

# Histopathological Compatibility of Narrow-Band Imaging International Colorectal Endoscopic Classification for Endoscopic Submucosal Dissection in Colorectal Lesions: A Single-Center Experience

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## Abstract

**Objective:** There are limited data on the applicability of the narrow-band imaging (NBI) International Colorectal Endoscopic (NICE) classification for colorectal lesions larger than 10 mm. The purpose of the present study was to evaluate the correlation between the NICE classification and histopathology of colorectal lesions larger than 10 mm resected using endoscopic submucosal dissection (ESD).

**Methods:** The present single-center retrospective study screened patients who underwent ESD between August 2019 and December 2020. The study included colorectal lesions that were larger than 10 mm and considered as NICE type 2 or type 3 in NBI examination. The correlation between the NICE classification and histopathology was the primary endpoint.

**Results:** In total, 64 colorectal lesions were included. There were 54 lesions in the NICE type 2 group and 10 lesions in the NICE type 3 group. The en bloc resection rate with ESD was 100%, and the R0 resection rate was 96%. Submucosal fibrosis was more common in the NICE type 3 group. The procedure durations were similar in both groups. Histopathological correlation was better in the NICE type 2 group. The submucosal invasion rate was higher in the NICE type 3 group ( $P < .05$ ).

**Conclusion:** The NICE classification may be insufficient for diagnosis of deep submucosal invasive colorectal lesions larger than 10 mm. Diagnostic ESD can be safely applied in some colorectal lesions considered as NICE type 3.

**Keywords:** Endoscopic submucosal dissection, histopathology, narrow-band imaging international colorectal endoscopic classification

## INTRODUCTION

Colorectal cancer (CRC) is an important health issue worldwide. CRC is the third most common cancer in men and the second in women.<sup>1</sup>

Endoscopic resection (ER) is now a widely accepted treatment for early-stage (intramucosal carcinoma [Tis] and some T1 tumors) CRC.<sup>2-4</sup> Because lymph node dissection may not be performed during ER, this treatment is recommended only for lesions without lymph node risk.<sup>2,3,5,6</sup> In CRC, the depth of submucosal invasion (SMI) is the most important predictive factor in determining lymph node risk before treatment. Therefore, it is mandatory to determine the depth of SMI for optimal treatment in patients undergoing ER.<sup>3,7,8</sup> As there is no risk of lymphovascular invasion (LVI) in Tis, ER can be safely performed.<sup>3,7</sup> For T1 CRC, the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines recommend ER for superficial SMI (SMs) if the SMI depth is less than 1000 µm in the pathological examination. However, these guidelines recommend surgical treatment for deep SMI (SMd) owing to the risk of lymph node metastasis, which can be up to 10%.<sup>3</sup> Endoscopic submucosal dissection (ESD) is the primarily recommended ER method because it ensures en bloc resection and accurate histopathological examination of colorectal lesions larger than 2 cm or with suspected SMI.<sup>3,9</sup>

In CRC, the depth of SMI can be determined using image-enhanced endoscopy, magnifying endoscopy, and/or endoscopic ultrasonography (EUS).<sup>2,10</sup> Among the image-enhanced endoscopy methods, the most widely used is narrow-band imaging (NBI).<sup>10</sup> Most of the classifications in which colorectal lesions are evaluated by NBI (Sano, Hiroshima, Showa, Japan NBI Expert Team classification [JNET]) include magnification. However, as the use of magnified endoscopes is limited in Western countries, the use of these classifications has been very limited.<sup>11</sup> The NBI International Colorectal Endoscopic (NICE) classification was developed by an international group in 2009.<sup>12</sup> This classification evaluates lesions without magnification. According to the NICE classification, lesions are divided into three groups according to color, surface pattern, and vascular pattern. Type 1 corresponds to the most likely pathology being non-adenomatous, type 2 being adenoma, and type 3 being SMd. For type 2, the diagnostic range is quite wide, ranging from low-grade dysplasia to SMs (Table 1).<sup>13</sup> With this classification, the in vivo optical diagnosis of diminutive polyps has facilitated the distinction between neoplastic and non-neoplastic lesions.<sup>14</sup> However, data on the applicability of NICE in colorectal lesions larger than 10 mm and its use in distinguishing SMd lesions are quite limited.<sup>13,15</sup>

This study aimed to evaluate the correlation between the NICE classification and histopathology of NICE type 2 or 3, polyps larger than 10 mm, and lateral spreading tumors (LSTs) in which ESD was performed.

METHODS

Endoscopic submucosal dissection was performed in 90 colorectal lesions from 90 patients at Trabzon Kanuni Training and Research Hospital between September 2019 and December 2020. Among these, 64 colorectal lesions of 64 patients larger than 10 mm and considered as NICE type 2 or 3 were included in the study (Figure 1). Patients in whom the NICE classification data were available but no NBI image was available (at least 5) and patients with a history of biopsy and/or ER were excluded from the study. The present single-center retrospective study was approved by the local ethics committee (Trabzon Kanuni Training and Research Hospital Date: March 15, 2021, decision number:2021/42). Informed consent was obtained from all patients.

Colonoscopy Procedure

All patients ingested a split-dose bowel preparation of sodium picosulphate/magnesium for bowel preparation. All procedures were performed using Olympus equipment (Olympus Exera processors and 180-190 series endoscopes, Olympus Medical Systems Corp Tokyo, Japan). Carbon dioxide insufflation was used for all procedures.

Morphology

All lesions were classified according to the Paris morphological classification.<sup>16</sup> Nonpolypoid lesions were also classified according to the LST classification.<sup>17</sup> The size and location of the lesion in the colon and rectum were noted. The right side of the colon was defined as proximal

to the splenic flexure. The left side of the colon was defined as descending colon to the sigmoid colon.

NICE Diagnosis

All lesions were initially detected using conventional viewing methods and were then examined using NBI without magnification to evaluate endoscopic surface features (Table 1) (Figures 2 and 3). The endoscopist in the study was trained and evaluated alongside an experienced endoscopist (O.O.) who has extensive experience in chromoendoscopy with NBI (> 100 cases) for polyp characterization with NBI and the use of NICE classification using a previously validated NBI training

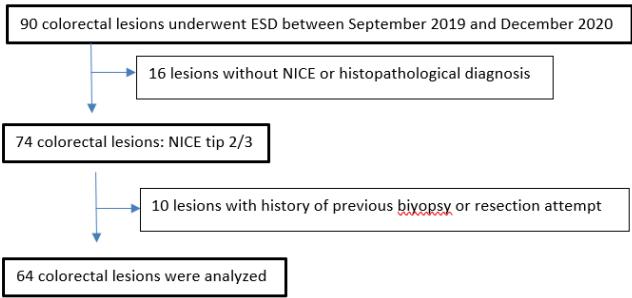


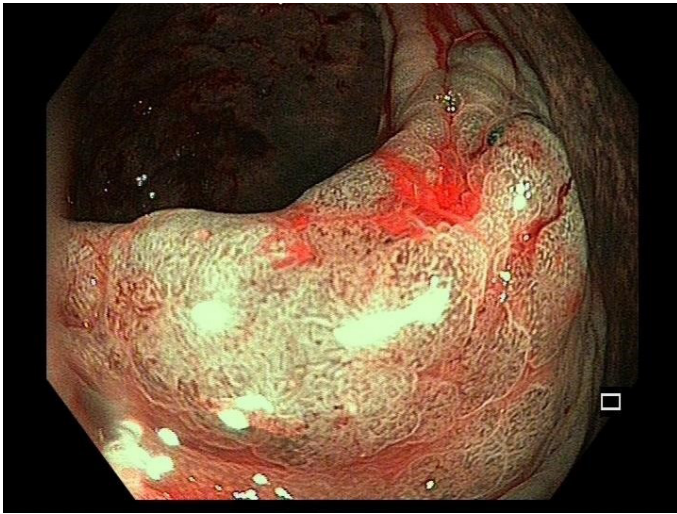
Figure 1. Study flow chart



Figure 2. Flat-type lesion (Paris Is+IIa), 15x12 mm in size. Endoscopic findings using narrow-band imaging. Lesion classified as NICE type 2

Table 1. Narrow-band imaging (NBI) International Colorectal Endoscopic (NICE) classification<sup>13</sup>

	Type 1	Type 2	Type 3
Color	Same or lighter than background	Browner relative to background (verify that color arises from vessels)	Brown to dark brown relative to background, sometimes patchy whiter areas
Vessels	None or isolated lacy vessels coursing across the lesion	Brown vessels surrounding white structures	Has area(s) with markedly distorted or missing vessels
Surface pattern	Dark or white spots of uniform size or homogeneous absence of pattern	Oval, tubular, or branched white structures surrounded by brown vessels	Areas with distortion or absence of pattern
Most likely pathology	Hyperplastic	Adenoma	Deep submucosally invasive cancer



**Figure 3.** Laterally spreading tumor, nongranular-pseudodepressed type lesion (Paris IIa + IIc), 27×20 mm in size. Endoscopic findings using narrow-band imaging. Lesion classified as NICE type 3

module. The endoscopist (A.M.B.) made a prediction with high confidence when he was 90% certain of the diagnosis. Lesions whose NICE diagnosis was confirmed after NBI images were reviewed by an experienced endoscopist (O.O.) and included in the study. For diagnoses made with high confidence, there had to be correlation between both the endoscopists' diagnoses (A.M.B and O.O.).

### ESD Procedure

All procedures were performed by a single endoscopist (A.M.B.) who was experienced in performing colorectal ESDs. ESD was performed using a dual knife or a dual knife J with a length of 1.5 mm (Olympus Medical Systems, Tokyo, Japan) powered by a high-frequency electrosurgical unit (VIO 200D, ERBE Elektromedizin, Tübingen, Germany).

The indications for ESD in NICE type 2 groups were evaluated based on the Japan Gastroenterological Endoscopy Society guidelines.<sup>18</sup> NICE type 2 lesions in which ESD was performed met at least one of the listed criteria: (i) nonlifting sign positive, (ii) lesion size >20 mm, (iii) flat morphology wherein en bloc resection with snare endoscopic mucosal resection (EMR) is difficult to perform, and (iiii) pseudodepressed (PD) appearance. Computed tomography (CT) or magnetic resonance imaging (MRI) without biopsy was indicated in all lesions evaluated as NICE type 3. Locoregional staging was performed with CT for lesions in the colon and MRI for lesions in the rectum. Surgery was recommended for patients with pathological lymphadenopathy (LAP) or suspected distant metastasis. Even if T2 was suspected, a repeat colonoscopy was planned for ESD in lesions without pathological LAP and distant metastasis within 2 weeks.

Submucosal fibrosis was divided into three groups based on the structure of the submucosal layer<sup>19</sup>: F0 = no fibrosis, F1 = mild fibrosis (appears as a blue transparent submucosal layer), and F2 = severe fibrosis (submucosal layer appears as a white muscle layer).

Dissection speed (mm<sup>2</sup>/min) was defined as the calculated ratio of the resected specimen area (mm<sup>2</sup>) divided by the procedure time (min).<sup>20</sup> The resected specimen area was calculated using the formula for ellipse area (mm<sup>2</sup>) = [longest length (mm) / 2] × [shortest length (mm) / 2] × 3.14.

### Histopathological Analysis

All lesions were stored in formaldehyde and underwent histopathological assessment by a pathologist. Histopathological analysis was performed by an expert gastrointestinal pathologist blinded to the NICE grouping. Histological findings were reported according to the Vienna classification of gastrointestinal neoplasia.<sup>21</sup> According to the JSCCR guidelines 2019, the pathological diagnosis was SMs when the depth of SMI was <1000 µm and SMd when the depth of SMI was >1000 µm. Curative resection was indicated in cases of intramucosal or SMs with negative vertical and lateral margins and without LVI.<sup>3</sup> Additional surgery was recommended when these criteria were not met.

### NICE–Histopathology Correlation

ESD procedure reports were analyzed by an independent clinician (A.A.), and the histopathology of the lesions classified as NICE type 2 or 3 was examined. The correlation between the NICE classification and histopathology was examined.

### Measured Outcomes

The primary endpoint was the correlation between NICE classification and histopathology. Secondary endpoint was the correlation between ESD and R0 resection rate, submucosal fibrosis rate, procedure duration, procedure complication rate, and hospital stay duration in NICE type 2 and 3 groups.

### Statistical Analysis

Statistical Package for Social Sciences version 22 (IBM SPSS Corp., Chicago, IL, USA) software was used for statistical calculations. Shapiro–Wilk test was used to test the normality of the data. Fisher's exact, chi-square, and Mann–Whitney *U* tests were used for categorical and continuous variables where appropriate. Furthermore, *P* value < .05 was considered statistically significant in all analyses.

### RESULTS

In total, 74 colorectal lesions (>10 mm and NICE type 2 or 3) were detected in 74 patients. Six patients with biopsy history and four patients with EMR were excluded from the study (Figure 1). Accordingly, 54 of the 64 lesions included in the study were considered as NICE type 2 and 10 as NICE type 3 (Table 2). The median age of the patients was 66 (range 46–96) years, wherein the patients with NICE type 3 lesions were older than those with NICE type 2 lesions (71 vs. 64, respectively, *P* = .02). In addition, 45 (70.3%) patients were male (Table 3).

Median lesion size was 25 (10–80) mm. The most common localization was left colon (43.7%). Furthermore, most lesions (56.2%) were non-polypoid (Table 2). The number of LST-granular (LST-G) lesions was much higher than that of LST-nongranular (LST-NG) lesions (LST-G/LST-NG = 27/9). While en bloc resection was achieved in all (100%) lesions, the R0 resection rate was 96%. Median procedure duration was 20 (5–300) minutes. Procedure duration and ESD dissection speed were similar in both groups. Submucosal fibrosis (F1/F2) was more common in the NICE type 3 group than in the NICE type 2 group (90% vs. 27%, respectively, *P* = .002). The rates of ESD-related perforation, delayed bleeding, and post-ESD electrocoagulation syndrome (PECS) were 3%, 1.5%, and 7.8%, respectively, with no difference between the two groups (*P* = .17, *P* = .66, and *P* = .32, respectively). In addition, the hospital stay duration was similar in both groups (Table 3).

In the NICE type 2 group, 52 of 54 lesions were considered as adenomatous polyps/LSTs, and 2 were sessile serrated adenomas. SMI was observed in three patients in the NICE type 2 group. All patients with



**Table 2. Preprocedural demographic data**

Parameters	N = 64
Age (years)	66 (46–96)
Gender (n)	
Male	45
Female	19
Tumor locations (n)	
Right colon	23
Left colon	28
Rectum	13
Tumor size (mm)	25 (10–80)
Characteristics of the lesion (n)	
Polypoid / Nonpolypoid	28/36
Granular / Nongranular	27/9
Depressed / Nondepressed	4/60
Adenomatous/ Non- adenomatous	62/2
Macroscopic view of tumor	
1p	9
1s	14
1s + 2a	11
1sp	5
2a	17
2a + 1s	3
2a + 2b	1
2a + 2c	4
NICE classification	
Type 2	54
Type 3	10
Pathology	
Low-grade neoplasm	28
High-grade dysplasia	13
Carcinoma in situ	8
Suspicious invasive carcinoma	1
Intramucosal carcinoma	4
Submucosal invasive carcinoma	8

NICE, Narrow-band imaging International Colorectal Endoscopic classification

SMI were considered as having SMs. In the NICE type 3 group, 5 of 10 lesions were considered as adenocarcinomas, 3 as high-grade dysplasia, 1 as carcinoma in situ, and 1 as intramucosal carcinoma. In the NICE type 3 group, 4 of 5 patients with SMI were considered as having SMs, and one was considered as having SMd. LVI was also observed in one of the SMs lesions in the NICE type 3 group. As a result, the SMI rate was significantly higher in the NICE type 3 group than that in the NICE type 2 group (50% vs. 5.6%, respectively,  $P < .05$ ). Surgical resection was recommended for two (25%) patients with SMI (patients with SMd and SMs + LVI positive) after ESD (Table 4). However, because the patients and their relatives did not approve of surgery, the patients were closely followed up. No recurrence was observed in the 1st year follow-up of both patients. In most of the lesions in the NICE type 2 group (96%), histopathology was compatible with the NICE classification. However, in the NICE type 3 group, the compatibility between histopathology and the NICE classification was low (10%). Owing to the insufficient number of patients, sensitivity and specificity analysis could not be performed. The SMI rate was higher for LST-NG lesions compared with that for LST-G lesions, albeit not significant (33% vs. 11%, respectively,  $P = .15$ ).

## DISCUSSION

The present single-center retrospective study revealed that the NICE classification is insufficient for predicting SMd in colorectal lesions

**Table 3. Comparison of the results of NICE type 2 and type 3 colorectal lesions**

Parameters	NICE type 2		NICE type 3		P
	N = 54	%	N = 10	%	
Age (years)	64 (46–96)		71 (64–78)		.02
Gender					
Male	38	70.4	7	70.0	.98
Female	16	29.6	3	30.0	
Tumor size (mm)	25 (10–70)		19 (10–80)		.38
Tumor localizations (n)					
Right colon	22	34.4	1	10.0	
Left colon	22	34.4	6	60.0	.18
Rectum	10	31.2	3	30.0	
Procedure duration (min)	25 (5–150)		21 (12–400)		.86
Dissection speed (mm <sup>2</sup> / min)	27.3 (8.8–67.6)		20.9 (7.7–36.3)		.06
Delayed hemorrhage					
Yes	1	1.9	0	0	
No	53	98.1	10	100.	.66
Perforation					
Yes	1	1.9	1	10.0	.17
No	53	98.1	9	90.0	
PECS					
Yes	5	9.3	0	0	.32
No	49	90.7	10	100.0	
Submucosal invasion					
Yes	3	5.6	5	50.0	< .001
No	51	94.4	5	50.0	
Deep submucosal invasion					
Yes	0	0	1	10.0	.02
No	54	100.0	9	90.0	
Lymphovascular invasion					
Yes	0	0	1	10.0	.02
No	54	100.0	9	90.0	
Fibrosis score					
0	34	63.0	1	10.0	
1	12	22.2	3	30.0	.002
2	8	14.8	6	60.0	
R0 resection					
Yes	52	96.3	9	90.0	.39
No	2	3.7	1	10.0	
Length of stay in hospital (day)	0 (0–3)		0 (0–1)		.64

NICE, Narrow-band imaging International Colorectal Endoscopic classification; PECS, Post-ESD electrocoagulation syndrome

larger than 10 mm. While diminutive polyps were evaluated in most of the studies on the NICE classification, the number of studies on polyps or LSTs >10 mm or even >20 mm is rather limited.<sup>13,15,22</sup> The present study is important as it demonstrates that the NICE classification cannot be used for predicting SMd in large polyps or LSTs because of all lesions being >10 mm or even 59% of the lesions being >20 mm.

The NICE classification is widely used in Western countries as it does not require magnification.<sup>10,14,15,22,23</sup> However, the NICE classification has four disadvantages: first, the lack of differentiation between serrated and hyperplastic polyps in the NICE type 1 classification.<sup>24</sup> The present study did not include the NICE type 1 lesions. Therefore, the use of the NICE classification for serrated lesions could not be evaluated. Second, findings of adenoma overlap with those of hyperplastic polyps and serrated polyps during NBI evaluation.<sup>24</sup> However, the overlap rate was very low in the present study. Only two LSTs, whose histopathology was con-

**Table 4. Demographic, endoscopic and histopathological data of colorectal lesions with submucosal invasion**

Patient	Age	Gender	Localization	Size (mm)	Paris classification	NICE	LST type	SMI	LVI
1	77	M	Sigmoid colon	12×10	2a	Type 3	LST-NG-FE	SMs	+
2	71	M	Sigmoid colon	18×15	1s	Type 3		SMs	–
3	59	M	Ascending colon	30×25	1s+2a	Type 2	LST-G-NM	SMs	–
4	76	F	Sigmoid colon	34×30	2a	Type 2	LST-G-H	SMs	–
5	68	F	Sigmoid colon	27×30	2a+1s	Type 3	LST-G-M	SMs	–
6	68	F	Sigmoid colon	27×20	2a+2c	Type 3	LST-NG-PD	SMs	–
7	65	F	Caecum	35×25	2a+2c	Type 2	LST-NG-PD	SMs	–
8	78	F	Sigmoid colon	30×22	1s	Type 3		SMd	–

NICE, Narrow-band imaging International Colorectal Endoscopic classification; SMI, Submucosal invasion; SMd, Submucosal deep invasive cancer; SMs, Submucosal shallow invasive cancer; LVI, Lymphovascular invasion; LST-G, Laterally spreading tumor, granular; LST-G-H, Laterally spreading tumor, granular-homogenous; LST-G-NM, Laterally spreading tumor, granular-nodular mixed; LST-NG, Laterally spreading tumor, nongranular; LST-NG-FE, Laterally spreading tumor, nongranular-flat elevated; LST-NG-PD, Laterally spreading tumor, nongranular-pseudodepressed.

sidered as sessile serrated adenoma, were included in the NICE type 2 group. Third, the diagnostic range of the NICE type 2 classification is very wide, which causes confusion in terms of treatment.<sup>6,13</sup> Endoscopic treatment methods recommended for low-grade adenomas and colorectal lesions with suspected SMI are different.<sup>13,18</sup> Therefore, the NICE classification is insufficient in this regard. The JNET classification has been developed to facilitate the distinction between SMs and noninvasive adenomatous lesions.<sup>6</sup> However, as the JNET classification requires magnification, its use in Western countries is extremely limited. Fourth, the NICE classification has low sensitivity (55%–83%) in recognizing SMd lesions.<sup>13–15</sup> In the present study, SMd was observed in only 1 (10%) of the 10 lesions in the NICE type 3 group. Therefore, based on our results of the limited number of patients, NICE classification may be insufficient to predict SMd.

In the treatment algorithm for the NICE classification, the recommended treatment for NICE type 2 lesions is ER, whereas that for NICE type 3 lesions is surgery.<sup>13</sup> As it is known that the NICE classification is insufficient in terms of diagnosing SMd, cross-sectional imaging is performed before treatment in colorectal lesions that are considered as NICE type 3 in our daily practice. Although EUS is the best imaging method for T staging of rectal tumors, the diagnostic accuracy rate has significantly increased recently, owing to the developments in MRI.<sup>25</sup> However, although the results of previous studies indicate that CT is inadequate for evaluating local T stage and moderately adequate for evaluating N stage, we consider that CT is particularly helpful in excluding distant metastases, such as pathological LAP and liver metastases.<sup>26</sup> In the present study, T2 invasion was suspected in only one patient after locoregional staging in the NICE type 3 group. However, because surgery was not suitable in the patient and there were signs of bleeding, resection with ESD was attempted. In the histopathological analysis of diagnostic ESD, SMs and LVI were observed. Although endoscopic cure could not be achieved in this patient, curative resection was achieved in 80% of the patients in the NICE type 3 group. Therefore, the present study is very important because it demonstrates that in the absence of any contraindication in cross-sectional imaging (such as pathological LAP or distant metastasis), diagnostic ESD in NICE type 3 lesions can save patients from unnecessary surgery.

ESD is an ER method primarily recommended by the guidelines, facilitating en bloc resection according to EMR, thereby allowing accurate histopathological evaluation, especially in flat colorectal lesions smaller than 20 mm.<sup>2,4,11</sup> In addition, ESD is recommended for colorectal lesions with suspected SMI regardless of their size.<sup>3</sup> In a prospective multicenter study by Puig et al.<sup>15</sup> that evaluated the role of the NICE classification in colorectal polyps larger than 10 mm, piecemeal EMR

rate was 21%, whereas the ESD rate was 1.3%. In the present study, the en bloc resection rate with ESD was 100%, and R0 resection rate was 96%. Therefore, we consider that the present study may reflect the histopathological correlation with the NICE classification more accurately, considering the failure to perform accurate histopathological evaluation after piecemeal EMR and recurrence rates of up to 40%.<sup>27</sup>

The dissection was found to be faster in the NICE type 2 group in the present study, albeit not significantly. The lower rate of submucosal invasion and fibrosis in the NICE type 2 group is considered to have an impact on this.

Although LSTs were not statistically significant when evaluated alone, the SMI rate was higher for LST-NG lesions compared with that for LST-G lesions. When the subgroups were examined, the LST-NG-PD group had the highest SMI rate, which was consistent with the existing literature.<sup>17,28</sup>

Most studies on the NICE classification have been performed by academic institutions.<sup>14,15,22,29</sup> In contrast, the present study was conducted in a community hospital. Therefore, the NICE classification is considered to reflect actual clinical data.

The present study has some limitations. First, it was a single-center, retrospective study. This prevents generalization of the findings. Second, the training module and prestudy test prepared with only selected photos may be insufficient for training, and the endoscopists' knowledge on NBI can be questioned. The endoscopist (A.M.B.) has received training for NBI and NICE classification at experienced centers. In addition, the diagnosis of NICE in the lesions included in the study was also confirmed by an experienced endoscopist (O.O.), and only the lesions with high confidence in the diagnosis of NICE by two endoscopists were included in the study. Moreover, the NICE classification is extremely easy to understand, and the study by Hewett et al. demonstrated that even medical school students who are not educated about polyps or NBI can correctly classify diminutive polyps with an accuracy rate of 87% only through sample images.<sup>30</sup> Third, the number of NICE type 3 samples was limited. However, the limited number of NICE type 3 samples was expected because we included only lesions resected by ESD. Considering this, multicenter studies are warranted in the future. Finally, the present study did not include the lesions considered as NICE type 3 that had distant metastases on systemic screening, which can create bias in the results.

In conclusion, the NICE classification may be insufficient for diagnosing SMd. Diagnostic ESD can be performed in some patients with

NICE type 3 lesions. In such patients, after determining the depth of invasion in the pathological evaluation after ESD, a decision should be made in terms of follow-up or advanced treatment by discussing with the patient.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Trabzon Kanuni Training and Research Hospital (Date: March 15, 2021, Decision No: 2021/42).

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

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