Magnifying narrow-band imaging of surface patterns for diagnosing colorectal cancer

MASASHI MISAWA[1], SHIN-EI KUDO[1], YOSHIKI WADA[1], HIROKI NAKAMURA[1],
NAOYA TOYOSHIMA[1], SEIKO HAYASHI[1], YUICHI MORI[1], TOYOKI KUDO[1],
TAKEMASA HAYASHI[1], KUNIHIKO WAKAMURA[1], HIDEYUKI MIYACHI[1],
FUYUHIKO YAMAMURA[1] and SHIGEHARU HAMATANI[2]

[1]Digestive Disease Center, and [2]Department of Pathology, Showa University,
Northern Yokohama Hospital, Tsuzuki, Yokohama 224-8503, Japan

Abstract. Narrow-band imaging (NBI) of surface microvessels of colorectal lesions is useful for differentiating neoplasms from non-neoplasms and for predicting histopathological diagnosis. Furthermore, NBI of surface microstructure, or 'surface pattern', is valuable for predicting histopathology in colorectal cancer. The aim of the present study was to investigate whether surface patterns could be used to predict invasion depth in colorectal cancer, and to compare the accuracy of surface pattern diagnosis in each macroscopic type. Between January 2010 and March 2011, a series of 357 consecutive patients with 378 early colorectal cancers were observed by magnifying NBI and the surface pattern was prospectively evaluated. Surface pattern was classified into 3 types: type I, microstructure was clearly recognised with uniform arrangement and form; type II, microstructure was obscured with heterogeneous arrangement and form; and type III, microstructure was invisible. We also classified the macroscopic type into 3 categories: depressed, protruded and flat elevated. Assuming that type III was an index of massively invasive lesions in the submucosal layer (SMm), the sensitivity, specificity and accuracy were 56.9, 91.7 and 85.7%, respectively. The sensitivity, specificity and accuracy of type III for the diagnosis of SMm in each macroscopic type were: depressed, 88.9, 40.0 and 63.2%, respectively; protruded: 34.8, 96.4 and 90.0%, respectively; and flat elevated, 54.2, 92.7 and 85.0%, respectively. These results suggest that the diagnostic accuracy of surface pattern was insufficient and particularly poor for depressed-type lesions.

Introduction

Narrow-band imaging (NBI) of surface microvessels of colorectal lesions is useful for differentiating neoplasms from non-neoplasms and for predicting histopathological diagnosis (1-8). We have reported that analysis of vascular patterns by magnifying NBI is useful for characterization of colorectal lesions (9-11). Currently, pit pattern diagnosis by magnifying chromoendoscopy is the gold standard for differentiating neoplasms from non-neoplasms and for estimating invasive depth of colorectal cancer. Type V_N (non-structure) pit pattern is an index of massively invasive lesions in the submucosal layer (12-14). More recently, it was reported that evaluation of the microstructure and microvessels of the superficial layer, which can be recognised using NBI, was useful for diagnosing invasion depth of colorectal tumours (15,16). In Japan, surface microstructure observation by magnifying NBI is called 'surface pattern' (17-20). Some reports have highlighted differences between pit structure observed by chromoendoscopy and surface pattern observed by magnifying NBI (2,20-22). In terms of macroscopic type, when we divided the morphology of superficial colorectal lesions into protruded, flat elevated and depressed, there were differences between typical pit patterns of depressed lesions and the others (13,23,24). We hypothesised that the surface pattern could be different between these macroscopic morphologies but there are very few reports on this in the literature. The wavelength range used in NBI does not permit visualization of severely irregular pit structure but it does emphasise haemoglobin-containing microvessels of the surface mucosa. These vessels appear brown, while the surface structure appears as a white zone because of the lack of microvessels in the marginal crypt epithelium. Therefore, we believe that the visibility of the surface pattern observed using magnifying NBI can be useful for diagnosis of invasion depth.

The aim of the present study was to investigate if surface pattern could be used to predict invasion depth in colorectal cancer, and compare the accuracy of surface pattern diagnosis in each macroscopic type.

Correspondence to: Dr Yoshiki Wada, Digestive Disease Center, Showa University, Northern Yokohama Hospital, 35-1 Chigasaki-chuo, Tsuzuki, Yokohama 224-8503, Japan
E-mail: w-yoshi@mtj.biglobe.ne.jp

Materials and methods

Patient selection. The present study took place at the Digestive Disease Center, Showa University, Northern Yokohama Hospital, between January 2010 and March 2011 and informed consent was obtained from all participating patients. In the present study, a series of 357 consecutive patients with 378 early colorectal cancers were observed by NBI magnification. During this period 2,120 adenomas, 132 hyperplastic polyps and 219 T2-T4 cancers were treated in our center.

Colonoscopic procedure. Bowel preparation consisted of administration of 2-3 l of polyethylene glycol solution in the morning before the procedure. Colonoscopy was performed using a video endoscopic system (EVIS, Lucera Spectrum; Olympus Co., Tokyo, Japan) with a CF-H260AZI optical magnification colonoscope with maximum x80 magnification (Olympus). The Olympus video image processor has 2 adjustable image processing features called structure enhancement and colour enhancement. Structure enhancement has 18 preset patterns, from 'A0' to 'A8' and from 'B0' to 'B8'. Enhanced microstructure imaging is seen at higher preset numbers. Colour enhancement has 3 preset modes: '1' is used for the upper gastrointestinal tract, '3' is used for the lower gastrointestinal tract and '2' is intermediate between '1' and '3'. The setting of structure enhancement was 'A8' and colour enhancement was set at '3'. When a lesion was detected by conventional colonoscopy, water was used to wash away mucus, and then the endoscopist took magnifying NBI images. The original image was transmitted using the standard protocol to the server that hosted the database, where it was converted into a compressed format developed by Solemio ENDO (Olympus). The image could be downloaded from the server in the JPEG format with no further loss in quality. The file size of the downloaded image was about 100 kB, with a pixel array of 640 x 480 and 24 bit colour. Stored images were randomly allocated to 2 readers (Y.W. and M.M.) for classifying the lesion according to the classification system given below. The 2 readers were blind to histopathology and separately evaluated all images. When they did not agree, we discussed and determined the surface pattern. In a substudy, inter- and intra-observer agreements of surface pattern were calculated for the 2 readers (M.M. and Y.W.). For this purpose, 40 images of magnifying NBI views were randomly selected from among all the target lesions by an endoscopist who was not involved in the assessment of the surface pattern. Four weeks after the initial assessment, the same images were randomly allocated to the readers for re-assessment. Inter-observer agreement was calculated from the results of the first reading and intra-observer agreement was determined by comparing the first and the second assessments. After magnifying NBI, indigo carmine or crystal violet dye staining of the lesion was used to determine morphological type. Endoscopic or surgical resection was performed, and the specimens were diagnosed by an experienced gastrointestinal histopathologist. Inclusion criteria included: i) early colorectal cancer [intramucosal cancer (M) which is classified as categories 4.2 or 4.4, and submucosal invasive cancer (SM) which is classified as category 5 in the revised Vienna classification] (25); ii) lesions observed by magnifying NBI; and ii) over 20 years of age. Exclusion criteria included: i) low- or high-grade adenoma (categories 3 or 4.1 in the revised Vienna classification); ii) advanced colorectal cancer (T2 or more); and iii) non-neoplastic lesions.

Surface pattern classification and macroscopic type. When observing colorectal lesions with magnifying NBI, regular pit pattern demarcated by the appearance of meshed brown capillary vessels can be seen without the application of any dye solution (1,4,26,27). In the case of a severely irregular pit pattern or non-structure (type V_I high-grade or type V_N pit pattern), the pit cannot be identified by magnifying NBI (26). In the present study, we grouped the surface patterns observed by magnifying NBI into 3 types: type I, surface microstructure of the lesion was clearly recognised as a white band with uniform arrangement and form; type II, microstructure was obscured, or arrangement and form was heterogeneous; and type III, microstructure was completely invisible (Fig. 1). When 2 or more surface patterns were recognised in a lesion, we adopted the most advanced pattern as representative of the lesion. The surface pattern was considered as more advanced in a descending order of III, II and I.

We classified the macroscopic type into 3 categories: depressed, protruded and flat elevated according to configuration (Fig. 2) (14,28). The so-called laterally spreading tumours (LSTs) can be divided into subgroups and are expressed as type IIa, IIc + IIa, or IIa + Is, according to the categories of the Paris classification (29). In the present study, we included type IIc + IIa LSTs in the depressed group, and the other subtypes of LSTs are included in the protruded or flat elevated group.

Histological examination. All resected specimens were retrieved and immediately fixed in 10% buffered formalin solution and examined histologically using haematoxylin-eosin staining. Pathological examinations were performed on haematoxylin and eosin stained sections. Histological diagnosis was made by a single pathologist who was blind to the endoscopic results, based on the revised Vienna classification (25). When correct diagnosis was difficult, the opinion of a second pathologist was sought to arrive at a final diagnosis. We used the Kudo classification for the degree of submucosal invasion and classified cancers accordingly (30,31). Sm1a or 1b cancer without vessel permeation does not metastasise. In contrast, sm1c, sm2 and sm3 lesions show a substantial proportion (~10%) of nodal metastasis (32). We defined the former lesions as slightly invasive submucosal cancers (SMs) and the latter lesions as massively invasive submucosal cancers (SMm) (Fig. 3).

Statistical analyses. Data were collected with predesigned forms and were entered into a statistical software program (R version 2.13.1, http://www.r-project.org/) for analysis. For the assessment, Student's t-test was used for age and mean size of the lesions. The Chi-square test and Fisher's exact test were used for gender ratio, location of the lesions and diagnostic efficacy of surface pattern. A cross tabulation could be created to display the numbers of lesions as follows: SMm and type III, SMm and type I or II, M-SMs and type III and M-SMs and type I or II. Based on this cross tabulation, we used Chi-square test or Fisher's exact test for diagnostic accuracy. Pairwise Chi-square tests or Fisher's exact tests followed by Bonferroni
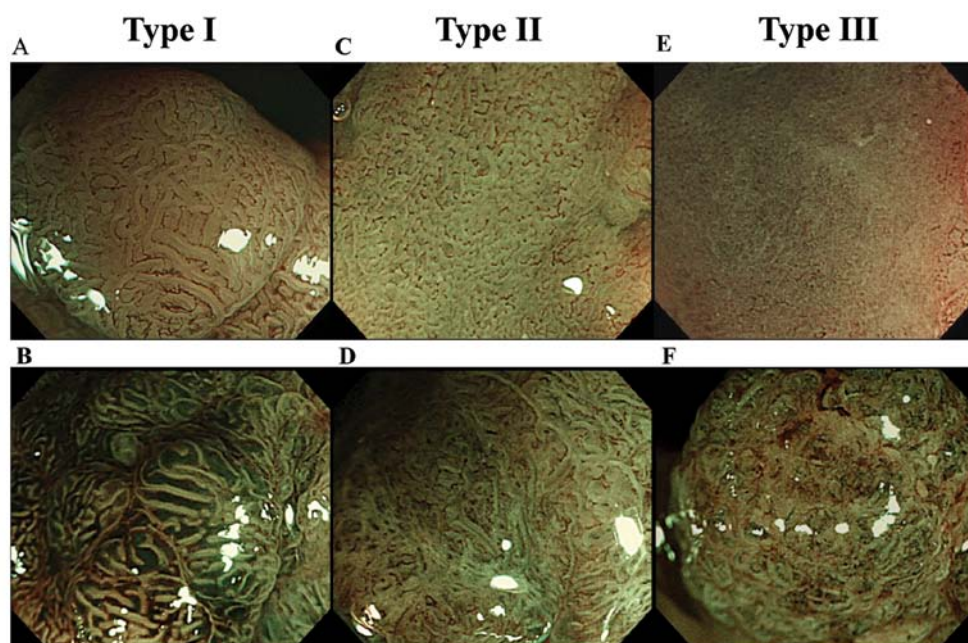
Figure 1. Our classification of surface pattern of colorectal lesions observed by magnifying NBI. (A and B) Type I: surface microstructure of the lesion was clearly recognised as a white band with uniform arrangement and form. (C and D) Type II: microstructure was obscure, or arrangement and form was inhomogeneous. (E and F) Type III: microstructure was completely invisible. (Original magnification, x80).
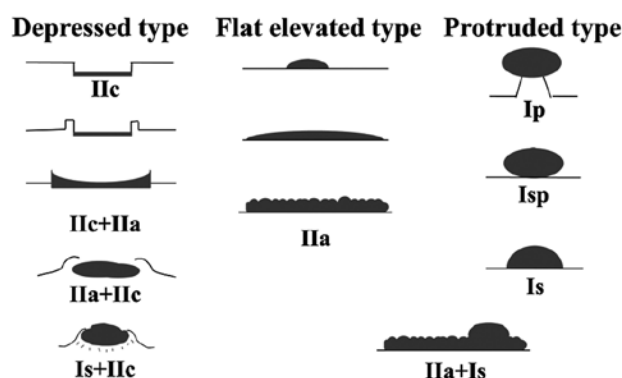

Figure 2. Gross configuration of colorectal neoplasm. The classification is a slight modification of the Japanese rule (ref. 28).
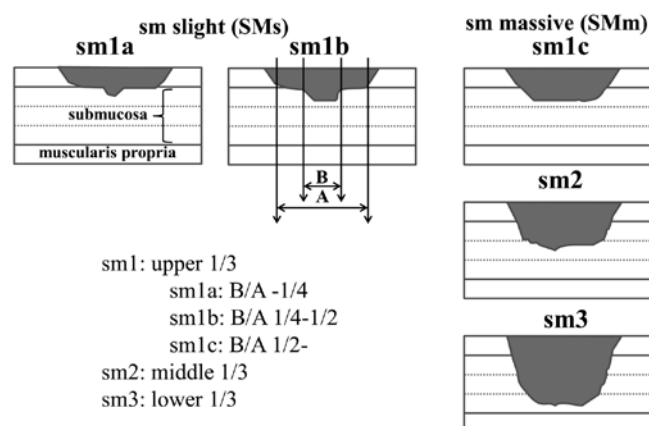

Figure 3. Classification of the degree of submucosal invasion. We divided submucosal cancers into sm1, sm2 and sm3, according to the depth of invasion, and further divided sm1 lesions into 1a, 1b and 1c, according to the width of invasion.

correction were used for the comparison of sensitivity, specificity and accuracy in each macroscopic type. Therefore, in the present study, we needed the statistical test 3 times, but this increased the type I error. However, the Bonferroni correction used here avoided the problem of a type I error caused by sequential application of a statistical test. Kappa statistics were used to calculate inter- and intraobserver agreement. P-values <0.05 were considered significant. Kappa 0 was considered as '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. The sensitivity, specificity and accuracy were calculated based on following definitions: surface pattern III plus SMm were true positive, surface pattern I or II plus SMm were false positive, surface pattern I or II and M-SMs were true negative and surface pattern III and M-SMs were false positive. The upper and lower 95% confidence interval

(CI) limits were calculated using a binomial distribution, with limits at a distance from the estimate equal to the product of 1.96 times the standard error. The present study was approved by the Ethics Committee of the Showa University Northern Yokohama Hospital (1207-01), and was registered with UMIN Clinical Trials, UMIN000007709.

Results

Patients and lesions. The clinicopathological features of patients and lesions of the present study are shown in Table I. There were no significant differences in gender ratio, age, size of the lesions and location.

Table I. Clinicopathological features of patients and lesions.

	Pathological diagnosis		
	M-SMs	SMm	P-value
Male:female	200:113	35:30	0.07[a]
Age ± SD (years)	64.5±11.6	66.9±9.6	0.11[b]
Mean size ± SD (mm)	20.9±16.8	24.1±16.2	0.16[b]
Location			
Right side of colon	98	21	0.84[a]
Left side of colon	132	25	
Rectum	83	19	

SD, standard deviation. [a]Chi-square test; [b]Student's t-test.

Table II. Relationship between pathological diagnosis and surface pattern for all lesions and each morphological group.

	Pathological diagnosis	Surface pattern I/II/III	P-value[a]
Depressed type	M-SMs	1/7/12	0.12
	SMm	-/2/16	
Protruded type	M-SMs	43/46/7	<0.001
	SMm	4/7/13	
Flat type	M-SMs	132/58/7	<0.001
	SMm	1/14/8	
Total	M-SMs	176/111/26	<0.001
	SMm	5/23/37	

[a]Chi-square test or Fisher's exact test.

In total, 56.9% of SMm were recognised as type III and 91.7% of M/SMs cancers were type I or II (Table II). When we assumed that type III was an index of SMm, the sensitivity, specificity, and accuracy of diagnosis were 56.9% (95% CI, 44.0-69.2), 91.7% (95% CI, 88.1-94.5), and 85.7% (95% CI, 81.8-89.1), respectively (P<0.001).

The sensitivity, specificity and accuracy of type III for the diagnosis of SMm in each macroscopic type were as follows: depressed type: 88.9% (95% CI, 65.3-98.6), 40.0% (95% CI, 19.1-64.0), and 63.2% (95% CI, 46.0-78.2), respectively (P=0.05); flat elevated type: 54.2% (95% CI, 32.8-74.5), 92.7% (95% CI, 85.6-97.0), and 85.0% (95% CI, 77.3-90.9), respectively (P<0.001); and protruded type: 34.8% (95% CI, 16.4-57.3), 96.4% (95% CI, 92.8-98.6), and 90.0% (95% CI, 85.3-93.6), respectively (P<0.001) (Table III). The specificity and accuracy of diagnosis of the depressed type was significantly lower, whereas sensitivity was significantly higher, than those of the other macroscopic types. Inter-observer agreement of kappa value was 0.75 (95% CI, 0.59-0.91), and intra-observer agreement of kappa value was 0.96 (95% CI, 0.89-1.03) for M.M. 0.93 (95% CI, 0.83-1.02) for Y.W.

Discussion

In the present study, we made two important clinical observations. First, the diagnostic accuracy of surface pattern was insufficient to decide treatment procedure in daily practice. Second, the diagnostic accuracy of surface pattern varied among each macroscopic type, with the depressed type faring the worst.

To decrease the frequency of false positives in the diagnosis of invasion depth of colorectal lesions a highly specific diagnostic modality is needed. Our previous report showed that V_I high-grade or V_N pit patterns in chromoendoscopy are considered diagnostic for SMm, and we could differentiate between SMm and SMs with a sensitivity of 89.7% and specificity of 88.0% (10). The specificity was similar to that for the present study, although the previous study included only submucosal invasive cancer. However, sensitivity was quite low in the present study (Table II) because there were several lesions in which the surface pattern could be recognised (type I or II) but they were SMm. These false negatives were especially more frequent in protruded and flat elevated cancers. Tanaka *et al* (26) reported that magnifying NBI was useful for diagnosed colorectal lesions that revealed a regular pit pattern. Ikematsu *et al* (33) described the efficacy of capillary pattern classification. Their classification was based on the irregularity of the microvascular pattern, without consideration for the surface pattern. Sensitivity, specificity and accuracy of their classification for differentiating M-SMs from SMm were 84.8, 88.7 and 87.7%, respectively. We realised that their result was a standard performance based on observation of the surface microvascular pattern by magnifying NBI. Kanao *et al* (15) previously classified colorectal lesions according to the magnifying NBI findings of the visibility of surface pattern and the irregularity of capillary pattern. Their classification was more useful for diagnosis of massively submucosal invasive cancer than capillary pattern alone (15-19). Oba *et al* (18) reported that the obscurity of surface pattern seen when using magnifying NBI was an acceptable indicator for deep submucosal invasive cancer. They described that a significantly high percentage of lesions with widely exposed desmoplastic reactions was the cause of the obscurity. As described in previous reports, the type V_N pit pattern is a well-established index of SMm (12-14). If the cancer is massively invasive, desmoplastic reactions accrue and expose the surface of the lesion and this exposed desmoplastic reaction can appear to be non-structural. Thus, we presume that the obscurity of the surface pattern revealed by magnifying NBI (it was a counterpart of type III in the present study) correlates with invasion depth. In fact, 58.7% of lesions identified as type III were SMm, and 17.2% of type II lesions were SMm (Table II). At first glance, the rate of SMm in type II was high, but there were significant differences between the rate of SMm in type II and III (P<0.001, Chi-square test). Oka *et al* (17) classified magnifying NBI findings into 5 patterns (A, B, C1, C2 and C3), their type C3 correspond approximately to our type III. Their classification consisted of evaluating not only the surface microvascular pattern but also the surface pattern of colorectal lesions. Sensitivity, specificity, and accuracy of type C3 for a diagnosis of SMm were 63.7, 99.2 and 94.0%, respectively. Thus, they concluded that type C3 was a useful

Table III. Diagnostic ability of surface pattern for early colorectal cancer for all lesions and each morphological group.

	Depressed type	Protruded type	Flat elevated type	P-value[a]			Total
				Depressed vs. protruded	Protruded vs. flat	Flat vs. depressed	
Sensitivity[b] (95% CI)%	88.9 (65.3-98.6)	54.2 (32.8-74.5)	34.8 (16.4-57.3)	0.016	NS	<0.001	56.9 (44.0-59.2)
Specificity[b] (95% CI)%	40.0 (19.1-64.0)	92.7 (85.6-97.0)	96.4 (92.8-98.6)	<0.001	NS	<0.001	91.7 (88.1-94.5)
Accuracy[b] (95% CI)%	63.2 (46.0-78.2)	85.0 (77.3-90.9)	90.0 (85.3-93.6)	<0.001	NS	NS	85.7 (81.8-89.1)

95% CI, 95% confidence interval; NS, not significant. [a]Pairwise Chi-square tests or Fisher's exact tests followed by Bonferroni correction. [b]Sensitivity, specificity and accuracy were calculated on the basis of the assumption that type III was diagnostic for SMm.
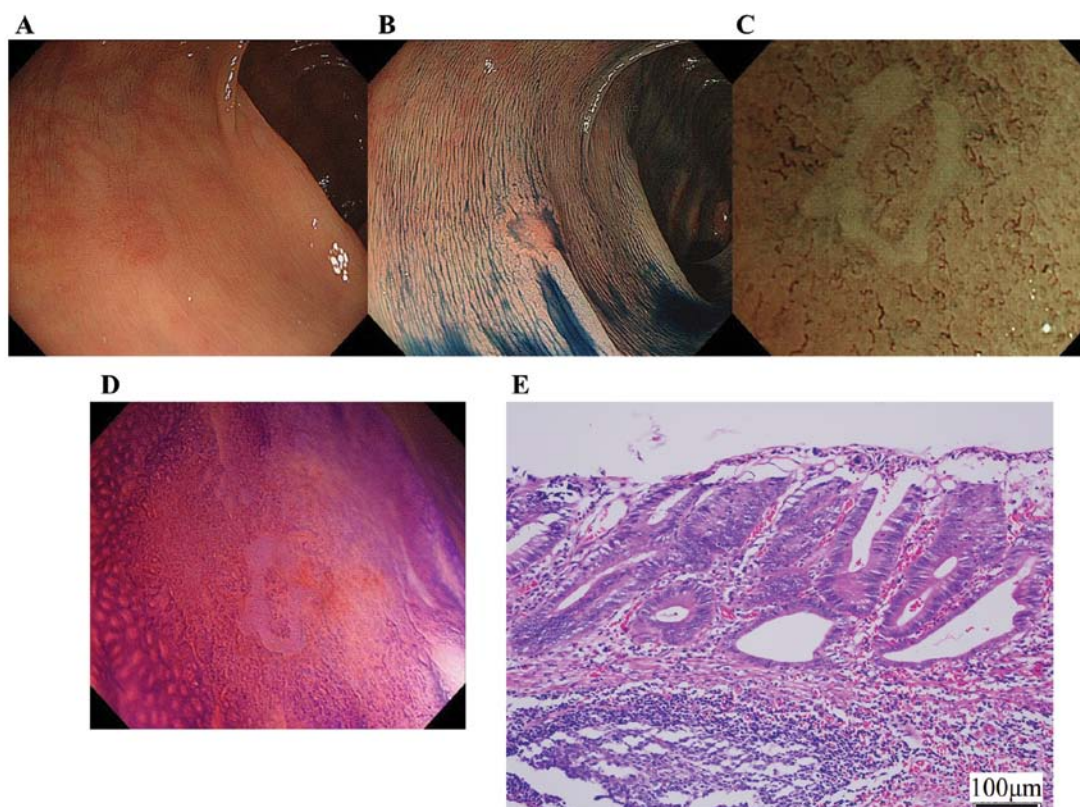

Figure 4. Depressed type lesions (IIc), size 5 mm. (A) On conventional view, there was a tiny reddish lesion. (B) Indigo carmine dye spraying clarified a depression within the lesion. (C) In a high magnification view with NBI, the surface pattern within the depression was type III. (D) After crystal violet staining, there were small roundish pits within the depression. (E) The lesion was endoscopically resected and was diagnosed pathologically as an intramucosal cancer (haematoxylin-eosin staining).

predictor of SMm. These results were more robust than ours, but their investigation included non-neoplastic lesions and low- or high-grade adenoma. If these lesions were excluded, sensitivity, specificity and accuracy were 63.7, 97.8 and 87.2%, respectively. This diagnostic accuracy is still high compared to our result; thus, using surface pattern alone for diagnosis in daily practice may be insufficient. However, according to the present study, 97.2% lesions which revealed type I surface

pattern were M-SMs (Table II). Therefore, we presume that type III or II need another modality such as chromoendoscopy or endoscopic ultrasonography, but type I might not need another modality.

From a morphological perspective, in the depressed type cancers, specificity and accuracy of type III for the diagnosis of SMm were significantly lower. In the present study, about 60% of M and SM depressed type cancers revealed non-struc-

tural surface pattern (type III). These results led to decreased specificity and accuracy for the diagnosis of SMm in depressed type cancers. However, some investigations report surface structure differences when using NBI compared to more traditional methods of analysis such as chromoendoscopy. Machida *et al* (2) compared magnifying chromoendoscopy with NBI, and reported that visualization of the surface structure of colorectal lesions observed by NBI was inferior to that of chromoendoscopy (P<0.05). Hirata *et al* (22) compared pit pattern diagnosis by magnifying NBI with magnifying chromoendoscopy in the same colorectal lesions. They reported that concordance for type V_I pit pattern was 78%, which was lower than that for other regular pit patterns. They suggested that low concordance obtained for type V_I pit pattern may reflect the difficulties of NBI assessment of type V_I pit pattern with mild atypia. Furthermore, East *et al* (21) reported that surface structures observed by NBI and pit pattern observed by chromoendoscopy were not always identical. They also calculated weighted kappa values of vascular pattern intensity and surface pattern, and found that agreement of vascular pattern (weighted k=0.64) was higher than that of surface pattern (weighted k=0.48). Tanaka *et al* (26) reported that the correspondence rate of pit pattern diagnosis between magnifying NBI and stereoscopic findings was 57% (4/7) for the V_N pit pattern. They reported that higher-grade irregular pit patterns are more difficult to detect by magnifying NBI. Hayashi *et al* (20) described that the surface pattern visible in NBI magnifying observation was clearly revealed to be inferior to the fine surface structure obtained by pit pattern diagnosis. To summarise previous reports, an irregular pit pattern like that of type V is scarcely visible by NBI. What was the reason for several M and SMs depressed type cancers presenting as type III? Commonly, the glands of depressed type cancers are small and have a compact arrangement, compared to other morphology (13,23). We think that very small and compactly arranged orifices of glands could be obscured during magnifying NBI. Therefore, care should be taken in assessing the surface pattern, especially in depressed types. We encountered such a lesion; this was a small reddish lesion in the transverse colon (Fig. 4A). After indigo carmine dye spraying, there was a clear depression within the lesion (Fig. 4B). Surface structure was completely invisible by magnifying NBI, thus, we classified this lesion as type III (Fig. 4C). Despite the invisibility of the surface structure, this was not an invasive cancer (Fig. 4E). Such depressed lesions require magnifying chromoendoscopy and direct evaluation of the orifice of the glands (Fig. 4D).

NBI has several advantages compared with chromoendoscopy. First, no dye solutions are required. Second, it is user friendly as it solely depends on the use of optical filters that are easily enabled by a manual switch on the handle of the endoscope. NBI will shorten examination times and reduce the burden on patients and endoscopists. Moreover, mucous attachment on the lesions can interfere with diagnosis, and washing the surface of a lesion with pronase solution takes additional time during pit pattern diagnosis by magnification colonoscopy with indigo carmine dye spraying or crystal violet staining.

The present study had several limitations. First, the surface pattern was judged by 2 individuals that were well experienced in magnifying NBI. Further investigation by less experienced endoscopists should also be performed to validate our findings. Second, candidate lesions were limited to early colorectal cancer. If they also included low-grade adenoma, as is seen in usual clinical practice, diagnostic ability might increase. Third, this was a pilot study, so we did not estimate the sample size before starting the study. However, we calculated post hoc power analysis based on Chi-square test, sample size was 378, effect size which was calculated based on our result was 0.52, degrees of freedom was 2, and level of significance was 0.05. Using these parameters, the power of the present study was 1.0, indicating a sufficient sample size.

In conclusion, the present study showed that the diagnostic accuracy of surface pattern was insufficient to decide treatment procedure in daily practice; the accuracy in depressed type lesions was particularly poor. However, additional studies are necessary for evaluation of the usefulness of surface pattern analysis by magnifying NBI.

Acknowledgements

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