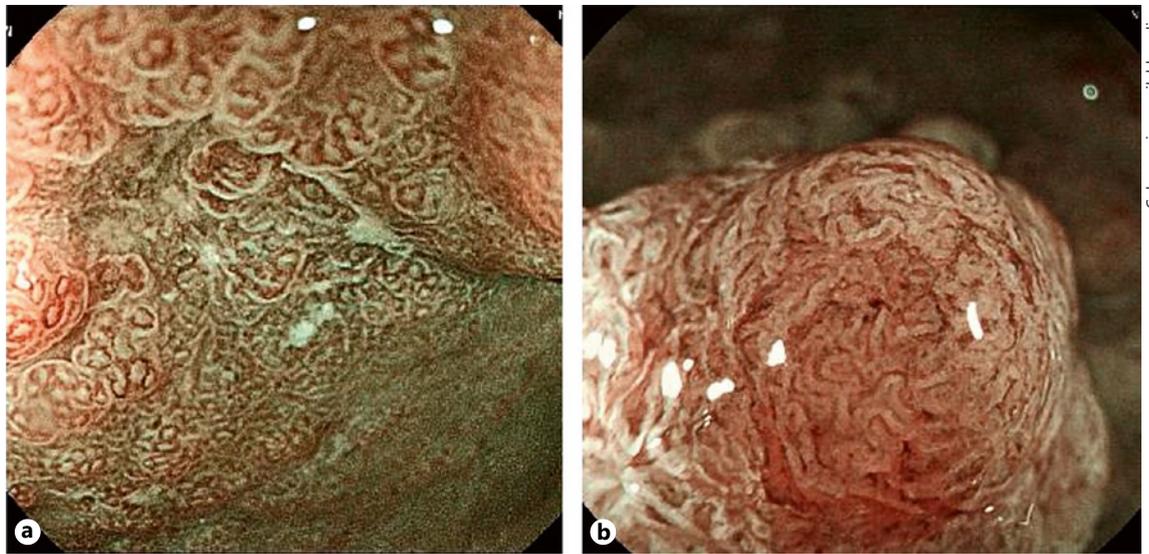
Fig. 2. Lesions misdiagnosed as Type 3. **a** HGD, 0–IIa, 25 mm. The "vessel pattern" was irregular without loose vessel areas and thick vessels, and the "surface pattern" was obscure without amorphous areas in the depression. The JNET classification diagnosis was "Type 2B". **b** HGD, 0–IIa + Is, 35 mm. The "vessel pattern" was variable in caliber without loose vessel areas or disrupted thick vessels, and the "Surface pattern" was irregular without amorphous areas at the nodular part. The JNET classification diagnosis was "Type 2B".

Next, the sensitivity (55.1% [45.2–64.3] vs. 42.0% [32.5–51.6], $p = 0.13$) and PPV (48.8% [40.0–56.9] vs. 40.3% [31.1–49.5], $p = 0.30$) were low for Type 2B in both groups, even when the confidence level was high. The reason for this outcome may be that Type 2B lesions include LGD, HGD, sSM, and dSM in the JNET classification. Accordingly, it is recommended to additionally perform pit pattern diagnosis of Type 2B lesions [8, 17]. It has also been suggested that Type 2B could be divided into 2B-low and 2B-high based on vascular irregularity and the surface pattern [17].

The NPV for Type 1 was high in both groups, indicating that HP/SSP and other lesions can be differentiated with high accuracy. The NPV was also high in Group T, possibly because the characteristics of NICE Type 1 and JNET Type 1 are similar. However, it is problematic that both HP and SSP are classified as Type 1 in the JNET classification. SSP is associated with a risk of carcinogenesis, unlike HP [25, 26], for which endoscopic treatment is definitely indicated. Therefore, differentiation between HP and SSP is necessary. In the present study, SSPs were more likely to be located in the right colon and tended to be larger than HPs. Even if a lesion is diagnosed as Type 1, it is possibly an SSP when it is located in the right colon and is large, suggesting that assessment of surgical resection may be necessary. The characteristic

magnifying endoscopy findings of SSP are still being investigated [27–29]. Establishment of a method for differentiating between HP and SSP by combining these findings with the JNET classification may be important in the future.

There were several limitations of this study; since it was retrospective, there was bias in the selection of images, and diagnosis was based on only one magnifying endoscopic image. In addition, large lesions were diagnosed from partial images, the number of cases was small, optical diagnosis was not done, the number of adenoma cases (which cause low diagnostic ability) was small compared with other studies, and intra-observer agreement was not evaluated.

In conclusion, diagnostic performance for Type 1 and Type 2A was high in both groups and that for Type 2B was also comparable. However, the PPV for Type 3 differed between the 2 groups, suggesting the necessity for familiarization with the irregular vessels and surface pattern of Type 2B, which are impossible to detect without magnifying endoscopy.

Statement of Ethics

The Ethics Committees of Nagoya University Hospital and Chang Gung Memorial Hospital approved this study. This study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000024747).

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

Funding Sources

There was no funding received for this study.

Author Contribution

All authors approved of the final version of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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